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PRACA POGLĄDOWA
REVIEW

The role of cortisol in etiology and treatment of bruxism – a literature review

Rola kortyzolu w etiologii i leczeniu bruksizmu – przegląd piśmiennictwa

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ABSTRACT

The aim of the study was to analyze the role of cortisol in both the treatment and etiology of bruxism. A literature review was conducted using the PubMed and Embase databases, focusing on publications from November 2013 to November 2023, with no language restrictions. The titles and abstracts were initially screened, followed by a full-text selection process. Observational studies and randomized controlled trials that assessed the relationship between diagnosed bruxism and salivary cortisol levels were included in the analysis. Methodological quality assessment and data extraction were performed on the included studies. Ultimately, eight articles were included in the review. The analysis revealed a significant correlation between higher cortisol concentrations and the occurrence of bruxism. Moreover, individuals with bruxism exhibited higher cortisol concentrations before the initiation of treatment compared to the post-treatment levels.

KEYWORDS

bruxism, cortisol, hydrocortisone, sleep bruxism

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STRESZCZENIE

Celem badania była analiza roli kortyzolu zarówno w leczeniu, jak i etiologii bruksizmu. Przeprowadzono przegląd piśmiennictwa dostępnego w bazach danych PubMed oraz Embase, opublikowanego w okresie od listopada 2013 r. do listopada 2023 r. bez ograniczeń językowych. W pierwszej kolejności przeprowadzono ocenę tytułów oraz abstraktów, a następnie dokonano selekcji na podstawie całych artykułów. Do analizy włączono badania obserwacyjne oraz randomizowane kontrolowane badania kliniczne, które oceniały związek między zdiagnozowanym bruksizmem a poziomem kortyzolu w ślinie. Przeprowadzono ocenę jakości metodologicznej badań i ekstrakcję danych. Finalnie do przeglądu włączono osiem artykułów. Analiza wykazała znaczącą korelację między wyższymi stężeniami kortyzolu a występowaniem bruksizmu. Ponadto u osób z bruksizmem stężenie kortyzolu przed rozpoczęciem leczenia było wyższe niż po jego zakończeniu.

SŁOWA KLUCZOWE

bruksizm, kortyzol, hydrokortyzon, bruksizm senny

INTRODUCTION

Cortisol and corticosterone are glucocorticosteroids produced by the zona fasciculata of the adrenal cortex and belong to the group of steroid hormones. Among them, cortisol is the primary hormone, whose secretion follows circadian rhythms, reaching its peak concentration in the morning and its lowest concentration in the evening [1].

The primary function of cortisol is to regulate blood glucose levels, particularly during stressful situations, by increasing its concentration in the bloodstream. Additionally, cortisol exhibits anti-inflammatory properties and influences various metabolic processes [2]. Cortisol acts on various tissues and organs, including the liver, muscles, and adipose tissue. In the liver, it increases glucose production through gluconeogenesis. In the muscles, it reduces glucose uptake and enhances protein degradation. In adipose tissue, it stimulates lipolysis [3,4].

Chronic stress and elevated cortisol levels can damage the hippocampus, which plays a crucial role in the regulation of emotions. This, in turn, may lead to chronic hypercortisolism, triggering a range of negative effects [5]. This affects glucose metabolism, leading to insulin resistance and obesity, as well as weakens the immune system, increasing susceptibility to infections and leading to immunosuppression. In the cardiovascular system, it may cause hypertension, while in the reproductive system, it can impact hormonal imbalances, the menstrual cycle in women, and sperm production in men. Additionally, it may lower neurotransmitter levels, resulting in sleep disturbances, anxiety, depression, and impaired cognitive function [1].

Stress and elevated cortisol levels are closely linked. Prolonged stress can lead to excessive tension in the masticatory muscles, which is considered a major etiological factor in bruxism [6].

Bruxism is characterized by repetitive activity of the masticatory muscles, manifested as unconscious clenching or grinding of the teeth, occurring both during sleep (sleep bruxism) and while awake (awake bruxism) [7]. It presents with stiffness and pain in the head and neck muscles, restricted mouth opening, and tooth wear. Chronic bruxism can lead to tooth fractures, hypertrophy of the masticatory muscles, and serious complications within the temporomandibular joint (TMJ) [8].

Manfredini et al. [9] estimate the prevalence of bruxism in adults to range between 8% and 31.4%, regardless of gender, with a decreasing tendency with age. The prevalence of daytime bruxism is estimated to range between 22.1% and 31% of the population, while approximately 12.8% ± 3.1% of the population suffers from sleep bruxism. This issue is increasingly being observed among children and adolescents.

The etiology of bruxism is complex, involving central, peripheral, and psychosocial factors [10].

Macaluso et al. [11] demonstrated an increased number of transient arousals during sleep in individuals with bruxism, associated with arousal responses and restless legs syndrome. No significant association was found between bruxism and occlusal factors, but a connection was observed with psychosocial factors such as stress, anxiety disorders, and environmental pressure [12,13,14,15] (Table I).

Table I. Potential etiological factors of bruxism

Central	Peripheral	Psychosocial
• Central arousal response	• Iatrogenic disorders of articulation and centric relation	• Stress
• Sleep disorders		• Anxiety
• Drug/substance use		• Frustration
• Alcohol/caffeine consumption		• Lack of social support
• Smoking		• Social pressure
• Genetic/inherited factors		

The aim of this study was to analyze the available literature concerning the role of cortisol in both the treatment and etiology of bruxism over the past decade.

MATERIAL AND METHODS

The literature review was conducted by searching online databases such as PubMed and Embase. Articles were sought on the etiology, diagnosis, and treatment of bruxism, with a focus on cortisol levels. The PubMed database was searched using the following phrases: "cortisol bruxism" [All fields]; ((hydrocortisone) OR (cortisone)) AND ((bruxism) OR (sleep bruxism)) [All fields]. The Embase database was searched using the phrases "bruxism" [All fields] and "hydrocortisone" [All fields]. Additionally, the references of the retrieved articles were manually searched. All available articles published between November 2013 and November 2023 were considered, with no language restrictions. The initial selection of articles was based on analysis of the titles and abstracts, and those that did not meet the inclusion criteria were excluded at this stage. The remaining articles were thoroughly analyzed in full by two independent reviewers. During this stage, the study characteristics, the number of subjects, methodology, and results were assessed.

Inclusion and exclusion criteria for the literature review

The literature review included observational studies and randomized controlled clinical trials that assessed the relationship between diagnosed bruxism and salivary cortisol levels. Excluded from the review were case reports, animal studies, in vitro studies, technical notes, dissertations, review articles, textbooks, studies that did not report cortisol levels, and studies involving children. The quality of the included studies was assessed based on the adequacy of the study design relative to the research objective, the risk of bias, the reliability of the results, statistical analysis, and the quality of reporting.

RESULTS

As a result of searching the databases using the specific search terms in addition to the inclusion and exclusion criteria, a total of 108 articles were identified, with 46 sourced from PubMed and 61 from Embase and 1 was found manually after searching. After analyzing the titles and abstracts, 29 articles were selected. The next step involved a thorough analysis of the full texts of the selected articles. Following the application of the selection criteria, a total of 8 studies were included in the literature review. Most of the studies demonstrated a significant correlation between the occurrence of bruxism and poorer psychosocial conditions [16,17,18, 19,20,21,22,23] (Figure 1).

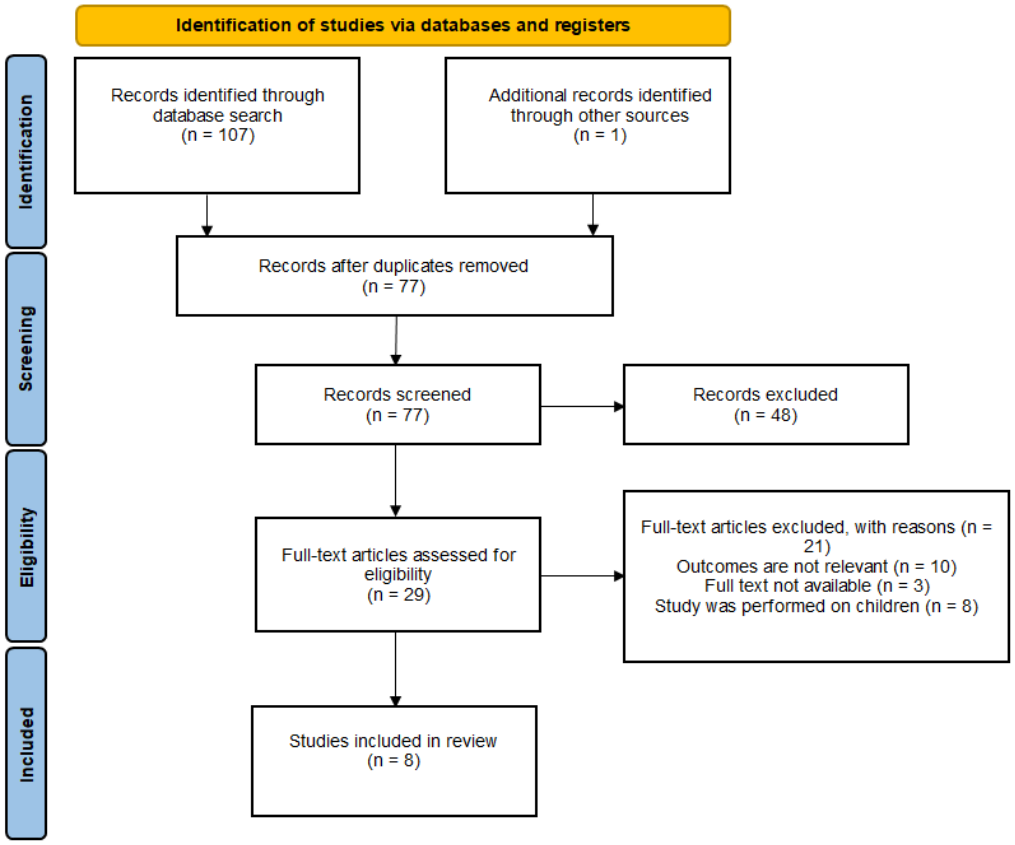

Fig. 1. Study selection flowchart.

The study by Fluerașu et al. [16] showed that individuals suffering from bruxism are more likely to experience stress, frustration, anxiety, and depressive states. A correlation was also found between the occurrence of pain and clicking sounds in the TMJ and higher cortisol levels. The cortisol concentrations were also noticeably higher in patients suffering from anxiety and in women. The authors suggest that cortisol measured in saliva could become a useful, non-invasive biomarker for assessing the presence and severity of bruxism.

The results of the study by Karakoulaki et al. [17] present a significant correlation between elevated salivary cortisol levels and severe stress. The study utilized BiteStrip, a device that allows the self--diagnosis of sleep bruxism. Positive results following the use of BiteStrip were also correlated with elevated salivary cortisol levels. In the study by Rosar et al. [18], which compared sleep before and after treatment in patients suffering from bruxism, it was proven that sleep quality, latency, and duration improved, while the frequency of sleep disturbances and the need for sleeping medications decreased.

In the study by Miletić et al. [19], the personality traits of patients suffering from bruxism were assessed. It was shown that depressive states, hypomania, and the suppression of aggression, which cause prolonged stress, can lead to the manifestation of symptoms of sleep bruxism. Khayamzadeh et al. [20] observed more frequent occurrences of depressive, anxiety, and stress states in patients suffering from sleep bruxism. Salameh et al. [21] demonstrated that the group of patients with bruxism had significantly higher stress levels than the healthy control group and were much more likely to experience anxiety and depressive states.

Cortisol levels in patients diagnosed with bruxism compared to healthy individuals

Six studies that analyzed the cortisol levels in patients with confirmed bruxism and in a control group comprising 397 adult participants were classified according to the established criteria included in the review (Table II).

The analyzed studies focused on evaluating salivary cortisol levels in patients diagnosed with bruxism compared to a group without this diagnosis. The examination of the mean values and standard deviations of the cortisol levels revealed a significant difference in favor of the control group, suggesting that individuals diagnosed with bruxism exhibited higher levels of salivary cortisol. Most of the articles utilized the same method for verifying salivary cortisol levels for both patients and the control group – the ELISA technique. However, the study conducted by Miletić et al. [19] used chemiluminescence techniques. The discrepancies in the results may stem from differences in the procedures and sample collection times. It is noteworthy that all the studies, except for the study by Khayamzadeh et al. [20], which did not provide information on the age of the studied population, used groups in a similar age range.

Cortisol levels before and after treatment in patients diagnosed with bruxism

For the literature review concerning treatment, two studies were included that compared cortisol levels before and after treatment. In this context, “treatment” encompasses therapeutic methods focused on alleviating stress, anxiety and muscle tension, which are essential in managing bruxism. These studies encompassed a total of 102 adult participants and were selected according to established criteria (Table III).

The study conducted by Rosar et al. [22], aimed to evaluate salivary cortisol levels before and after treatment in patients diagnosed with bruxism, compared them to a group of patients without this condition. This treatment involved the use of an interocclusal appliance designed to reduce masticatory muscle activity, thereby alleviating stress and tension in the temporomandibular region. In contrast, the study by Al-Oudah et al. [23] divided patients diagnosed with bruxism into two groups: one group received treatment with oral Chlordiazepoxide tablets (5 mg), an anxiolytic benzodiazepine aimed at managing anxiety, a significant contributing factor to bruxism. The tablets were administered once daily after the evening meal for 10 days, while the other group received a placebo in the form of orally disintegrating tablets, also administered once daily after the evening meal for the same period. The cortisol levels were then evaluated. Both studies observed significant reductions in cortisol levels following treatment, which suggests the effectiveness of therapeutic interventions in reducing the levels of this hormone [22,23].

Table II. Characteristics of studies comparing cortisol levels between individuals with diagnosed bruxism and healthy patients

Author	Year and country of publication	Type of study	Number of participants	Number of patients with bruxism	Average age of patients with bruxism	Cortisol levels in patients with bruxism	Number of healthy participants	Average age of healthy participants	Cortisol levels in healthy participants	Measurement technique	Sample collection time
Fluerașu et al. [16]	2019 Romania	analytical, observational, cohort, cross-sectional, and prospective study	60	30	24 (23–24.5) years	5.63 µg/dL (4.49–10.44)	30	23 (20.75–23) years	3.11 µg/dL (1.37–6.58)	elisa	7:00
Karakoulaki et al. [17]	2015 Greece	case-control study	45	25	34.5 ± 6.4 years	0.37 ± 0.08 µg/dL	20	34.5 ± 6.4 years	0.27 ± 0.06 µg/dL	elisa	7:00–9:00
Miletić et al. [19]	2018 Serbia	cross-sectional study	65	23	26.56 years	45.75 ± 17.54 nmol/L	42	26.3 years	34.42 ± 7.80 nmol/L	chemilu-minescence	no later than 9:00
Khayamzadeh et al. [20]	2019 Iran	case-control study	64	32	–	4.28 ± 0.14 ng/mL	32	–	3.68 ± 0.19 ng/mL	elisa	9:00–11:00
Salameh et al. [21]	2015 Syria	case-control study	120	60	19–44 years	21.78 ± 13.69	60	19–44 years	7.13 ± 4.28	elisa	I. Upon awakening II. 30 minutes after awakening III. 60 minutes after awakening
Rosar et al. [18]	2021 Brazil	cross-sectional study	43	28	22.57 (2.74) years	I 0.19 (0.21) µg/dL II 0.24 (0.28) µg/dL	15	21.60 (1.2) years	I 0.16 (0.13) µg/dL II 0.16 (0.09) µg/dL	elisa	I. Upon awakening II. 30 minutes after awakening

Table III. Characteristics of studies comparing cortisol levels before and after bruxism treatment

Characteristics	Rosar et al. [22]	Al-Oudah et al. [23]
Year and country of publication	2017, Brazil	2021, Iraq
Type of study	case-control study	randomized clinical trial
Number of participants	43	59
Number of participants in study group	28	30
Mean age of participants in study group	22.6 (2.7) years	45.0 ± 6 years
Cortisol levels before treatment in study group	5.9 (5.3)	81.08 (7.95)
Cortisol levels after treatment in study group	I month after treatment 2.6 (4.2) II months after treatment 2.5 (5.3)	78.98 (3.52)
Number of participants in control group	15	29
Mean age of participants in control group	21.6 (1.7) years	45.0 ± 6 years
Cortisol levels before treatment in control group	4.9 (2.0)	81.42 (7.32)
Cortisol levels after treatment in control group	I month after treatment 4.4 (3.3) II months after treatment 4.3 (2.1)	80.96 (6.93)
Measurement technique	elisa	N/A
Sample collection time	upon awakening and 30 minutes after awakening	N/A

DISCUSSION

In this literature review, the role of cortisol, a steroid hormone produced by the adrenal cortex, was analyzed in detail in the context of the etiology and treatment of bruxism. This relationship is crucial as cortisol plays a significant role in the body's stress response, which may directly influence the occurrence of bruxism. The results of available studies indicate a clear association between elevated salivary cortisol levels and the frequency of bruxism, which may be linked to etiological factors such as anxiety disorders, apprehension, frustration, and stress.

Studies comparing the cortisol levels in patients diagnosed with bruxism and those without this diagnosis confirmed higher cortisol values in individuals suffering from this condition. These findings underscore that cortisol levels may be an important factor in the development and progression of this disease. An important aspect is also the analysis of cortisol levels before and after bruxism treatment. Studies have shown significant reductions in cortisol levels following treatment in patients with bruxism. This is a significant observation, suggesting that therapy may impact not only the symptoms of bruxism but also the level of stress hormone in the body, confirming the existing correlation between these factors.

The results of the literature analysis confirm the association between cortisol and bruxism and highlight the need to consider psychosocial factors in the diagnosis and treatment of this condition. Nonetheless, further research is needed to better understand this correlation, which could contribute to the development of more effective therapeutic strategies. Future studies should focus on more precisely defining the mechanisms through which cortisol influences bruxism, potentially opening new avenues for the prevention and treatment of this condition.

CONCLUSIONS

The analysis of the literature clearly indicates a significant correlation between bruxism and elevated cortisol levels. These findings suggest that cortisol, as the primary stress hormone, may play a crucial role in the development and progression of bruxism. These observations emphasize the importance of considering both psychosocial factors, such as stress and anxiety, as well as hormonal factors, in the diagnosis and treatment of this condition. The fact that bruxism and elevated cortisol levels coexist opens new perspectives for understanding the pathomechanisms of this condition. Knowledge of the causes of this correlation will make it possible to develop targeted therapeutic approaches that focus not only on the symptoms, but also on the causes of the disease. Given these results, further research is needed to gain a more comprehensive understanding of the complex interaction between cortisol and bruxism, which will consider both the psychological and biological aspects.

Author's contribution

Study design – S. Baron
Data collection – W. Galińska, I. Burliga
Manuscript preparation – W. Galińska, I. Burliga, M. Moskała
Literature research – W. Galińska, I. Burliga
Final approval of the version to be published – S. Baron

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OPIS PRZYPADKU
CASE REPORT

Morphea profunda – a case report of deep localized scleroderma with severe thorax deformity

Twardzina głęboka – opis przypadku ze znaczną deformacją klatki piersiowej

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ABSTRACT

Deep scleroderma is a rare form of limited scleroderma characterised by deep sclerosis that may involve the muscles, fascia, subcutaneous tissue and deep layers of the skin. The lesions usually occur in the paraspinal line and may be predisposed by factors such as infections, injuries, exposure to radiation or the use of stimulants. Due to an insufficient level of awareness among healthcare professionals, diagnosis can be significantly delayed, and irreversible as well as crippling deformities can result. The study presents the case of a 67-year-old female patient with deep scleroderma whose lesions occur in an unusual location on the anterior surface of the thorax. This case demonstrates the importance of early diagnosis and the introduction of appropriate therapy in the active phase of the disease to avoid such severe consequences.

KEYWORDS

localized scleroderma, deep localized scleroderma, connective tissue

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STRESZCZENIE

Twardzina głęboka jest rzadką formą twardziny ograniczonej, charakteryzującą się występowaniem głębokich stwardnień, mogących obejmować mięśnie, powięzi, tkankę podskórną oraz głębokie warstwy skóry. Zmiany zwykle występują w linii przykręgosłupowej, a do ich powstawania mogą predysponować czynniki wyzwalające, takie jak infekcje, urazy, ekspozycja na promieniowanie lub stosowanie używek. Ze względu na niedostateczny poziom świadomości pracowników opieki zdrowotnej diagnoza może być znacznie opóźniona, a w konsekwencji może dochodzić do nieodwracalnych i okaleczających deformacji. W pracy przedstawiono opis przypadku 67-letniej pacjentki z twardziną głęboką, u której zmiany chorobowe występują w nietypowej lokalizacji w obrębie przedniej powierzchni klatki piersiowej. Przypadek ukazuje, jak ważne jest wczesne postawienie właściwej diagnozy oraz wprowadzenie odpowiedniej terapii w aktywnej fazie choroby, aby uniknąć tak poważnych powikłań.

SŁOWA KLUCZOWE

twardzina ograniczona, twardzina głęboka, tkanka łączna

INTRODUCTION

Deep scleroderma is a rare form of localized scleroderma (LoSc, morphea; < 5%) characterized by the presence of deep sclerotic lesions affecting the muscles, fasciae, subcutaneous tissue and deeper layers of the dermis [1]. Infection, injury, radiation or drugs can potentially trigger the disease [2]. It may affect both children and adults. Skin manifestations are not accompanied by any subjective symptoms or the involvement of internal organs

CASE DESCRIPTION

A 67-year-old woman with a history of morphea profunda presented to the dermatology department with multiple diffuse sclerotic changes involving the characteristic of hardened tumors, poorly demarcated and overstretched scars, constant inflammation and discoloration in the chest region (Figure 1). On cutaneous examination in the right breast area, there was an erythematous infiltrative lesion present with a small crust on top, painful at palpation (Figure 2). Medial within the right breast there was a fistula, slightly painful at palpation. The nipples were free of lesions. Magnetic resonance imaging (MRI) showed the connective tissue changes of the characteristic of fibrous changes located in the skin and subcutaneous tissue of the anterior chest wall, which is typical for scleroderma. Computed tomography revealed sclerotic infiltration of the skin of both breasts, post-inflammatory fibrous changes with accompanying minor calcifications at the apices of the lungs, enlargement of the lymph nodes in the right axilla and Schmorl's nodes in the lower thoracic vertebrae. The symptoms were first observed in 1984; initially the differential diagnosis included breast cancer and panniculitis non febrilis, however, in 1995 a biopsy was performed and confirmed the diagnosis of morphea profunda. Over the years, the patient has been treated in various ways. Her medical history included medications such as thymostimulinum (TFX), Augmentin, dapsone, isotretinoin, ciprofloxacin, ceftriaxone, a eutectic mixture of local anesthetics (EMLA), cefuroxime, tobramycin ointment, cooling ointment with hydrocortisone and periodic topical mupirocin. The patient had concomitant diseases including chronic obstructive pulmonary disease (COPD), cardiac arrhythmia and a gallbladder polyp. The laboratory results only demonstrated a high cholesterol level (8.3 mm/l) and white blood cells in the upper limit of the norm (10 000/µl). *Staphylococcus epidermidis* was identified in the swab. The patient was started on Cefuroxime 2 × 1.5 g intravenously, probiotic and cold compresses with wound disinfection solution were applied locally. The treatment recommendations after hospitalization included methotrexate (MTX) 15–25 mg/week, prednisone 0.5–1 mg/kg body weight/day in 2 divided into doses for 2–4 weeks with a gradual dose reduction, and mycophenolate mofetil (MMF) 1–2 g/day.

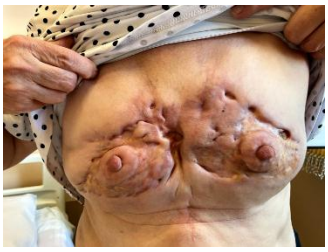

Fig. 1. Skin lesions in form of hardened tumors. Poorly demarcated, overstretched scars. Skin is discoloured, covered by chronic inflammatory process. Nipples are free of lesions.

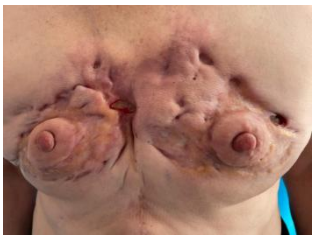

Fig. 2. In region of right breast, erythematous and infiltrative lesion with crust on top and fistula at sternum.

DISCUSSION

Limited scleroderma is a chronic connective tissue disease. The peak incidence is between the ages of 20 and 40 [1]. The disease is more common in Caucasians and females (female:male – 4:2) [3]. The etiopathogenesis of LoSc is not fully understood, but genetic and environmental factors, as well as immunological and vascular disorders, are thought to be crucial in the development of the condition [1].

There are known cases that LoSc-type lesions occurred due to mechanical injury, long-term pressure, and the usage of drugs. The role of *Borrelia burgdorferi* spirochetes in the development of LoSc is debatable, but currently it is not recommended to routinely determine the level of anti-*B. burgdorferi* antibodies [4].

Clinically, the disease involves three phases: early inflammatory (active, lasting an average of 3–4 years), progressive sclerosis and atrophic (atrophic). Limited scleroderma usually does not progress to systemic scleroderma [1].

According to the latest classification, there are five main clinical types of LoSc – deep scleroderma is one of them. The case we present is an example of a severe deformity in the thorax resulting from a long-standing course of deep scleroderma.

In every patient with deep morphea, a thorough medical history should be taken to determine the onset of lesions, conduct a thorough physical examination, and assess disease activity or severity and tissue damage, as well as the possible progression of lesions. A special questionnaire for assessing activity/severity and tissue damage (Localized Scleroderma Cutaneous Assessment Toll – LoSCAT) is used for this purpose [5]. Investigations in cases of morphea profunda may show peripheral eosinophilia, high gamma-globulinemia and raised erythrocyte sedimentation rate (ESR) [5]. Although serologic abnormalities like antinuclear antibodies, anti-double stranded-DNA, anti-single stranded-DNA, anti-histone antibodies and a rheumatoid factor have been discovered in morphea patients, regular testing for them is not advised [6]. It is also worthwhile to perform imaging studies (especially MRI) [7], which will undoubtedly facilitate the evaluation of the effectiveness of the implemented treatment or the progression of the disease in further follow-up [4]. MRI has its limitations, such as the high cost of the examination, the long examination time, accessibility or the low signal-to-noise ratio for the superficial layers [8]. Deep scleroderma does not involve internal organs, hence diagnosing the patient for organ changes is not required [4].

Excised skin should be taken for histopathological examination only in doubtful situations with an unclear clinical picture, in order to establish the diagnosis. Deep scleroderma should be differentiated from subcutaneous tissue inflammation and the subcutaneous (deep) variety of lupus erythematosus [4].

If morphea profunda is diagnosed, aggressive treatment is required in the active phase of the disease. The treatment of choice is glucocorticosteroids in the form of intravenous infusions of methylprednisolone at a dose of 500–1000 mg/day for 3 days. Treatment should be continued for at least 3–6 months. An alternative to parenteral treatment is oral prednisolone therapy. It is recommended to administer 0.5–2 mg/kg/day of prednisolone for 2–4 weeks, followed by a gradual reduction of the dose. During long-term glucocorticosteroid therapy, patients should be monitored for adverse effects such as osteoporosis [9]. Glucocorticosteroids can be used in monotherapy or in combination with methotrexate. The recommended dose of methotrexate in adults is 12.5–25 mg/week. Treatment should be continued for at least 12 months. Methotrexate intolerance or drug resistance is an indication to consider mycophenolate mofetil (1–2 g/day) [10]. Patients should be screened for hepatitis B and C before starting methotrexate treatment. While taking methotrexate, patients require a complete blood count every three months to monitor for methotrexate toxicity, which can cause cytopenia and elevated liver parameters. Folic acid preparations should also be supplemented during therapy with this drug to prevent side effects [9].

During the inactive period, the morphology of the plaque changes – erythema disappears, hyper-pigmentation occurs, sclerosis subsides and features of atrophy of the skin and/or subcutaneous tissue are present. Such lesions that do not show activity for at least 6 months do not require drug treatment [11].

CONCLUSIONS

The case is reported in view of its extensive morphea profunda with irreversible chest deformity. This case demonstrates the importance of introducing appropriate therapy in the active phase of the disease to avoid such severe complications.

Author's contribution

Study design – N. Tekiela, A. Guberniak, K. Polak, B. Bergler-Czop
Manuscript preparation – N. Tekiela, A. Guberniak K. Polak
Literature research – N. Tekiela, K. Polak, B. Miziołek
Final approval of the version to be published – B. Bergler-Czop, B. Miziołek

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PRACA POGLĄDOWA
REVIEW

Cerebral venous sinus thrombosis in pediatric population – a literature review

Zakrzepica zatok żylnych mózgowia w populacji pediatrycznej – przegląd literatury

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ABSTRACT

Cerebral venous sinus thrombosis (CVST) is a rare neurological disorder in the pediatric population. It occurs in children of all ages; nevertheless, newborns and infants younger than three months represent up to 43% of cases. The etiology is multifactorial, often encompassing various predisposing conditions. An early and accurate diagnosis and well-chosen treatment are crucial for better outcomes. The process of diagnosis might cause several difficulties as the symptoms tend to be non-specific. In different age groups the neurological signs may vary, and thus elongate the time between the first contact with the doctor and the initiation of treatment. What is more, there is no marker that is suitable in this diagnostic course. Due to such difficulties, different neuroimaging techniques such as cranial ultrasound, magnetic resonance imaging, and magnetic resonance venography should be used. CVST might lead to severe neurological and cognitive complications. Fortunately, appropriate treatment can help lower the mortality rate and prevent those complications. In this paper, we summarize the current knowledge of CVST in children.

KEYWORDS

stroke, pediatrics, anticoagulants, cognitive impairment

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STRESZCZENIE

Zakrzepica zatok żylnych mózgowia (*cerebral venous sinus thrombosis* – CVST) to rzadkie, ale poważne schorzenie neurologiczne w populacji pediatrycznej. Występuje u dzieci w każdym wieku, ale noworodki i niemowlęta poniżej trzeciego miesiąca życia stanowią nawet do 43% przypadków. Etiologia tego schorzenia jest wieloczynnikowa, obejmuje wiele różnych predysponujących stanów i chorób. Wczesna i dokładna diagnoza oraz dobrze poprowadzona terapia są kluczowe dla uzyskania lepszych wyników leczenia. Proces diagnostyki może być utrudniony z powodu niespecyficznych objawów. W różnych grupach wiekowych objawy mogą się różnić, co może się przyczyniać do wydłużenia czasu pomiędzy pierwszym kontaktem z lekarzem a zainicjowaniem leczenia. Ponadto nie ma aktualnie żadnego markera, który mógłby zostać użyty w celu postawienia diagnozy. Z powodu tych trudności w diagnostyce zakrzepicy u dzieci w zależności od wieku pacjenta stosuje się odmienne techniki neuroobrazowania, takie jak ultrasonografia przezczaszkowa, rezonans magnetyczny lub wenografia rezonansu magnetycznego. CVST może powodować poważne neurologiczne i kognitywne powikłania. Na szczęście odpowiednio poprowadzone leczenie może obniżyć wskaźnik śmiertelności, a także zapobiec tym powikłaniom. W niniejszej pracy podsumowano aktualną wiedzę na temat CVST u dzieci.

SŁOWA KLUCZOWE

udar, pediatria, antykoagulanty, upośledzenie funkcji poznawczych

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is an uncommon but potentially serious condition in the pediatric population. It accounts for less than 1% of strokes in children [1]. CVST is characterized by thrombus formation in the intercranial venous system. Blood clots can form in different sinuses. Therefore, the symptoms and disease presentation vary between individual patients, without any specific clinical signs. According to the study by deVeber et al. [2], the estimated annual incidence rate of CVST is 0.67 per 100 children. They stated that neonates account for nearly half of the CVST cases. There are indeed more recent studies where the proportion of neonates is lower. However, there is a high possibility that their prevalence is underestimated. Because of the oligosymptomatic course of the disease, lacking neurological signs, the diagnosis of CVST is often not raised in this age group [3].

CVST is a multifactorial disease arising from various medical conditions, such as infections, metabolic causes, thrombophilia and neoplasm [4]. Often more than one factor leads to the development of the disease. The diagnosis of the disease is based on neuroimaging studies. Imaging techniques used in CVST include computed tomography scan, magnetic resonance imaging, venography and cranial ultrasound. The imaging modalities are chosen based on the patient's age [5]. The management strategies involve anticoagulation therapy, whose purpose is to stop the thrombus enlargement and dissolve it. Anticoagulation therapy can be administered at any age, with special caution in the youngest patients. A multidisciplinary approach involving pediatricians, neurologists, and hematologists is crucial for optimal outcomes. Further research is needed to enhance our understanding of this condition and improve therapeutic strategies for affected children.

MATERIAL AND METHODS

For the search of articles, PubMed and EMBASE databases were used, as well as references from relevant articles and internet sources. The search terms included "CVST children", "CVST pediatric", "cerebral venous sinus thrombosis children", "CVST diagnosis children", and "CVST treatment children". We excluded articles older than 2001, and regarding the diagnosis and treatment, stricter inclusion criteria were used – only studies from 2019 to July 2024 were included.

DISCUSSION

Risk factors

The conditions associated with an increased risk for CVST differ between pediatric and adult patients. The most common risk factors in children are dehydration, infections, such as mastoiditis or meningitis, and head trauma. Other less common, but equally significant causes are malignancies, especially acute lymphoblastic leukemia, systemic lupus erythematosus, and inherited thrombophilia.

Nonetheless, in the neonate subgroup, the most frequent factors were maternal thrombophilia, respiratory distress, mechanical ventilation, perinatal asphyxia, and meconium aspiration [6]. What is more, there are studies suggesting that anemia or inflammatory bowel disease are linked to CVST development [7,8,9].

Diagnosis

CVST is a serious clinical condition that might be found in patients of every age. Regarding a recent pediatric health information system database study, more than 17% of the hospitalizations concerned

neonates. It is crucial to have a better understanding of CVST in neonatal patients as they often present fewer symptoms and thus the diagnosis is hindered. Some of the newborns might present encephalopathic symptoms and seizures, however, predominantly the symptoms are non-specific. When compared to older children, congenital heart disease and sepsis are more common in CVST patients, which might contribute to higher mortality rates in this population [3]. What is more, usually, contrary to older children, no signs of increased intracranial pressure are found in newborns [1,3]. On the other hand, regarding some recent studies, the most commonly reported symptoms in older children are drowsiness (87.5% of the patients), seizures followed by headache (50%), headaches (62.5%), fever (46%) and vomiting (43%) [10,11]. Furthermore, decreased consciousness and headache without another apparent cause in young patients might indicate a need for further examination to confirm or exclude CVST [11]. What is more, head trauma may pose another diagnostic difficulty owing to a similar presentation of symptoms. Notably, headaches related to isolated CVST tend to be more diffuse and to progress over days, while a change in the characteristics of the pain suggests another underlying cause or complication. Thus, it is crucial to stay alert, especially in pediatric patients after head injury [12].

There is a study suggesting that low hemoglobin and anemia might be used as a biomarker in pediatric CVST as a positive association of anemia with multiple sinus involvement was revealed in a retrospective study. Unfortunately, there is not enough research to assess whether those laboratory findings might be commonly used in the diagnosing process [8]. Since there is no specific CVST marker, imaging techniques are essential in the management of CVST patients, especially newborns. The imaging modalities remained similar in both age groups, nevertheless, the neonates were examined by means of head ultrasound more often, while CT without contrast was less common [3]. According to one study, an attenuation of the affected sinus is increased in patients with CVST on the computed tomography, and consequently, increased densitometric values are present in the site of venous thrombosis [13].

Furthermore, in most cases, magnetic resonance with angiography in venous time is believed to be sufficient to confirm CVST. Numerous studies found that the sagittal and transverse sinus are some of the most frequent sites of neonatal CVST, while more than half of the infant population presented multiple sinus involvement [14].

Treatment

In the available recent literature, most children are treated using anticoagulation (65–97%) [15,16,17]. Enoxaparin and unfractionated heparin (UFH) are reported to remain the first choice of CVST treatment in both neonates and older children, while direct oral anticoagulants (DOACs) were used rather only in older patients [3]. Debates are still ongoing on whether anticoagulation is a safe therapeutic option, especially among newborns because of hemorrhagic risk. On the other hand, a recent study revealed that this therapy was initiated in 82% without complications [1]. Moreover, in another study, none of the treated infants, including those with pre-treatment hemorrhage, suffered from a worsened or new hemorrhage [14]. Anticoagulation seems to be associated with a lower risk of severe neurological and cognitive impairment since children treated with anticoagulants had better outcomes at the follow-up, including long-term complications [18]. What is more, in the study carried out by Sutter et al. [19], almost half of the patients treated with anticoagulation presented complete recanalization on imaging, and more than $^{1}/_{3}$ had partial recanalization. Notably, none of those patients suffered from adverse events resulting from this therapy.

In some cases, additional treatment might be needed, especially when other clinical conditions are present. A study of 35 children with papilledema in association with CVST revealed that all of them required acetazolamide and/or lumbar puncture aside from anticoagulation [15]. Importantly, some CVST patients might require endovascular therapy. The most frequent indications include worsening of Glasgow Coma Scale (GCS) and other symptoms despite anticoagulation. Complete resolution of the symptoms and the complete recanalization associated with it can be achieved in more than half of this patient group [17].

Neurological complications and outcomes

A cross-sectional analysis by Proaño et al. [20] evaluated the outcomes of children with CVST. They found that the median age was 8 years, and the highest prevalence was observed in neonates. Long-term neurological complications were reported in 40–60% of the survivors, while ¼ of the children suffered a stroke. The children who had a stroke as a complication of CVST were more likely to require mechanical ventilation and had increased mortality. According to Teksam et al. [21], ischemic and hemorrhagic brain injuries are very common complications of CVST, especially in neonates and infants, which may be a result of immature compensating mechanisms. However, the brain lesions observed in imaging studies were smaller in the neonates compared to the older children.

Another study investigated 42 children diagnosed with CVST. Three patients died quickly due to CVST, and two patients died later. The follow-up for the survivors ranged from 6 months to 10 years. The researchers found that $^{2}/_{3}$ of the children developed neurological complications or cognitive difficulties. Less than 5% of

this population suffered from permanent hemiparesis, 7% had reduced visual acuity and 5% had epilepsy. $^1/_3$ of the children were diagnosed with idiopathic intracranial hypertension (IIH), however, no children diagnosed with cognitive dysfunction developed IIH. It was also established that a favorable cognitive outcome was observed more often in older children, those without parenchymal lesions. Later and/or sigmoid sinus involvement also resulted in better cognitive outcomes, albeit it increased the risk of IIH [22].

A study from 2009 by Mallick et al. [23] supports the above findings. The follow-up ranged from 5 months to 6 years and during its period 9% of the patients died. In the remaining children, more than $^1/_3$ developed IIH. Less than 10% of the children had residual hemiparesis and only one child had residual sixth nerve palsy.

DeVeber et al. [2] reviewed the medical records of 160 children, 69 of whom were newborns, and assessed the neurological outcome in 143 of them. From the beginning of CVST to the last follow-up neurological deficits were present in 38% of the children. The most common neurological deficits were motor impairment present in 80% of cases, cognitive impairment in 10%, developmental delay in 9%, speech impairment in 6% and visual impairment also in 6%. Moreover, other neurological deficits occurred in 26% of the patients.

Seizures

Other frequently present neurological complications are seizures since they might be observed in 15–25% during follow-up (newborns accounted up to 57%) [2,14]. The occurrence of infarction in all the age groups and the occurrence of seizures as a symptom of CVST were the two main factors associated with adverse neurological outcomes. What is more, as mentioned before, seizures may not only be complications, but also one of the symptoms of CVST in children. In a 2020 study, twenty-four children were enrolled into a one year follow-up, assessing seizure recurrence, the use of antiepileptic medications, the diagnosis of epilepsy and the Engel score. On admission 37.5% of this group suffered from acute seizures, while after one year a quarter of the patients were diagnosed with epilepsy. Unfortunately, there are no clinical predicting factors, and thus further research is still needed to better understand and prevent serious neurological complications [24].

Cognitive impairment

Compared to the previously mentioned studies, in a study by De Schryver et al. [25], the percentage of children with neurological deficits and cognitive impairments after CVST appears to be much lower. In their study during a follow-up evaluation of 12 children, only one of them presented with mild impairment of skilled movements, while the rest of the patients had no neurological abnormalities. In most of the children cognitive development was assessed. The measured intelligence scores were average or above average. Mild cognitive problems were found in less than 20% of this group: difficulty with written language and diminished cognitive efficiency. The assessment of cognitive development was not possible in two children due to their young age and insufficient language skills. Similar results were observed in a study by Hetherington et al. [26] where the children achieved a mean intelligence score slightly below average (97.8 IQ).

Infants

Christensen et al. [14] collected medical records of 26 preterm infants, a group previously not included in any of the studies. The median gestational age was 34.9 and the median birth weight was 2400 g. 50% of the pre-term infants showed no neurological impairment during follow-up. Nonetheless, 25% of the children developed mild-moderate impairment and 25% severe impairment. According to the authors, the neurocognitive outcomes were not favorable, which may be related to brain parenchymal lesions in most of the patients. Furthermore, another recent study indicates that newborns not only need longer hospital stays but also have higher mortality rates compared to older children [3].

CONCLUSIONS

CVST presents a diagnostic challenge for many clinicians. Its diverse etiology and lack of specific symptoms, especially in younger patients, delays the diagnosis or even leaves the thrombus unrecognized. CVST is a severe diagnosis with a possibility of serious neurological complications or even death. Therefore, it is important to raise vigilance among healthcare professionals. On the other hand, the use of imaging techniques is usually sufficient to make a proper diagnosis. Although there are running discussions on the safety and dose of anticoagulation medicaments, it seems that this therapy enables physicians to achieve favorable outcomes. Unfortunately, taking the rarity of this condition into consideration, there is still not enough literature on this subject in the pediatric population. Further research is essential to asses all the aspects of the disease.

Author's contribution

Study design – A. Dąbrowska, J. Mastalerz, M. Szyszka
Data collection – A. Dąbrowska, J. Mastalerz, M. Szyszka
Manuscript preparation – A. Dąbrowska, J. Mastalerz, M. Szyszka
Literature research – A. Dąbrowska, J. Mastalerz, M. Szyszka
Final approval of the version to be published – A. Dąbrowska, J. Mastalerz, M. Szyszka

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PRACA ORYGINALNA
ORIGINAL PAPER

Mobile phone applications used to monitor age-related macular degeneration

Aplikacje na telefony komórkowe stosowane do monitorowania zwyrodnienia plamki żółtej związanego z wiekiem

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ABSTRACT

INTRODUCTION: Age-related macular degeneration (AMD) is a leading cause of vision loss among elderly individuals. The aim of the study was to analyze the practical value of available mobile applications used to monitor AMD.
MATERIAL AND METHODS: Between March 1–31, 2023, a quantitative and qualitative analysis of smartphone applications – available in Polish and English in the Google Play Store – was conducted using the keywords "age-related macular degeneration" and "AMD". The analysis included four qualitative criteria, scored on a scale of 0–2 points each: 1) disease monitoring capability, 2) user data protection, 3) availability of verbal instructions, and 4) application usability. Based on the total scores, the applications were classified into five quality levels: very high (8 pts), high (7 pts), medium (6 pts), below medium (5 pts), and low (≤ 4 pts). An ophthalmologist tested each app that met the inclusion criteria.
RESULTS: Of the 249 identified applications, only 14 met the inclusion criteria for analysis. Among these, two were classified as very high quality, three as high quality (none of which were in Polish), one as medium quality, and eight as low quality. Only two out of the 14 applications addressed AMD patients' needs, such as vision limitations and the use of verbal instructions.
CONCLUSIONS: The available applications in Polish offered no added value over the traditional paper-based Amsler test. For mobile applications to effectively aid in AMD monitoring, key aspects such as availability (preferably free) and quality, including data security, should be prioritized. Creating evaluation teams that include medical experts, IT specialists, and patient representatives would enhance the development and assessment of AMD-focused mobile applications.

KEYWORDS

age-related macular degeneration, AMD, mobile app, e-health in ophthalmology, mobile patient monitoring, mobile health, usability evaluation

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STRESZCZENIE

WPROWADZENIE: Zwyrodnienie plamki żółtej związane z wiekiem (*age-related macular degeneration* – AMD) jest główną przyczyną utraty wzroku u osób starszych. Celem badania była analiza praktycznej wartości dostępnych aplikacji mobilnych służących do monitorowania AMD.

MATERIAŁ I METODY: W okresie od 1 do 31 marca 2023 r. przeprowadzono analizę ilościową i jakościową aplikacji na smartfony – dostępnych w języku polskim i angielskim w sklepie Google Play – z użyciem słów kluczowych „zwyrodnienie plamki żółtej związane z wiekiem" i „AMD". Analiza obejmowała cztery kryteria jakościowe, oceniane w skali od 0 do 2 punktów każde: 1) możliwość monitorowania choroby, 2) ochrona danych użytkownika, 3) dostępność instrukcji ustnych oraz 4) użyteczność aplikacji. Na podstawie łącznej liczby punktów wyróżniono pięć poziomów jakości aplikacji: bardzo wysoki (8 pkt), wysoki (7 pkt), średni (6 pkt), poniżej średniego (5 pkt) oraz niski (≤ 4 pkt). Okulista przetestował każdą aplikację spełniającą kryteria włączenia.

WYNIKI: Spośród 249 zidentyfikowanych aplikacji tylko 14 spełniło kryteria włączenia do analizy. Spośród nich dwie scharakteryzowano jako bardzo wysokiej jakości, trzy jako wysokiej jakości (żadna z nich nie była w języku polskim), jedną jako średniej jakości i osiem jako niskiej jakości. Tylko dwie z 14 aplikacji odpowiadały potrzebom pacjentów z AMD, takim jak ograniczenia widzenia i stosowanie instrukcji ustnych.

WNIOSKI: Dostępne aplikacje w języku polskim nie oferowały żadnej wartości dodanej w porównaniu z tradycyjnym papierowym testem Amslera. Aby aplikacje mobilne skutecznie pomagały w monitorowaniu AMD, należy nadać priorytet kluczowym aspektom, takim jak dostępność (najlepiej bezpłatna) i jakość, w tym bezpieczeństwo danych. Utworzenie zespołów ewaluacyjnych, w których skład weszliby eksperci medyczni, specjaliści ds. IT i przedstawiciele pacjentów, usprawniłoby rozwój i ocenę aplikacji mobilnych ukierunkowanych na monitorowanie AMD.

SŁOWA KLUCZOWE

zwyrodnienie plamki związane z wiekiem, AMD, aplikacja mobilna, e-zdrowie w okulistyce, mobilne monitorowanie pacjenta, *mobile health*, ocena użyteczności

INTRODUCTION

Age-related macular degeneration (AMD) is an eye disease that is the leading cause of blindness in the industrialized world in people over 65 years of age [1]. Aging causes damage to the macula – the part of the eye that controls sharp, straight-ahead vision. AMD does not cause complete blindness but rather the loss of central vision [2]. In 2020, the number of people with AMD worldwide was 196 million [3]. Statistically, 80–85% of cases are limited to "dry" AMD with slower vision deprivation and statistically more preferable outcomes. The other 15–20% of patients are diagnosed with rapidly progressing neovascular, "wet" AMD, which is associated with the formation of choroidal neovascularization (CNV) and in a short time leads to factual blindness [4]. There are multiple variables, internal and external, that have been shown to increase the chance of AMD development. The risks non-modifiable for AMD include age over 60, Caucasian ethnicity [5], a family history of AMD, and the dysregulation of multiple genetic variants [6,7]. The modifiable factors that increase the risk of AMD are the presence of chronic diseases associated with oxidative stress such as atherosclerosis, and hyperlipidemia [8]. Smoking is the most consistently reported modifiable risk factor for AMD and is associated with a 2–4-fold increased risk for any form of AMD [9,10]. In turn, higher adherence to a Mediterranean diet was associated with a reduced risk of progression to advanced AMD [9,11,12]. In addition, studies have identified 39 proteins associated with visual function deprivation [13]. Gu et al. [14] suggest that defective systemic phagocytosis is associated with both intermediate and late stages of AMD, highlighting a potential role in the accumulation of cell debris that occurs early in the disease process. Another risk factor for AMD is drusen, which appears in the outer layers of the macula, i.e. the photoreceptor layer, the retinal pigment epithelium layer, and Bruch's membrane as extracellular deposits of lipids, proteins, and cellular debris. These sub-RPE deposits are seen with the progression of normal aging; however, depending on the size, number, location, and type of drusen involved, they can be associated with an increased risk of developing AMD [15].

Due to the possible asymptomatic course of AMD in its early, monocular stage, screening tests are essential for early diagnosis and adequate treatment. While no screening test can replace a visit to the ophthalmologist's office, there are simple methods to detect and monitor deformations in the macular structure. The most common is the Amsler grid. Straight lines appear to be curved and wavy in AMD patients and some other retinal pathologies [16]. Self-monitoring in AMD patients has involved the use of an Amsler chart (grid) since the late 1960s. The Amsler grid can evaluate the central 20° visual field when used at a 30 cm testing distance. The identification of subtle changes in visual function (such as distortion) may suggest AMD disease activity or recurrence [17,18]. The Amsler grid is the simplest form of a "remote/self-monitoring" test in chronic macular diseases available on smartphones. Some of these apps have the advantage of marking scotomas or distorted lines on the Amsler grid using the touch screen. Next, the images can be stored locally or

digitally transmitted to the ophthalmologist. This can be especially helpful in assessing changes over time [19]. Remote patient monitoring may help facilitate access to specialized care [20].

The benefits of telemedicine are promising in the case of ophthalmology, which is a specialization based on imaging diagnostics [21]. The popularization of ophthalmic programs is an opportunity for better access to screening tools at an appropriate frequency [22]. Nevertheless, a few barriers may occur in the use of teleophthalmology: concern regarding the accuracy, high cost of the initial investment, poor quality of images, and unavailability of trained staff [23,24,25].

The ever-growing variety of available applications for chronic disease management poses difficulties regarding the choice of the most useful app available for both the specialists and patients involved [26].

Usability is a prerequisite for the success of health and wellness mobile apps [27]. Further advances in digital technology is an opportunity to improve the management of AMD [17].

Although applications for the phone are widely available, there are no guidelines assessing the quality of the applications so that they can be used in the best possible way, are adapted directly to a given disease and are safe for the patient.

The aim of the study was to analyze the practical value of available mobile applications used to monitor AMD.

MATERIAL AND METHODS

This study conducted a quantitative and qualitative analysis of AMD mobile applications, those related to the diagnosis and monitoring of the eye disease – AMD. The qualitative criteria were selected based on literature analysis [26,27].

The Play Store and Google Play Store were searched between March 1–31, 2023 for AMD-related applications. Keywords such as "AMD", and "age-related macular degeneration" were used. An ophthalmologist tested each app that met the inclusion criteria.

The data collection included whether the application was available for free or not and in English/Polish language.

The exclusion criteria constituted games and apps on eye diseases unrelated to AMD, and applications in a language other than English or Polish.

The criteria for assessing the quality of the application were as follows: 1) disease monitoring (the ability to save the results) 0–2 pts; 2) protection of user data (password protection) 0–2 pts; 3) presence of oral instructions 0–2 pts; 4) usability 0–2 pts.

The following quality criteria were adopted according to the number of points obtained (range 0–8 pts):

- ≤ 4 pts (≤ 50%) – low quality
- 5 pts (62.5%) – quality below average
- 6 pts (75%) – average quality
- 7 pts (87.5%) – high quality
- 8 pts (100%) – very high quality.

The evaluation criteria for the example of AMD applications are shown in Figure 1.

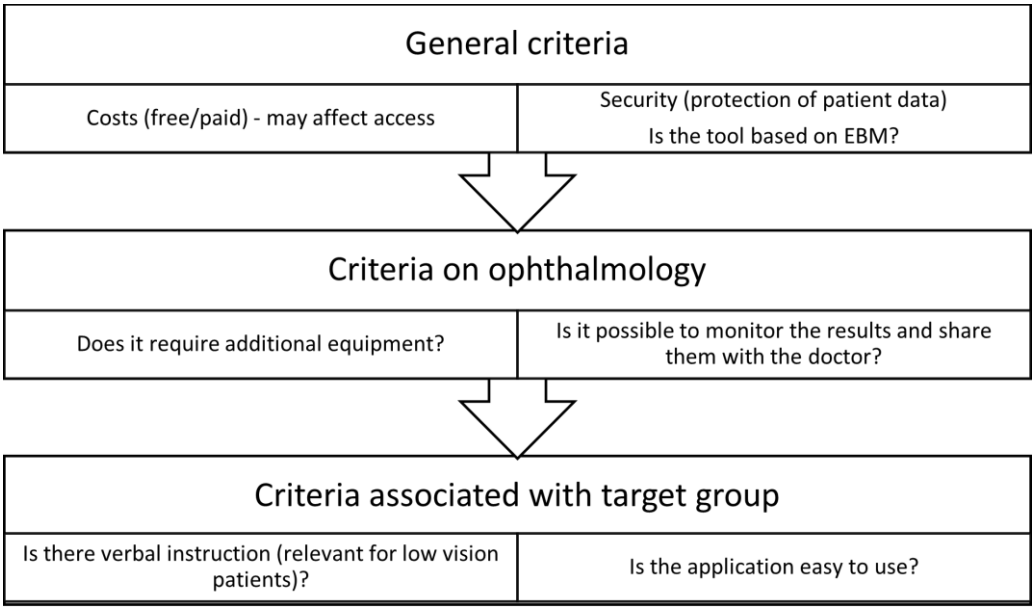

Fig. 1. Application evaluation criteria.

RESULTS

After the first search, 249 applications were found. After the rejection of non-AMD-related applications or in a language other than English or Polish, 48 applications concerning the AMD disease (Figure 2).

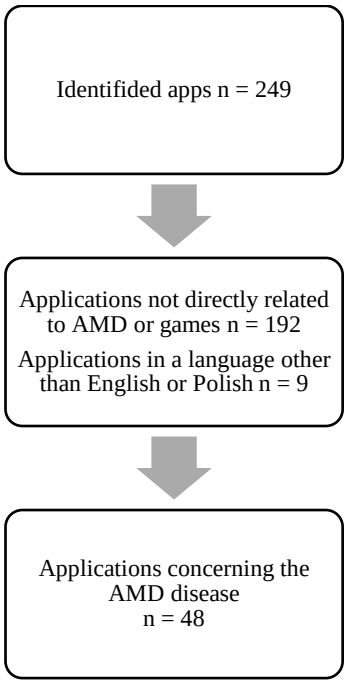

Fig. 2. Application collection process.

Distribution of applications – quantitative evaluation of the application

Out of the 48 applications concerning the AMD disease entity, 20 were related only to education about AMD, 7 applications related to nutrition and herbal medicine in AMD, and 6 applications in optical aid. Finally, applications whose purpose was the self-diagnosis and/or monitoring of AMD were included in the study. All the eligible apps were downloaded to test devices for final evaluation. 1 application was excluded from the study due to the inability to open it. 14 mobile applications were included in the final analysis.

Quality assessment of AMD diagnostic and/or monitoring applications

In this study, we observed that only 2 of the analyzed applications were classified as high-quality, and the majority scored 4 pts or less (57.14%; Table I).

Table I. Quality assessment of AMD diagnostic and/or monitoring applications (N = 14)

Number of points obtained	Number of applications N (%)
8 – very high quality	2 (14.29%)
7 – high quality	3 (21.42%)
6 – medium quality	1 (7.14%)
5 – quality below medium	0
≤ 4 – low quality	8 (57.14%)

AMD diagnostics and monitoring – applications available in Polish

In the analyzed period, only one application was available in Polish. It was an application available for free and had verbal instructions, however, it was not possible to mark the results on the Amsler grid nor to save them, and thus monitor changes in the disease progression.

DISCUSSION

After conducting a quantitative analysis, we showed that out of the 249 available mobile applications from the AMD area, only 14 were dedicated to AMD monitoring, of which only 1 was available in Polish.

When analyzing the available applications in terms of quality, only 2/14 applications took into account the needs of AMD patients, including vision limitations and the need to use verbal instructions. In addition, for applications to be effective tools supporting the treatment monitoring process, it is important to introduce a function that allows results to be saved, which requires the user to set up an account and raise the standards of protection of sensitive data. Therefore, traditional, paper measurement tools (Amsler test) have certain advantages over applications: a) they eliminate the risk of leakage of the patient's data, b) they are easily available in the ophthalmologist's office, c) they do not require a telephone or skills related to it, which is particularly important for this group of patients.

There is now a significant increase in digital health in ophthalmology. As Skrzypecki et al. [28] showed in a study analysis of the market for patient-oriented mobile applications in ophthalmology, the greatest number of applications was found for the subspecialization of macular degeneration (AMD). Lombardo et al. [29] stated that the benefits of prevention and early disease detection for prompt and effective treatment can be enormous to reduce the social and economic burden of AMD. Such activities

should require the identification of patients at a higher risk of disease progression and the development of novel diagnostic technologies.

In this study, most of the analyzed applications were free (85.50%). Both the financial costs and language barriers can significantly affect the accessibility of the application. Nonetheless, not only the availability but also the quality of the application is essential for the patient as apps of poor quality can be difficult to use or have low diagnostic value and will ultimately fail to accomplish their goals [30]. Therefore, it is essential to have a set of criteria that can be used by all stakeholders to guide the application development and quality assessment process [31]. Few available health applications have undergone a thorough validation process, which results in a lack of trust in the healthcare profession [32]. Byambasuren et al. [33] suggest that independent and trustworthy sources should evaluate mHealth applications and recommend a set of trustworthy applications for healthcare professionals to refer patients to. Choritz et al. [19] demonstrate in their research that there are currently not enough certified and validated digital health applications for purposes that are already clinically safe for use. One of the solutions to this problem may be prescription-only applications designed for the healthcare environment and home [34].

The first problem observed during the analysis of the available applications is the fact that most of them (80% N = 198) did not refer directly to the disease in question. The process of searching for the right application may demotivate patients from using this technology, especially since AMD concerns the elderly.

In this study, of the 14 assessed applications from the Self-diagnosis applications category, the majority were low-quality applications (57.14%). As in the Yu et al. [35] study, the utility of the ForeseeHome home monitoring of AMD was limited, with a high false-positive rate for detecting AMD. In contrast, the study by Schmid et al. [36] evaluated the Amsler test and showed that the dot alignment test is a reliable, intuitive, and freely available self-monitoring tool that allows patients to screen and monitor their macular function regularly at home using their smartphones or tablets.

Research on mobile applications in AMD disease is promising. Gross et al. [37] showed that patients capable of performing mobile hyperacuity home monitoring benefit in terms of visual acuity and discontinue treatment less often than patients not using home monitoring. Also, Islam et al. [38] compared the results of home monitoring for macular distortion using a smartphone app with a hospital visual acuity (VA) assessment and found that the smartphone-based self-tests for the macular disease could serve as reliable indicators of worsening of the disease. Chen and Adelman [39] evaluated the Hyperacuity App (HAC) as a disease progression screen tool in AMD and concluded that HAC has the potential for screening AMD. In turn, Schmid et al. [36] assessed the reliability and performance of the Food and Drug Administration (FDA) approved application for the self-detection of AMD.

As shown by a systematic review from 2021, the potential for the development of digital technologies not related to artificial intelligence is highly anticipated in ophthalmology. It is helpful to use the full potential of digital health technologies in ophthalmology to correctly identify real clinical problems and match current needs with appropriate innovation in the field of digital health [40].

This study also has its limitations – the analysis does not include applications available on the iPhone. In this study, we only analyzed applications in Polish and English, which is not an analysis of all the available applications in the case of AMD. Future research should consider evaluating the security of data storage in more detail, like profile personalization, and end-to-end data encryption if the results are stored externally, and to use the advantage of the knowledge and experience of IT specialists in app evaluation.

CONCLUSIONS

The optimal characteristics for the AMD screening mobile application were determined: 1) having verbal instruction as AMD patients have impaired visual acuity; 2) being available in the native language of a given country – for easier understanding; 3) free of charge – for availability; 4) with the possibility of saving the results, and thus monitoring changes in AMD progression.

Considering the fact that AMD disease mainly affects people over the age of 60, applications available in English may be an obstacle for Polish patients. The creation of a high-quality application in Polish could positively affect the diagnosis and monitoring of AMD among the Polish elderly population. Due to the large number of available applications, and the long process of finding an application that meets certain requirements, medical personnel should be able to recommend the best possible application customized to the patient's needs. This study shows how important it is to use application quality assessment in cooperation with specific specialists so that the created applications are as reliable and helpful as possible for both the patient and the assessment of the results received by means of the application.

Using the experience of other countries, it is worth introducing legal regulations in Poland regarding mobile applications, and then take action to inform

patients at the primary care level about reliable mobile applications, the use of which could bring tangible benefits.

Our research can facilitate the development of high-quality AMD applications necessary for the diagnosis and treatment process – helpful for doctors and patients.

Advantages and limitations

Due to the rapid development of mobile applications and the impossibility of using uniform criteria for evaluating mobile applications for all disease entities, this article presents specific criteria for evaluating applications only for AMD. A limitation of the study is that it included only apps available for smartphones and did not include apps available for iPhones.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author's contribution

Study design – A. Rogalska, E. Kurzak
Data collection – A. Rogalska, E. Kurzak
Data interpretation – E. Kurzak
Statistical analysis – Not applicable
Manuscript preparation – A. Rogalska, E. Kurzak
Literature research – A. Rogalska

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OPIS PRZYPADKU
CASE REPORT

From thread to yarn, and yarn to thread: a complex case of persistent left superior vena cava

Od nitki do kłębka, od kłębka do nitki: złożony przypadek przetrwałej lewej żyły głównej górnej

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ABSTRACT

INTRODUCTION: Persistent left superior vena cava (PLSVC) is a rare venous anomaly, occurring in 0.3–0.5% of the general population and up to 4.3% of patients with heart defects. It forms from the junction of the left subclavian and internal jugular veins, passes through the left mediastinum, and drains into the right atrium via the coronary sinus. Usually asymptomatic, it is typically discovered incidentally during imaging and may be associated with an atrial septal defect (ASD).

CASE REPORT: A 52-year-old female patient with persistent atrial fibrillation, a history of ischemic stroke in the left hemisphere of the brain, uncontrolled hypertension, and diagnosed with ASD type 2, was referred for pulmonary vein isolation (PVI) due to symptomatic arrhythmia of European Heart Rhythm Association class IIb and New York Heart Association class II severity. After unsuccessful PVI, pharmacological cardioversion was attempted, followed by electrical cardioversion, which temporarily restored sinus rhythm. Echocardiography revealed moderate tricuspid valve regurgitation and an enlarged coronary sinus. Cardiac computed tomography was ordered, revealing the presence of a PLSVC, into which the left superior pulmonary vein drains, with rightward displacement of the interatrial septum and a patent foramen ovale (PFO). After cardiac surgery consultation, the patient was qualified for defect correction.

CONCLUSIONS: PLSVC may be associated with congenital defects such as ASD type 2/PFO, which is relevant in the treatment of arrhythmias and defect correction. An enlarged coronary sinus on echocardiography should raise suspicion of PLSVC. The presence of PLSVC is significant when placing devices with central venous access.

KEYWORDS

persistent left superior vena cava, atrial septal defect, coronary sinus

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STRESZCZENIE

WPROWADZENIE: Przetrwała lewa żyła główna górna (*persistent left superior vena cava* – PLSVC) jest rzadką anomalią krążenia żylnego, wynikającą z nieprawidłowości w embriogenezie. Występuje u 0,3–0,5% ogólnej populacji oraz nawet u 4,3% pacjentów z wadami serca. Powstaje na skutek połączenia lewej żyły podobojczykowej i żyły szyjnej wewnętrznej, przechodzi przez lewą stronę śródpiersia i zazwyczaj uchodzi do prawego przedsionka przez zatokę wieńcową. Zwykle jest bezobjawowa i często wykrywana przypadkowo podczas badań obrazowych układu krążenia. Może współistnieć z ubytkiem przegrody międzyprzedsionkowej (*atrial septal defect* – ASD).
OPIS PRZYPADKU: 52-letnia pacjentka z utrwalonym migotaniem przedsionków, przebytym udarem niedokrwiennym lewej półkuli mózgu, niekontrolowanym nadciśnieniem tętniczym i rozpoznanym ASD typu 2 została skierowana na izolację żył płucnych (*pulmonary vein isolation* – PVI) z powodu objawowej arytmii o nasileniu IIb według European Heart Rhythm Association i klasy II według New York Heart Association. Po nieudanej PVI podjęto próbę kardiowersji farmakologicznej, a następnie elektrycznej, która jedynie tymczasowo przywróciła rytm zatokowy. Badanie echokardiograficzne wykazało umiarkowaną niedomykalność zastawki trójdzielnej i powiększoną zatokę wieńcową. Zlecono wykonanie tomografii komputerowej serca, ujawniając obecność PLSVC, do której uchodzi lewa żyła płucna górna, z przesunięciem przegrody międzyprzedsionkowej w prawo i drożnym otworem owalnym (*patent foramen ovale* – PFO). Po konsultacji kardiochirurgicznej pacjentka została zakwalifikowana do korekcji wady.
WNIOSKI: PLSVC może towarzyszyć wadom wrodzonym takim jak ASD typu 2/PFO, co ma znaczenie w leczeniu arytmii oraz korekcji wad. Powiększona zatoka wieńcowa w echokardiografii powinna budzić podejrzenie PLSVC. Obecność PLSVC jest istotna przy umieszczaniu urządzeń z centralnym dostępem żylnym, ponieważ może stanowić trudności.

SŁOWA KLUCZOWE

przetrwała lewa żyła główna górna, ubytek przegrody międzyprzedsionkowej, zatoka wieńcowa

INTRODUCTION

Persistent left superior vena cava (PLSVC) is a vascular anomaly in which the vein drains into the right atrium through the coronary sinus at the junction of the left internal jugular and subclavian veins due to abnormal development of the left cardinal vein [1]. It is present in about 0.3–0.5% of the general population and in about 4.3% of patients with heart defects. This congenital anomaly is usually asymptomatic and does not cause any physiological problems. However, it may become a significant problem in several clinical situations. Various complications related to PLSVC are encountered in anesthesia, renal, oncological and cardiovascular procedures. The presence of PLSVC is usually incidentally detected during the placement of a pacemaker (PM), an implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) leads [2].

CASE REPORT

A 52-year-old woman reported as planned at the end of June 2023 to the 1st Department of Cardiology at the Prof. Leszek Giec Upper Silesian Medical Center of the Medical University of Silesia to restore sinus rhythm by means of pulmonary vein isolation (PVI) ablation and to qualify for the closure of an atrial septal defect type 2 (ASD type 2). The patient was treated chronically for poorly tolerated, persistent atrial fibrillation (AF), treated with anticoagulation using rivaroxaban 1 × 20 mg, diagnosed with ASD type 2 after an ischemic stroke of the left hemisphere of the brain in March 2023, with unregulated arterial hypertension. Additionally, the patient suffers from hypothyroidism – post-strumectomy, depressive disorders and obesity (body mass index – 27.34).

The patient has a family history with cardiovascular disorders. In the clinical picture, the patient had been experiencing heart palpitations with a feeling of arrhythmia of European Heart Rhythm Association (EHRA) class IIb intensity for many years, with no typical symptoms of angina pectoris, reporting non-specific chest pain associated with arrhythmia unrelated to exercise. The patient was assessed as class II on the New York Heart Association (NYHA) scale, 4 points on the CHA2DS2-VASc scale corresponding to the risk of thromboembolic complications, and 2 points on the scale for assessing the risk of bleeding – HAS-BLED scale.

On admission, during the first hospitalization, the state of the patient's cardiovascular and respiratory systems was stable. The resting an electrocardiogram (ECG) showed AF with a ventricular rate of 100/min, and dyselectrolytemia was present in the laboratory tests. The patient underwent transthoracic echocardiography, which demonstrated asynchrony of interventricular septal contraction, normal left ventricular systolic function, left ventricular hypertrophy, severe tricuspid valve regurgitation, mild mitral valve regurgitation, moderate pulmonary valve regurgitation, and a dilated coronary sinus. Transesophageal echocardiography (TEE) confirmed a dilated coronary sinus measuring 32 × 19 mm (Figure 1, 2), an ASD with a permanent left-right shunt measuring 7 × 17 mm (Figure 3), severe/moderate tricuspid valve regurgitation (Figure 4), and mild mitral valve regurgitation.

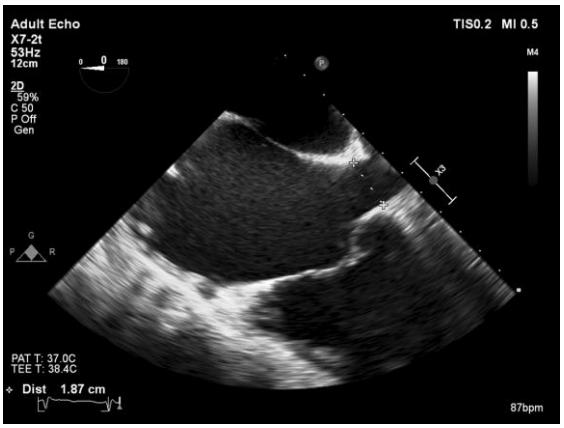

Fig. 1. Transesophageal echocardiography showing enlarged coronary sinus – 32 × 19 mm.

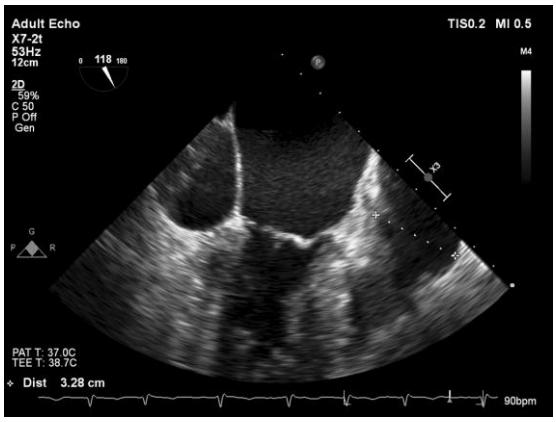

Fig. 2. Transesophageal echocardiography showing enlarged coronary sinus – 32 × 19 mm.

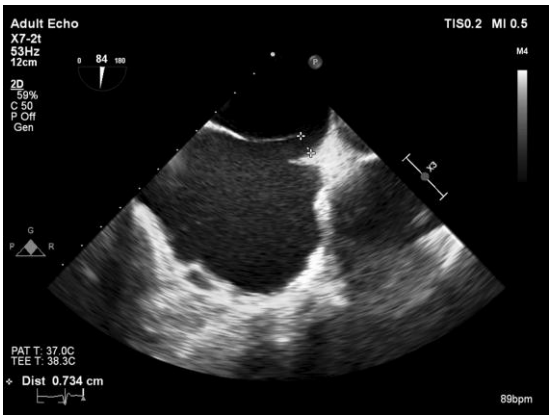

Fig. 3. Transesophageal echocardiography – visible patent foramen ovale canal – 7 mm.

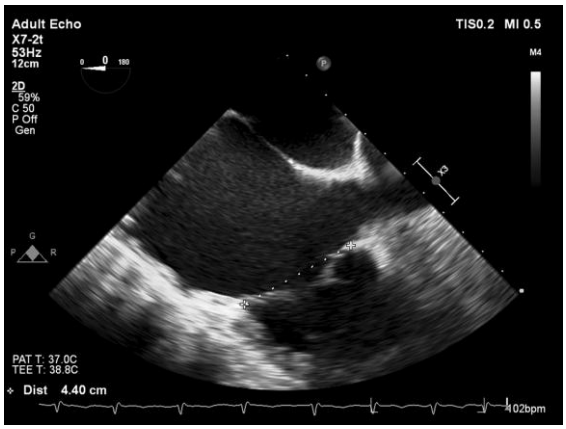

Fig. 4. Transesophageal echocardiography revealing tricuspid ring measuring 44 mm.

On the 27th of June 2023 the patient underwent a planned circumferential ablation of the pulmonary veins, achieving their electrical isolation. Using a transseptal approach, a mapping electrode (Lasso) and an ablation electrode (SmartTouch) were introduced into the left atrium. Mapping was performed using the CARTO 3 electroanatomical system. It showed the presence of the left common pulmonary vein. Then the procedure was extended to include an ablation line on the roof and posterior wall, creating BOX, and an oblique line on the anterior wall from the mitral annulus to the right pulmonary veins. During the procedure, pharmacological cardioversion was performed using 300 mg of antazoline and 600 mg of amiodarone, which was unsuccessful.

Subsequently, electrical cardioversion (CVE) was performed, successfully restoring sinus rhythm, but after 24 hours there was a recurrence of typical atrial flutter with a QRS rate of 65/min, which was well tolerated by the patient. Antiarrhythmic therapy with amiodarone was administered until the patient's admission to the hospital for the performance of CVE.

After the optimization of treatment and scheduling of the percutaneous closure of ASD type 2, the patient was discharged with recommendations. In October 2023, the patient underwent an outpatient CT scan of the heart, which revealed the presence of a congenital heart defect in the form of PLSVC, with draining of the left upper pulmonary vein, with a right shift of the interatrial septum and a visible, wide 1.9 × 0.4 cm, patent foramen ovale (PFO; Figure 5, 6).

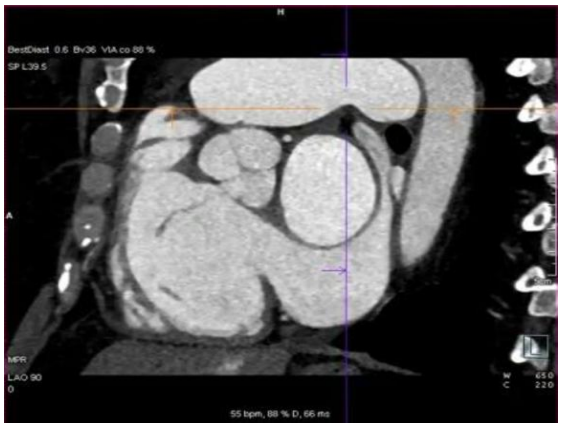

Fig. 5. Cardiac computed tomography showing congenital heart defect in form of PLSVC.

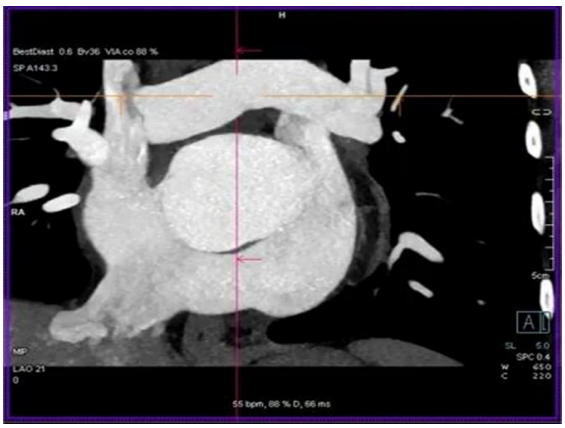

Fig. 6. Cardiac computed tomography showing congenital heart defect in form of PLSVC, into which left superior pulmonary vein drains, with rightward displacement of atrial septum.

During the second hospitalization in November 2023 for the purpose of undergoing CVE, the procedure was abandoned in favor of pharmacological cardioversion with restoration of sinus rhythm, which was performed without complications. After echocardiography, which showed no changes compared to the previous one, the patient underwent cardiac surgery consultation and was qualified for surgical correction of the congenital defect.

DISCUSSION

A comprehensive knowledge of the standard anatomical structures of the major vessels, especially in the thorax, is crucial for any clinician. PLSVC is the most common systemic venous anomaly in the thorax, with a reported prevalence of up to 0.5% in the general population and up to 10% in patients with congenital heart disease (CHD) [3]. It is worth noting that individuals with PLSVC typically do not show symptoms, and as many as 80% of those affected have normal vasculature on the right side [4]. Our patient's case, in which PLSVC was diagnosed at the age of 54, exemplifies such an incidental finding. In cases of PLSVC, commonly associated congenital cardiac disorders include an ASD, similar to the case of our patient, a ventricular septal defect sequenced with coarctation of the aorta, transposition of the great vessels, tetralogy of Fallot, and abnormal pulmonary vein connections [5].

Knowledge of embryology aids in understanding congenital malformations of the superior vena cava (SVC). In the 5th week of fetal life, three pairs of cardinal veins drain the embryo's body: the anterior cardinal veins drain the cephalic portion, and the posterior cardinal veins drain the caudal portion. Both empty into the short paired common cardinal veins, which eventually drain into the sinus venosus. The formation of the vena cava system is marked by the development of anastomoses between the left and right sides, redirecting blood from the left side to the right side. The development of the vena cava and associated veins involves the differentiation and regression of specific embryonic veins to form the mature structures found in the adult cardiovascular system. Specifically, the right anterior and common cardinal veins as well as the right horn of the sinus venosus form the right SVC and part of the azygos vein. On the left side, the anterior cardinal vein contributes to the left superior intercostal vein and the left brachiocephalic vein, while its regression forms the ligament of Marshall, and the left horn of the sinus venosus forms the coronary sinus [6]. The awareness of a PLSVC is crucial for patients undergoing invasive procedures such as CRT, PM implantation, or central venous catheterization as this anatomical variant can complicate these interventions [7]. Therefore, pre-procedural identification and understanding of PLSVC are essential for successfully planning and executing these invasive interventions, ensuring patient safety and optimal outcomes. The awareness of our patient's PLSVC would have enhanced the effectiveness of cardiac ablation by allowing tailored planning according to their unique anatomy. PLSVC diagnosis typically relies on contrast echocardiography, revealing coronary sinus dilation and opacification [8].

In summary, based on the gathered information and the case of our patient, it is essential to consider the diagnosis of PLSVC whenever symptoms such as a dilated coronary sinus or ASD type 2/PFO are present. Early identification of this anomaly allows effective treatment, improves the patient's quality of life, and prevents the late complications that may arise from a missed diagnosis.

CONCLUSIONS

Asymptomatic isolated PLSVC is a benign pathology but it can be associated with other heart defects. The

presence of an enlarged coronary sinus detected during echocardiography should always raise the suspicion of an additional anomaly, such as a PLSVC, as it may contribute to complications of electrophysiology procedures.

This anomaly is often accompanied by other congenital heart defects including a PFO or ASD type 2, which is significant for planning and conducting invasive treatments, which may require cardiac surgery, as in this case.

Authors' contribution

Study design – J. Dołęga, K. Krzywiecka, N. Lekston, K. Mizia-Stec
Manuscript preparation – J. Dołęga, A. Machnik, K. Krzywiecka, N. Lekston
Literature research – J. Dołęga, A. Machnik
Final approval of the version to be published – K. Mizia-Stec

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OPIS PRZYPADKU
CASE REPORT

Streptococcus pyogenes sepsis in 32-year-old man as rare complication of bacterial pharyngitis

Sepsa o etiologii *Streptococcus pyogenes* u 32-letniego mężczyzny jako rzadkie powikłanie bakteryjnego zapalenia gardła

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ABSTRACT

Group A beta-hemolytic streptococci (*Streptococcus pyogenes* – *S. pyogenes*) are the etiological factor of a wide range of infections, primarily pharyngitis, inflammation of the skin and subcutaneous tissue, as well as invasive infections. They can also lead to immunological complications, such as acute glomerulonephritis, rheumatic fever, and rheumatic heart disease. Although *S. pyogenes* may be the etiological factor for sepsis, sepsis of this etiology is rarely observed as a complication of upper respiratory tract infections in clinical practice. The aim of this paper is to present a case report of a 32-year-old man, previously untreated for chronic diseases, who was hospitalized for sepsis caused by *S. pyogenes*, which was a complication of an upper respiratory tract infection. As a result of targeted treatment with benzyl penicillin, significant improvement in the clinical condition of the patient and normalization of the inflammatory parameters were achieved. Due to a significant increase in the cardiac troponin serum concentration during hospitalization, the diagnostics were extended to include evaluation of the cardiovascular system.

KEYWORDS

sepsis, *Streptococcus pyogenes*, bacterial pharyngitis, troponin

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STRESZCZENIE

Paciorkowce beta-hemolizujące grupy A (*Streptococcus pyogenes* – *S. pyogenes*) są czynnikiem etiologicznym szerokiego spektrum zakażeń, przede wszystkim zapalenia gardła, zapalenia skóry i tkanki podskórnej, a także zakażeń inwazyjnych. Mogą również prowadzić do powikłań o charakterze immunologicznym, takich jak ostre kłębuszkowe zapalenia nerek, gorączka reumatyczna i reumatyczna choroba serca. Chociaż *S. pyogenes* może być czynnikiem etiologicznym sepsy, to w praktyce klinicznej rzadko obserwuje się posocznicę o takiej etiologii jako powikłanie infekcji górnych dróg oddechowych. Celem niniejszej publikacji jest przedstawienie opisu przypadku 32-letniego mężczyzny, nieleczonego wcześniej z powodu chorób przewlekłych, hospitalizowanego z powodu posocznicy wywołanej przez *S. pyogenes*, będącej powikłaniem infekcji górnych dróg oddechowych. W wyniku zastosowanego leczenia celowanego za pomocą penicyliny benzylowej uzyskano znaczącą poprawę stanu klinicznego chorego oraz normalizację parametrów zapalnych. Z uwagi na znamienny wzrost stężenia troponiny sercowej w surowicy w trakcie hospitalizacji diagnostykę poszerzono o ocenę układu sercowo-naczyniowego.

SŁOWA KLUCZOWE

sepsa, *Streptococcus pyogenes*, bakteryjne zapalenie gardła, troponina

INTRODUCTION

Sepsis is a medical condition that includes features of generalized infection, understood primarily as the presence of pathogenic microorganisms in the blood, and systemic inflammatory response syndrome [1]. Sepsis is not a homogeneous disease entity, but depending on the primary cause and source of infection in addition to the etiological factor, it may have a diverse course and clinical picture [2,3]. Due to the spreading resistance of bacteria to available antibiotics, the treatment of sepsis and other bacterial infections is becoming more problematic [4]. Sepsis and its treatment also pose a significant financial burden on the healthcare system. The quick and accurate diagnosis of sepsis is very important because it is crucial to start treatment early as untreated sepsis can quickly lead to the development of multi-organ failure and death [5].

In the case of patients hospitalized in internal medicine departments, sepsis often develops in the course of organ infections, such as pneumonia, urinary tract infections or gastrointestinal tract infections, especially in the case of people with numerous risk factors for the development of infection, i.e. elderly people with multi-morbidities, disabilities, and severe frailty syndrome [6]. In clinical practice, sepsis cases are less frequently observed in young people with no chronic diseases or disabilities. Moreover, sepsis as a complication of upper respiratory tract infections is rare.

The purpose of this paper is to present a case report of a 32-year-old man, previously untreated for chronic diseases, who was hospitalized because of sepsis caused by *Streptococcus pyogenes* (*S. pyogenes*), which was a complication of an upper respiratory tract infection.

CASE REPORT

Anamnesis and physical examination

A 32-year-old male patient was brought to the emergency room by the Emergency Medical Team. In the anamnesis, he complained of fever up to approximately 40.0 degrees Celsius, cough with sputum, pain in the paranasal sinuses area, and muscle pain. He also complained of discomfort when urinating. According to the patient, the symptoms had been present for approximately three days. Moreover, during the two weeks preceding admission to the hospital, the patient was treated for symptoms of upper respiratory tract infection with amoxicillin and clavulanic acid. However, the patient did not follow the doctor's recommendations, in particular the recommendation to rest and stay in bed for several days, and he took the prescribed medications irregularly. To that time, the patient had not had any chronic diseases and did not use any medications on a regular basis. He denied allergies, including to medications. He denied having undergone any surgical treatment. He denied smoking, but admitted that he drank beer every day.

At the time of admission to the Clinic, the patient was conscious and did not present any disturbances of consciousness. During auscultation of the lung fields, no obvious pathological changes were detected. The heart rate was regular with a frequency of approximately 120 beats per minute. The abdomen was soft and painless, without pathological resistance or peritoneal symptoms. There was no swelling in the lower limbs. No significant pathological changes were found in the skin. During the physical examination, an excessive accumulation of fat tissue, typical of obesity, was noted. Physical examination of the throat

revealed no mucosal redness or other abnormalities. There were, however, signs of caries.
The 12-lead electrocardiography (ECG) on admission revealed sinus tachycardia at the rate of 120 per minute, and the blood pressure was approximately 135/80 mmHg.
In the initial days of hospitalization, the patient also periodically reported abdominal pain, which responded well to treatment, but a repeated physical examination did not reveal any changes.

Laboratory tests

The laboratory tests revealed significantly increased values of inflammatory parameters. The concentration of C-reactive protein (CRP) in the blood was 179.66 mg/L, and the next day (i.e. after several hours) it was 439.11 mg/L, even though the patient received an antibiotic immediately after admission to the Clinic. In subsequent tests, the concentration of CRP systematically decreased. The concentration of procalcitonin was also significantly elevated upon admission to the hospital (12.46 ng/mL) with a systematic decrease during the course of treatment. Leucocytosis at admission was relatively low ($11.8 \times 10^3/\mu L$) but with a clear shift in the percentage towards neutrophils (90.3%). The fibrinogen level was also significantly elevated (> 9.0 g/L; the fibrinogen measurement was not repeated during hospitalization). The sedimentation rate of red blood cells was significantly accelerated (73 mm/h; the measurement was not repeated during hospitalization).
Immediately after admission of the patient to the Clinic, biological material was collected for microbiological tests (blood, sputum, and urine). The blood culture revealed group A beta-hemolytic Streptococcus (*Streptococcus pyogenes*) with good sensitivity to penicillin. Pathogenic microorganism growth was not detected in the sputum or urine cultures.
At admission, slightly elevated aspartate aminotransferase activity was found (52.6 U/L) with normal alanine aminotransferase activity (32.4 U/L). During hospitalization, a transient, non-significant increase in transaminase activity values was observed. Increased gamma-glutamyl transferase activity was also demonstrated (up to 206.0 U/L), with a tendency to normalize during hospitalization. The alkaline phosphatase activity was normal. The concentrations of bilirubin and total protein, as well as the values of prothrombin time and kaolin-cephalin time, were normal. Renal function evaluated by the serum creatinine concentration and estimated glomerular filtration rate (eGFR) was normal throughout the hospitalization period. During the initial period of hospitalization, slight hyponatremia (132 mmol/L) was observed, with subsequent normalization. Moreover, no significant disturbances in water-electrolyte and acid-base balance were observed.
In terms of the plasma lipid profile, there was a significantly reduced concentration of high-density lipoprotein cholesterol (16.9 mg/dL) and an increased concentration of triglycerides (221.0 mg/dL), with normal concentrations of the total cholesterol (111.0 mg/dL) and low-density lipoprotein (49.0 mg/dL). The fasting venous plasma glucose concentration was normal. The thyroid function parameters were normal.
During hospitalization, the HbS antigen in the blood and antibodies typical of human immunodeficiency virus infection were also determined (negative results). Serum protein electrophoresis was performed (without significant abnormalities).
During hospitalization, a significant increase in the cardiac troponin concentration in the blood was observed, followed by normalization (Figure 1).

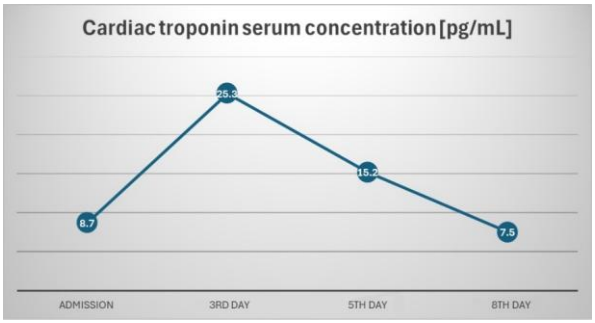

Fig. 1. Change in cardiac troponin serum concentration during hospitalization.

Anthropometric measurements

The basic anthropometric measurements showed features of central obesity (body mass index 33.1 kg/m^2, waist circumference 107 cm). Body composition analysis was performed using the bioelectrical impedance method and a TANITA MC-780 apparatus to supplement the basic anthropometric measurements. The percentage of fat was estimated at 27.9%.

Diagnostic imaging

A classic chest radiograph was performed, which described inflammatory-looking pericardial densities in the middle-lower field of the right lung (Figure 2). Due to the abdominal pain reported during the initial period of hospitalization, an abdominal radiograph was performed, which revealed no signs of intestinal obstruction or perforation of the gastrointestinal tract.

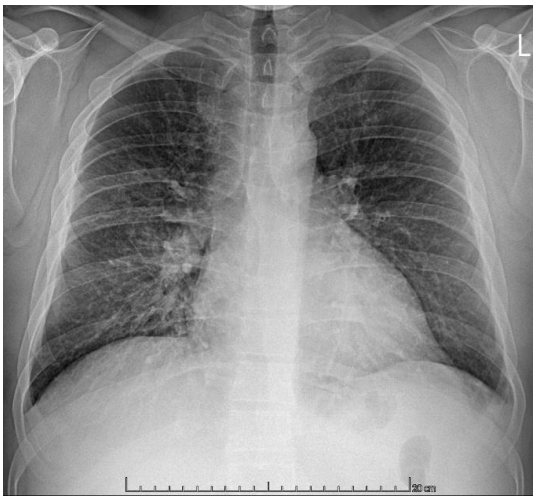

Fig. 2. Chest radiograph. Pericardial inflammatory masses were found in middle-lower field of right lung.

Owing to the reported pain in the area of the paranasal sinuses, the diagnostics were extended to include computed tomography, which showed post-inflammatory thickening of the mucosa (Figure 3A and 3B).

An abdominal ultrasound was performed, which revealed an enlarged liver with signs of steatosis and foci of hyposteatosis, without focal lesions. Apart from that, no abnormalities were found, but it should be emphasized that the imaging conditions were suboptimal (the abdominal aorta and pancreas could not be assessed).

Treatment

Immediately after the patient's admission to the Clinic, empirical antibiotic therapy with a third-generation cephalosporin (ceftriaxone) was initiated. Before antibiotic administration, blood and urine were collected for culture. After receiving the blood culture results (about 24 hours after admission to the Department), ceftriaxone was replaced with crystalline penicillin. During hospitalization, intravenous hydration with potassium supplementation, steroid therapy, mucolytic treatment, antithrombotic prophylaxis with low molecular weight heparin, as well as painkillers and antipyretics (metamizole and paracetamol) were also used.

During the therapy, significant improvement in the patient's clinical condition and a systematic decrease in the values of inflammatory parameters were observed. The full distribution of inflammatory parameter values is presented in Table I.

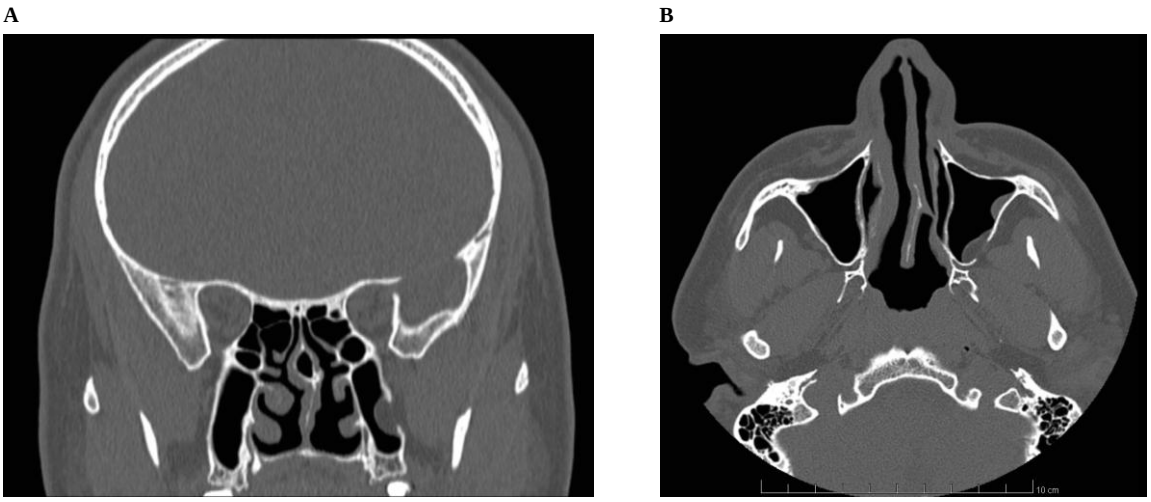

Fig. 3. Computed tomography image of paranasal sinuses (post-inflammatory changes).

Table I. Change in values of inflammatory parameters during hospitalization

Day number	Leucocytosis [×10³/μL]	Neutrophil percentage [%]	C-reactive protein [mg/L]	Procalcitonin [ng/mL]
Admission	11.8	90.3	179.66	12.46
1	12.0	90.5	439.11	not measured
3	8.3	71.6	150.76	4.31
5	8.8	60.1	45.47	1.27
8	7.4	48.3	11.13	not measured
14	6.6	48.8	2.98	0.06

During hospitalization, elevated blood pressure values were also observed, therefore arterial hypertension was diagnosed and treatment with perindopril and indapamide was initiated.
Due to the observed increase in liver enzyme activity, treatment with ursodeoxycholic acid was used.

Assessment of the cardiovascular system and metabolic status

After the patient's clinical condition stabilized during hospitalization, the cardiovascular system was also assessed owing to the diagnosed arterial hypertension and the above-described increase in serum cardiac troponin concentration. Moreover, because of obesity, diagnosed metabolic syndrome and metabolic fatty liver disease, body composition analysis was performed.
Transthoracic echocardiography showed only a trace of pathological fluid in the pericardium, as well as a borderline thickness of the left ventricular myocardium (11 mm in the interventricular septum and 10 mm in the inferolateral wall). No valve defects were detected. The size of the heart chambers and great arteries was assessed as normal, as was the systolic and diastolic function of the left ventricle and the systolic function of the right ventricle. During Holter ECG monitoring, only single supraventricular extra beats were detected. 24-hour monitoring of blood pressure showed elevated blood pressure values. Ultrasound of the carotid and vertebral arteries did not show atherosclerotic lesions, and the blood flow velocity and spectrum were normal. The value of the ankle-brachial index was normal both on the right and left side (1.1 and 1.05, respectively). The value of the carotid--femoral pulse wave velocity (Sphygmocor XCEL, AtCor Medical, Australia) was within the normal range, although it was quite high in relation to the age (7.7 m/s). The measurement of the central arterial pressure and pulse wave analysis parameters did not reveal any abnormalities.

DISCUSSION

Group A beta-hemolytic streptococci (*S. pyogenes*) remain a relatively rare etiological factor of sepsis among patients hospitalized in the internal medicine department. The patient described in this publication was a young, previously chronically untreated, obese man who abused alcohol and was diagnosed during hospitalization with metabolic syndrome, hypertension, dyslipidaemia, and metabolic fatty liver disease. In the two weeks preceding hospitalization, he was treated for a respiratory infection, but he did not fully comply with the medical recommendations. Upon admission to the hospital, he presented fever, cough, and muscle pain. As a result of the treatment, the patient's condition improved and he was discharged home on the sixteenth day of hospitalization.
Streptococcus pyogenes remains an important etiological factor of different diseases, among which the following should be emphasised: purulent tonsillitis, erysipelas, pharyngitis, and cellulitis; invasive infections (necrotizing fasciitis, bacteremia, and meningitis); toxin-mediated diseases such as scarlet fever and streptococcal toxic shock syndrome (STSS); as well as immune-mediated diseases such as acute glomerulonephritis, acute rheumatic fever, and rheumatic heart disease [7]. Among the virulence factors of *S. pyogenes*, the following seem to be significant: M protein [8], streptococcal cysteine protease (SpeB) [9], streptococcus C5a peptidase (SCPA) [10], streptolysin O [11], and *S. pyogenes* cell--envelope protease (SpyCEP) [12]. Bacterial protein R28 was shown to target the human CEACAM1 receptor, which is considered to play a role in the pathogenesis of puerperal sepsis caused by *S. pyogenes* [13].
In 2018, a case of an elderly woman with *S. pyogenes*--caused sepsis was described, presenting symptoms of septic shock and septic arthritis, whose illness ended in death despite penicillin treatment in combination with clindamycin [14]. In 2022, a team from the United States described the case of an 18-year-old girl who developed *S. pyogenes* sepsis during treatment for genital infection with herpes simplex virus type 2 (HSV-2) [15].
The basis for typing *S. pyogenes* is the presence of a specific isoform of the M protein. Currently, the gold standard remains typing based not on the serological method, but molecular typing based on the DNA sequence within the *emm* gene [16]. Individual serotypes differ in their tendency to cause specific diseases brought about by *S. pyogenes*. For example, *emm* types 1, 4, 12, 49, 55, 57, and 60 tend to cause acute glomerulonephritis, and *emm* type 28 tends to cause puerperal sepsis [17]. Unfortunately, in the case we described, no typing of the *S. pyogenes* strain was performed, which would undoubtedly have been a valuable addition to the collected information. Interestingly, according to recent research, the diversity of *S. pyogenes* strains varies in different countries around the world, showing a negative correlation with the degree of socioeconomic development of a given region of the world [18].
In the course of infections caused by *S. pyogenes*, heart damage may develop in the course of rheumatic fever. This is the result of the similarity of some structures within human tissues to the M protein, which is related to the possibility of antibodies generated during infection that react with the body's own tissues [17]. Resulting from the fact that in our case a significant increase in cardiac troponin concentration was found during hospitalisation, the diagnostics were extended to

include non-invasive assessment of the cardiovascular system, which revealed no significant abnormalities. Hence, it was concluded that the increase in the cardiac troponin concentration was the result of acute myocardial damage in the course of generalized infection [19].

It should be noted that infections caused by *S. pyogenes* remain a major public health problem. It is estimated that there are over 600 million cases of pharyngitis and over 100 million infections of the skin and subcutaneous tissue of this type in the world each year. It is also estimated that over half a million deaths worldwide each year are caused by the complications of infections caused by *S. pyogenes* [20]. Therefore, the development of effective methods of immunoprophylaxis against infections caused by *S. pyogenes* remains a very important challenge. Despite research conducted in this direction for many years, no vaccine is yet available, although many preparations with various mechanisms of action are in the research stage, primarily preclinical [7].

A significant limitation of the paper we have prepared is the lack of long-term follow-up of the patient after discharge from the Clinic. On the other hand, however, the strength of this paper is the careful clinical assessment of the patient, taking into account various aspects, including a detailed assessment of the cardiometabolic health using numerous additional tests. It is especially important because diabetes and its complications was discussed as significant for the clinical course of infection and the antimicrobial treatment [21].

CONCLUSIONS

Streptococcus pyogenes remains a significant etiologic factor for severe infections, also in young people. In the presented case report, the patient was diagnosed with several chronic diseases which are associated with an increased risk of infection. It is difficult to predict how important the impact of chronic diseases diagnosed in the clinical course of infection was, finally, complicated by sepsis.

Upper respiratory tract infection with features of bacterial aetiology should always be carefully assessed in each case with regard to the necessity of antibiotic treatment, but on the other hand, the unnecessary use of antibiotics should obviously be avoided.

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Authors' contribution

Study design – G.K. Jakubiak
Data collection – G.K. Jakubiak, P. Oleś
Manuscript preparation – G.K. Jakubiak, G. Cieślar, A. Stanek
Literature research – G.K. Jakubiak
Final approval of the version to be published – G.K. Jakubiak, P. Oleś, G. Cieślar, A. Stanek

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PRACA POGLĄDOWA
REVIEW

Long-term course of disease in 71-year-old patient with diagnosis of small cell lung cancer – case report and literature review

Wieloletni przebieg choroby u 71-letniego pacjenta z rozpoznaniem raka drobnokomórkowego płuca – opis przypadku i przegląd piśmiennictwa

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ABSTRACT

Small cell lung cancer is the most aggressive cancer that originates in the lung. Current treatment options are based on systemic treatment (chemotherapy, immunotherapy) and radiotherapy. Only in rare cases is it possible to perform surgical treatment. Despite its high sensitivity to chemotherapy and radiotherapy, only a small percentage of patients achieve long-term survival. The following case presents a patient after four lines of chemotherapeutic treatment and radiotherapy, which enabled 5-year disease control, along with an analysis of the available therapeutic options, their side effects and factors affecting the response to treatment.

KEYWORDS

small cell lung cancer, chemotherapy, radiotherapy, long-term survival

STRESZCZENIE

Rak drobnokomórkowy płuca jest najbardziej agresywnym nowotworem wywodzącym się z płuc. Obecne opcje leczenia opierają się na leczeniu systemowym (chemioterapia, immunoterapia) i radioterapii. Jedynie w rzadkich przypadkach możliwe jest wdrożenie leczenia chirurgicznego. Pomimo wysokiej wrażliwości na chemioterapię i radioterapię tylko niewielki odsetek pacjentów osiąga długoterminowe przeżycie. W pracy przedstawiono przypadek pacjenta po czterech liniach chemioterapii i radioterapii, które umożliwiły 5-letnią kontrolę choroby, wraz z analizą dostępnych opcji terapeutycznych, ich skutków ubocznych, a także czynników wpływających na odpowiedź na leczenie.

SŁOWA KLUCZOWE

rak drobnokomórkowy płuca, chemioterapia, radioterapia, przeżycie długoterminowe

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INTRODUCTION

Lung cancer remains one of the most frequently occurring cancers worldwide, ranking second in terms of incidence in both women and men, although first in terms of mortality [1]. The estimates are 2.2 million new cases and 1.79 million deaths per year due to lung cancer on a worldwide scale [2]. Histologically, lung cancer is divided into the non-small cell type (non--small cell lung cancer – NSCLC) and the small cell type (small cell lung cancer – SCLC). NSCLC is characterised by a higher incidence than other types of lung cancers and is categorised into several histological subtypes, of which adenocarcinoma is the most common, followed by squamous cell carcinoma and large cell carcinoma [3]. Nevertheless, SCLC, which represents approximately 10–15% of all lung cancers [4], is associated with a more aggressive course, a high growth rate, earlier metastasis and low survival rates.

SCLC is a cancer that correlates strongly with tobacco exposure [4], and to a lesser extent, radon exposure [5]. Patients with SCLC most commonly present with symptoms originating from the respiratory system such as cough, dyspnoea and haemoptysis, which may or may not be accompanied by systemic symptoms (e.g. weakness, weight loss) [6]. Of all the types of lung cancer, SCLC is the most frequently associated with paraneoplastic syndrome. Paraneoplastic syndrome represents a distant manifestation of malignant tumors that is not directly related to tumor invasion and metastasis [7].

Endocrine disorders (inadequate vasopressin secretion syndrome, ectopic Cushing's syndrome, acromegaly, malignant hypercalcaemia) and neurological disorders (the Lambert-Eaton syndrome, myasthenia gravis, limbic encephalitis, subacute sensory neuropathy), are most commonly reported in the course of SCLC. Of all those mentioned, the Lambert-Eaton syndrome and inadequate vasopressin secretion syndrome are the most frequent. The presence of paraneoplastic syndromes in undiagnosed patients enables early diagnosis and increases the chances of survival [8].

The estimated 5-year median survival rate in SCLC is 6.4% [9]. In assessing the stage of SCLC, a classification into limited (TNM I-III) and advanced (disseminated) stage disease (TNM IV) is used. Limited-stage SCLC (LS-SCLC) is characterised by the restriction of infiltrative lesions to one half of the thorax as determined by imaging, although it admits bilateral supraclavicular lymph node involvement and the possibility of treatment with a tolerable radiation field [9].

In more than two-thirds of patients, small cell carcinoma is detected at an extensive-stage (ES-SCLC) [4]. Thus, ES-SCLC is any case beyond the boundaries of the limited stage [9]. The most common sites of metastasis are the second lung, brain, liver, adrenal glands and bones [10]. In LS-SCLC, the basis of treatment is chemotherapy.

Radiotherapy and elective radiotherapy of the brain, and in a few limited cases, surgical intervention, are also used. In ES-SCLC, treatment consists primarily of chemotherapy, radiotherapy, and immunotherapy, which has been implemented in recent years [11] and has contributed to increased overall survival and progression-free time when combined with standard chemotherapy [12].

We present the case of a 71-year-old patient with LS-SCLC who achieved good disease control for 5 years after diagnosis with a 4th line of systemic treatment and radiotherapy.

CASE REPORT

A 66-year-old patient with a diagnosis of small cell carcinoma of the left lung was admitted to the pulmonology department in April 2019 to start systemic treatment. The infiltrative lesion was detected incidentally in February 2019 during a chest X-ray due to pneumonia. Subsequently, chest computed tomography (CT scan of the chest) confirmed the presence of a 35 × 44 × 24 mm tumor of the upper lobe of the left lung (Figure 1A), multiple fine nodule lesions (tree-in-bud-appearance) and infiltrative--atelectasis densities within the right lung, as well as fine nodule densities in the remaining lung parenchyma (Figure 1B). In the mediastinum, oval lymph nodes with a diameter of 11 mm in group IV R were visualised, otherwise not exceeding 10 mm in diameter in the short axis.

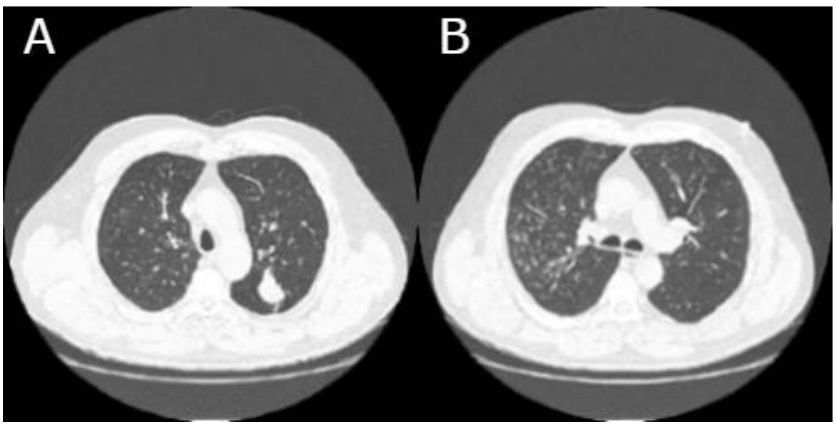

Fig. 1. Computed tomography of lung (02/2019): A – tumor of upper lobe of left lung measuring 35 × 44 × 24 mm; B – fine nodule lesions of budding tree type and infiltrative-atelectasis densities.

In the diagnostic pathway, bronchofiberoscopy was initially performed, in which no abnormalities were found. A precise histopathological diagnosis was made possible by fine-needle aspiration biopsy (FNA) under CT guidance in March 2019, in the department of thoracic surgery of the local hospital (Figure 2).

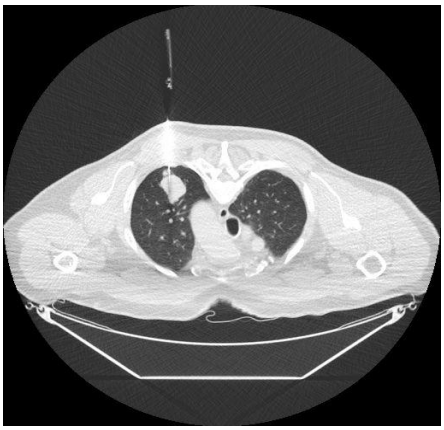

Fig. 2. Fine-needle aspiration biopsy under computed tomography guidance in prone position (03/2019).

The patient has a history of hypertension, ischaemic heart disease (post-PCI status), as well as post--cholecystectomy syndrome. The patient stopped smoking in February 2019. Prior to this, the patient smoked approximately 25 cigarettes per day for 30 years, which equates to 38 pack-years. A family history of cancer revealed a diagnosis of breast cancer in the patient's mother. The patient did not report symptoms originating from the respiratory system such as dyspnoea, haemoptysis or cough. The patient did not present with symptoms of paraneoplastic syndrome.

The Oncological Consilium decided to administer chemotherapy based on cisplatin and etoposide in four three-week cycles, which was started in April 2019. However, chemotherapy was complicated by neutropenia and anaemia, requiring a human granulocyte growth factor derivative. Consequently, from cycle 2 onwards, the treatment was modified by implementing carboplatin.

After completing chemotherapy, a follow-up CT scan of the chest was performed in August 2019. Compared to the scan performed 6 months earlier, it showed regression of the dimensions of the tumor structure to 13 × 21 mm in the upper lobe of the left lung. A fine nodular lesion and a band of atelectasis also appeared. There was also near-complete regression of the micronodular tree-in-bud type lesions and infiltrative--atelectasis lesions in the middle lobe of the right lung (Figure 3).

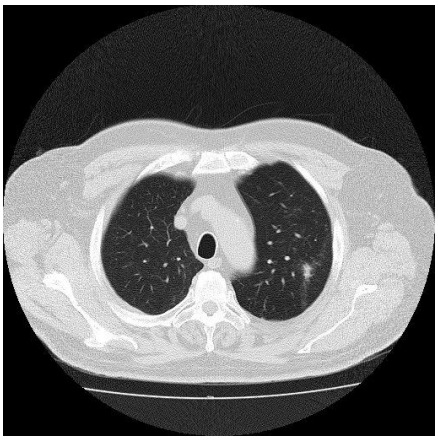

Fig. 3. Computed tomography scan of thorax (08/2019): regression in size of left upper lobe tumor to 13 × 21 mm, almost complete regression of tree-in-bud micronodular lesions and infiltrative-atelectasis lesions in middle lobe of right lung.

Subsequently, the patient was scheduled for radiotherapy of the thorax to the tumor area at a total dose of 56 Gy and radiotherapy to the hilar, mediastinal and supraclavicular nodes of the left side at a total dose of 40 Gy. Three weeks after the completion of thoracic radiotherapy, elective radiotherapy of the brain to a total dose of 30 Gy was performed.

As a radiological follow-up, a CT scan of the lumbar spine performed in February 2020 described a further reduction in the size of the nodular lesion (10 × 9 mm)

with a nodular band in the left peak and nodular lesions at the bronchovascular bundle in the posterior part of segment 1/2L, as well as regression of the nodular lesion in the anterior part of the upper lobe of the left lung.

Owing to the radiological progression found on the subsequent follow-up CT scan of the lung in May 2020, which described a small increase in the size (14 × 10 mm) of the infiltrative and banded atelectatic lesions in the top of the left lung (Figure 4), a second line of chemotherapeutic treatment based on etoposide in monotherapy (6 cycles) was administered, which was completed in September 2020.

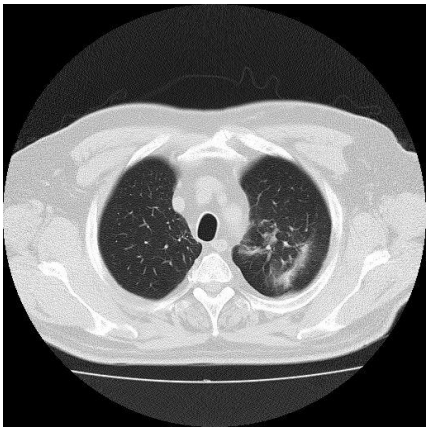

Fig. 4. Computed tomography scan of thorax (05/2020): enlargement of dimensions of infiltrative and banded atelectatic lesions in left lung apex.

As a result of the administered treatment, radiological regression was again achieved in the form of a reduction in the volume of the infiltrative-atelectatic lesions in the left lung apex. A CT scan of the lung performed in November 2021 revealed radiological progression of lung cancer. Among the atelectatic band-like lesions a nodular lesion measuring 24 × 20 mm was discovered in segment 1+2 of the upper lobe of the of the left lung, which was not present on previous CT scans (Figure 5). Consequently, repeat radiotherapy of the area of recurrence in the left lung at a total dose of 24 Gy was administered in December 2021. A follow-up CT scan after radiotherapy revealed a slight reduction in the size of the tumor, measuring 22 × 22 × 14 mm in segment 1+2 of the upper lobe of the left lung.

In November 2021, a CT scan of the lung revealed the presence of an enlarged nodular lesion (37 × 30 × 20 mm) in the upper lobe of the left lung (Figure 6), indicating the progression of the neoplastic process. In addition, a suspicious single nodular lesion on the tract of the left oblique interlobar fissure was described, which potentially corresponded to the intrapulmonary lymph nodes.

A CT scan of the head with contrast was also performed, which did not reveal the presence of metastatic foci. Due to the local recurrence of small cell carcinoma of the lung left lung, the patient was qualified for repeat radiotherapy of the left lung lesion at a total dose of 30 Gy with respiratory gating.

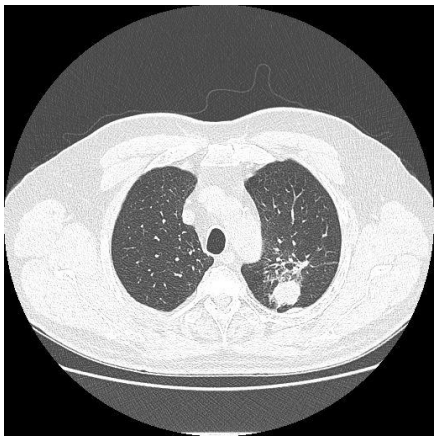

Fig. 5. Computed tomography scan of lung (11/2021) – new nodular lesion measuring 24 × 20 mm in segment 1+2 of upper lobe of left lung previously absent.

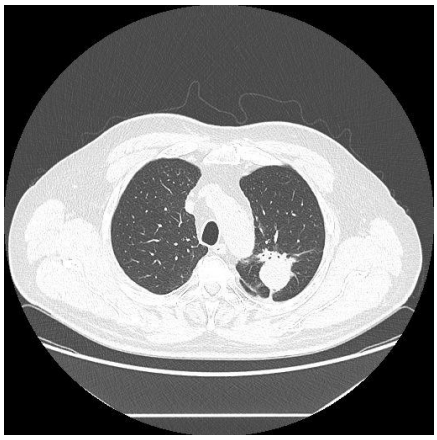

Fig. 6. Computed tomography scan of lung (11/2022) – re-enlargement of nodular lesion in upper lobe of left lung to 37 × 30 × 20 mm.

In April 2023, a follow-up CT scan of the lung once again revealed an enlargement (38 × 36 mm) and altered infiltrate morphology in the upper lobe of the left lung and significant progression of left hilar and mediastinal lymphadenopathy. As a result, 3rd line chemotherapy was immediately administered, comprising 6 cycles of carboplatin and etoposide. During the last cycle of chemotherapy, the dose of chemotherapeutics was modified because of severe anaemia. The applied treatment resulted in regression of the areas of ground glass around the tumor of the upper lobe of the left lung, with comparable dimensions of the tumor lesion. Regression of nodal lesions was also observed in the left hilar and mediastinum and along the left lung oblique fissure.

At the radiological follow-up in September 2023, the CT scan showed a stationary image of the tumor of the upper lobe of the lung left lung, a new nodular lesion in

segment 3 of the left lung and a fine nodular lesion 10 mm in diameter in segment 10 of the right lung (Figure 7). As a consequence of radiological progression, the decision was taken to qualify the patient for a 4th line chemotherapy scheme of topotecan in monotherapy (4 cycles). The treatment was complicated by anaemia and thrombocytopenia, requiring multiple transfusions of red blood cell (RBC) concentrates, the administration of steroid therapy and granulocyte colony-stimulating factors. At the end of the 3-month chemotherapy course, a head CT scan was performed, which described cortical-subcortical atrophy and retrograde vascular changes in the cerebral hemispheres, with no lesions suspected to be metastatic. A chest CT revealed a reduction in the diameter of the tumor of the upper lobe of the left lung, regression of the nodular lesions in segment 3 of the left lung and in segment 10 of the right lung. Progression of a predominantly budding tree type lesion at the base of the right lung was also described.

The patient's last hospitalization was in April 2024. A CT scan of the thorax was performed (Figure 8), which demonstrated marked progression of the left upper lobe tumor (to a dimension of 54 mm in the transverse plane) with infiltration of the vascular structures of the left hilum compared with the earlier study. A CT scan of the brain did not show foci with an image typical of metastasis. Resulting from the progression of the disease, the patient's history of treatment, and his general status (ECOG 3 – Eastern Cooperative Oncology Group performance scale), the patient was disqualified from continuing systemic treatment. The patient was discharged from the hospital in a stable condition and referred to the hospice for further symptomatic treatment.

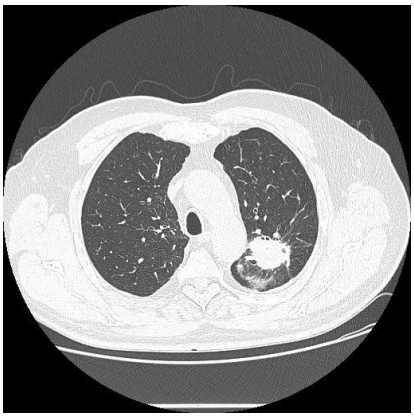

Fig. 7. Computed tomography scan of lung (09/2023): stationary left upper lobe tumor, appearance of new nodular lesions in segment 3 of left lung and fine nodular lesions in segment 10 of right lung.

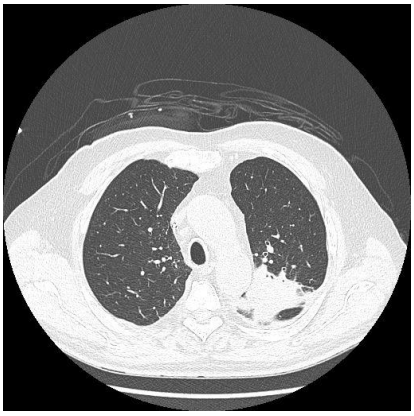

Fig. 8. Computed tomography scan of thorax (04/2024): progression of left upper lobe tumor to 54 mm in transverse plane, with infiltration of vascular structures of left lung hilum.

The exact clinical course of the disease is shown in Figure 9.

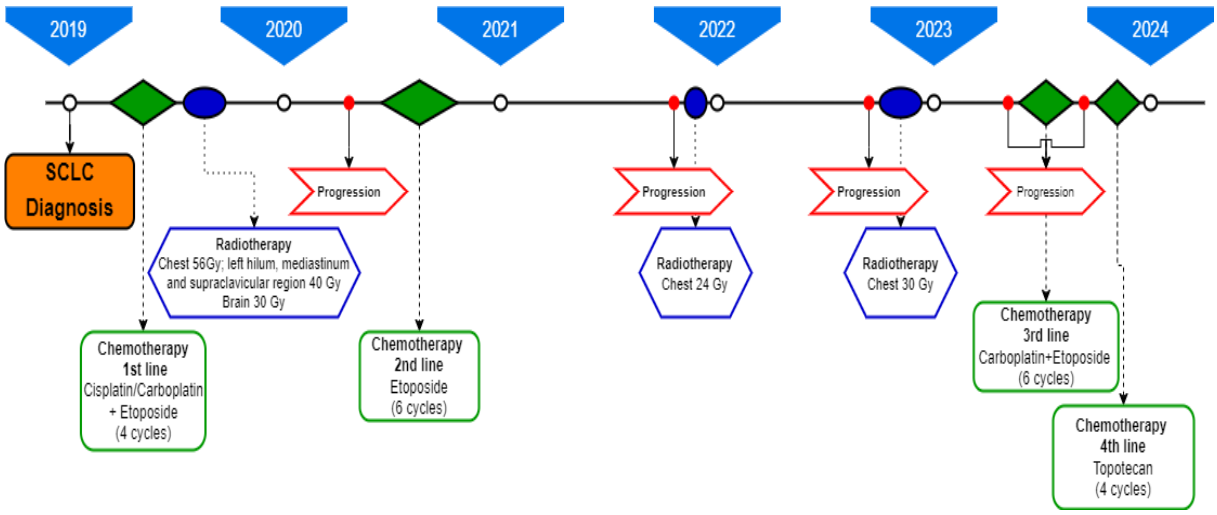

Fig. 9. Course of disease and treatment.

DISCUSSION

A comprehensive analysis of the SCLC genome has revealed a high degree of genetic instability, with a near-universal inactivation of the tumor suppressor genes *TP53* and *RB1*, as well as a high mutation burden [13]. The *TP53* gene is involved in a remarkable number of biological processes, such as DNA repair, cell cycle inhibition, apoptosis and autophagy [14]. In contrast, the *RB1* gene is primarily responsible for cell cycle blockade [15]. The fact that *TP53* and *RB1* are mutated in almost all SCLC cases may provide insight into the characteristics of this tumor that are commonly observed in clinical practice. The tumor lesion demonstrates both rapid and aggressive growth, while the initial response to chemotherapy and radiotherapy is notably favourable [16]. In consideration of the above, a diagnosis of SCLC is associated with an extremely poor prognosis. Furthermore, only in rare cases does systemic treatment enable long-term control of the disease. The presented case of a patient with SCLC remaining on treatment for 5 years is an extremely rare occurrence.

The long-term survival of a patient diagnosed with SCLC is defined as a period exceeding 24 months, in both the limited and disseminated stages [17]. The median overall survival of a patient with LS-SCLC is 17 months [18]. In the case presented above, the patient's 5-year survival is significantly beyond this limit.

As previously stated, surgical treatment of LS-SCLC is undertaken in a few cases. According to scientific societies, only 5% of patients qualify for radical treatment [19]. Due to the diagnosis and extent of the cancerous process, the patient was disqualified from surgery. Only a small group of patients with limited--stage SCLC are eligible for surgery. The primary treatment of SCLC is systemic chemotherapy, with platinum-based therapeutic agents (cisplatin, carboplatin) in combination with topoisomerase inhibitors (such as etoposide, topotecan, irinotecan) representing a crucial component. The combination of this treatment with or without other therapies, such as radiotherapy, has been demonstrated to be both effective and safe [13]. According to the guidelines, in the 1st line of treatment the patient received chemotherapy based on a platinum derivative and etoposide, supplemented with thoracic radiotherapy and elective radiation of the brain.

It is of significant importance to note that following the achievement of remission or stabilization, the patient is required to undergo periodic radiological follow-up. According to the recommendations of the National Comprehensive Cancer Network (NCCN), a follow-up CT scan every 2–6 months is recommended for cancer patients [20]. In the presented case, the patient therefore underwent a follow-up radiological examination at approximately three-month intervals.

Although SCLC is a highly chemotherapy-sensitive cancer, with an 80% response rate to chemotherapy, recurrence occurs within 6 months in the majority of patients [21]. In the case presented here, when disease progression was detected, systemic treatment was reintroduced with good results. The decision regarding the 2nd line chemotherapy and subsequent lines is determined by the response to previous treatment and the time over which progression occurred. In patients who have demonstrated sensitivity to platinum-based therapies and have had a treatment-free interval exceeding 3 months, it is possible to undertake a second round of platinum-based chemotherapy in combination with etoposide [22]. Therefore, the second line of treatment in the presented case was etoposide in monotherapy (6 cycles), followed by repeat radiotherapy to the tumor area. In addition, disease dissemination to the brain was excluded. In the third line of treatment, implemented after a further 5 months of prior therapy, 6 cycles of carboplatin and etoposide were administered, where the doses were reduced in the last cycle because of increased anaemia. After recurrent radiological progression, fourth-line treatment based on topotecan in monotherapy was implemented. Currently, topotecan is the only drug approved for the treatment of patients with SCLC who experience a relapse after treatment with prior agents [6]. In the reported case, complications after topotecan treatment in the form of anaemia and thrombocytopenia demanded the use of RBC transfusions, steroid therapy and epoetin alfa.

The case history allows longitudinal observation of the patient over time, with assessment of the effects of the treatment and the potential side effects of the therapy. Thus, the systemic treatment implemented in the patient was not without side effects. The treatment was modified (e.g. by implementing carboplatin in place of cisplatin) or the drug doses were reduced due to the observed haematological disorders (neutropenia and anaemia) [13]. The occurrence of adverse effects associated with chemotherapy is not uncommon. According to reports, chemotherapy used in SCLC is complicated by a range of side effects such as nausea and vomiting (65%), alopecia (25%), infection (36%), anaemia (37%), leukopenia (42%), thrombocytopenia (54%), and granulocytopenia (22%) [23]. The patient exhibited signs of hair loss throughout the course of chemotherapy in the described case, while the occurrence of myelotoxicity may be attributed to the administration of platinum derivatives [13]. In the case above, the patient tolerated the chemotherapeutic treatment well. Apart from haematological disorders, the chemotherapy did not significantly impact the patient's quality of life. Five years after treatment, the

patient remained in good health and was able to perform basic daily activities (ECOG 0).

Radiotherapy also plays a significant role in the treatment of SCLC. The evidence gathered in studies to date suggests that initiating radiotherapy at the earliest possible stage, preferably during the first or second cycle of chemotherapy, is optimal. Nevertheless, there is the possibility of sequential radiotherapy in frail or elderly patients [10]. In the discussed case, sequential radiotherapy of the thorax and elective radiotherapy of the brain were used. Elective brain radiotherapy in SCLC was demonstrated to reduce the incidence of brain metastases and improve overall survival in patients who respond to initial treatment [24].

Given the unfavourable prognosis, there is considerable anticipation surrounding the introduction of immunotherapy. From July 2021, patients with advanced SCLC in Poland, meeting the eligibility criteria for the program, have the opportunity to receive immunochemotherapy as 1st-line treatment. Atezolizumab is a fully humanised anti-PD-L1 monoclonal antibody that inhibits PD-L1 and B7-1 signaling, thereby restoring tumor-specific T1 lymphocyte immunity. In combination with carboplatin and etoposide, it has been approved for first-line treatment in ES-SCLC in the EU, USA, China, and other countries [25]. Studies have demonstrated improvement in overall survival with the combination of atezolizumab and chemotherapy. A 12-month and 18-month follow-up period revealed that 13% more patients were alive in the group treated with atezolizumab and chemotherapy than in the group receiving a placebo and chemotherapy [26]. The combination of atezolizumab and chemotherapy is associated with a higher incidence of adverse events due to chemotherapy itself (58–82% compared with 50–70% for chemotherapy alone) and additional adverse effects of an immunological origin (such as rash, hypothyroidism, hepatitis). Nonetheless, in the final conclusion, the clinical benefits outweighed the minimal increase in adverse effects, as these, especially those of immunological origin, were of low severity and manageable with appropriate treatment [27]. Due to the availability of the aforementioned programme only in 1st-line treatment, it was not possible to add immunotherapy to the treatment plan for the patient in the presented case after the diagnosis and initiation of treatment.

This raises the question of what determines the response to systemic treatment in SCLC patients. In other words, why will one patient respond to systemic treatment with long-term remission, while another will not have a positive response? The factors influencing the clinical course of SCLC include age, gender, and various laboratory tests, such as baseline lactate dehydrogenase (LDH), sodium, serum creatinine or a baseline neutrophil-to-lymphocyte ratio, as well as the patient's performance status [6]. Analysing sequentially, in LS-SCLC, age below 70 years, female sex and good patient status (ECOG 0–1) are associated with a better prognosis, and normal baseline LDH levels are associated with better organ function [28,29]. In contrast, baseline low sodium levels, high creatinine levels [30] and a high neutrophil--to-lymphocyte ratio (> 4.15) [31] are indicative of worse organ function in SCLC. The patient in the presented case, aged 66 at the time of diagnosis, exhibited normal levels of LDH (169 IU/L), sodium (141 mmol/l) and creatinine (78 μmol/l), along with a baseline neutrophil-to-lymphocyte ratio of 1.77. All the laboratory parameters and age, as well as the patient's performance status (at ECOG diagnosis 0), were favourable prognostic factors. Only male sex remained an unfavourable prognostic factor.

A further significant issue is the patient's body mass index (BMI) and weight loss over the course of the disease or treatment. A strong association has been demonstrated between BMI (> 28) and weight loss (< 5%) and overall survival in patients with lung cancer. However, this association is more pronounced in cases of advanced NSCLC than in those of SCLC [32]. In accordance with the aforementioned findings, weight loss is associated with reduced survival rates, whereas obesity is correlated with prolonged survival. In the case under discussion, the patient's BMI at the commencement of treatment was 31.9 kg/m^2, which may be regarded as a favourable prognostic factor. Furthermore, no significant weight loss was observed over the course of subsequent years.

Another negative prognostic factor in SCLC is cigarette smoking. A Chinese institution has reported that nicotinism is an unfavourable independent prognostic factor for overall survival and progression-free survival [33]. It is noteworthy that the patient had been a long--standing smoker and had quit a year before his cancer diagnosis. According to reports, the risk of lung cancer does not decrease until 10–15 years after smoking cessation [34].

The case presented above for the long-term treatment of SCLC is not isolated. Tartarone et al. [35] presented the case of a patient with LS-SCLC who was treated seven years after the diagnosis of SCLC. A similar case of 7-year survival in SCLC was described by Rafei et al. [36]. A Chinese institution documented a case of 9-year patient survival from the moment of SCLC diagnosis [37]. A case in which a patient was treated successfully with several cycles of chemotherapy for 36 months was described in ES-SCLC [38]. It is noteworthy that a similar case of 8-year survival in stage IV SCLC was described in a patient with a diagnosis dating back to 1987, which was long before the implementation of immunotherapy [39]. Long-term survival is also achievable in young patients, as documented in a 41-year-old female patient with

ES-SCLC treated for 6 years [40]. Of particular interest is the case of a 62-year-old man with a diagnosis of ES-SCLC with synchronous brain metastases, who received radiotherapy to the brain, chest and chemotherapy as part of his treatment plan. Subsequent to this, he was diagnosed with two intracranial recurrences 3.5 years and 6 years after his initial diagnosis. In both instances of recurrence, the patient underwent stereotactic radiotherapy and exhibited no physical decline. At the time of the case report, the patient was alive 6 years and 4 months from the moment of diagnosis and demonstrated functional independence throughout [41].

The above cases illustrate that patients of varying ages and clinical presentations may exhibit unexpectedly prolonged survival times. This discovery offers the tantalising prospect that in the future the survival of patients diagnosed with SCLC will become a matter of routine.

CONCLUSIONS

At this time, the long-term treatment of SCLC is an isolated phenomenon. Owing to the aggressive nature of the disease, metastases to distant organs are observed at an early stage. Although SCLC is a chemosensitive cancer, the responses are typically observed to be of a relatively short duration.

In the light of the aforementioned characteristics, the regular radiological follow-up of patients during the observation period and the implementation of systemic treatment or radiotherapy in the event of disease progression is crucial. Nevertheless, the observed isolated cases of long-term treatment of SCLC instill optimism that the disease will eventually become a chronic condition and that the implementation of appropriate therapy will enable progression-free time to be gained and overall survival to be prolonged for patients.

Authors' contribution

Study design – S. Kostorz-Nosal, P. Kalisz, B. Gałuszka, S. Skoczyński
Data collection – P. Kalisz, S. Kostorz-Nosal, I. Zielińska-Leś, D. Jastrzębski
Manuscript preparation – P. Kalisz, B. Gałuszka, S. Kostorz-Nosal, I. Zielińska-Leś
Literature research – P. Kalisz, D. Jastrzębski, D. Syguła, D. Ziora
Final approval of the version to be published – S. Skoczyński, D. Jastrzębski, D. Ziora, S. Kostorz-Nosal

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PRACA ORYGINALNA
ORIGINAL PAPER

Endothelial function/damage markers and NGAL – intraoperative assessment in blood specimens obtained from different sampling sites during open repair of abdominal aortic aneurysm

Śródoperacyjne stężenia wskaźników czynności/uszkodzenia śródbłonka oraz NGAL oznaczanych w próbkach krwi pochodzących z różnych źródeł naczyniowych w trakcie zabiegu naprawczego tętniaka aorty brzusznej metodą otwartą

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ABSTRACT

INTRODUCTION: The aim of the study was to investigate the dynamics of changes in the concentrations of neutrophil gelatinase-associated lipocalin (NGAL), an acute kidney injury biomarker, as well as endothelial function/damage markers including P-selectin, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and the von Willebrand factor (vWf) in blood specimens obtained from different sampling sites during open abdominal aortic aneurysm (AAA) repair.

MATERIAL AND METHODS: Thirty-three patients qualified for elective open repair (ORe) were enrolled in the study. All the mentioned parameters were determined in blood samples drawn from: 1) the cubital vein prior to surgery, and then intraoperatively, 2) the renal vein before aortic cross-clamping, 3) renal vein immediately before aortic cross-clamp removal, 4) cubital vein immediately before aortic cross-clamp removal, 5) inferior vena cava immediately before aortic cross-clamp removal, 6) renal vein at 5 minutes after aortic cross-clamp removal and 7) cubital vein at 5 minutes after aortic cross-clamp removal.

RESULTS: The P-selectin, ICAM-1 and VCAM-1 concentrations were found to have decreased in the cubital samples drawn immediately before aortic clamp removal and at 5 minutes after aortic clamp removal vs the pre-surgery cubital samples. Rapid changes during surgery were also found in the NGAL, vWf and VCAM-1 concentrations.

CONCLUSIONS: The obtained results seem to evidence the development of an inflammatory response while open AAA repair is still in progress.

KEYWORDS

abdominal aortic aneurysm, P-selectin, ICAM-1, VCAM-1, NGAL

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STRESZCZENIE

WPROWADZENIE: Celem pracy było zbadanie dynamiki zmian stężenia lipokainy związanej z żelatynazą neutrofilów (*neutrophil gelatinase-associated lipocalin* – NGAL), która jest wskaźnikiem ostrego uszkodzenia nerek, oraz wskaźników czynności/uszkodzenia śródbłonka: selektyny P, cząsteczki adhezji międzykomórkowej 1 (*intercellular adhesion molecule 1* – ICAM-1), cząstki adhezyjnej śródbłonka naczyniowego 1 (*vascular cell adhesion molecule 1* – VCAM-1) i czynnika von Willebranda (*von Willebrand factor* – vWf) w próbkach krwi pobieranych z różnych obszarów naczyniowych podczas elektywnej operacji naprawczej tętniaka aorty brzusznej (*abdominal aortic aneurysm* – AAA) metodą otwartą.

MATERIAŁ I METODY: Badanie objęło grupę 33 chorych zakwalifikowanych do planowego zabiegu metodą otwartą (*open repair* – ORe). Wszystkie wymienione parametry oznaczono w próbkach krwi pobranych: 1) przed zabiegiem z żyły łokciowej oraz w trakcie zabiegu; 2) z żyły nerkowej przed założeniem zacisku aorty; 3) z żyły nerkowej bezpośrednio przed zwolnieniem zacisku aorty; 4) z żyły łokciowej bezpośrednio przed zwolnieniem zacisku aorty; 5) z żyły głównej dolnej bezpośrednio przed zwolnieniem zacisku aorty; 6) z żyły nerkowej w 5 minucie po zwolnieniu zacisku aorty; 7) z żyły łokciowej w 5 minucie po zwolnieniu zacisku aorty.

WYNIKI: Stwierdzono zmniejszenie stężenia selektyny P, ICAM-1 i VCAM-1 w próbkach pobranych z żyły łokciowej bezpośrednio przed zdjęciem zacisku aorty oraz 5 minut po zdjęciu zacisku aorty w porównaniu z wartościami przed zabiegiem. Ponadto obserwowano nagłe zmiany stężenia NGAL, vWf i VCAM-1 podczas zabiegu.

WNIOSKI: Uzyskane wyniki wydają się przemawiać za rozwojem stanu zapalnego już w trakcie zabiegu operacyjnego AAA metodą otwartą.

SŁOWA KLUCZOWE

tętniak aorty brzusznej, selektyna P, ICAM-1, VCAM-1, NGAL

INTRODUCTION

An abdominal aortic aneurysm (AAA) is a major complication of atherosclerosis – a civilization disease. AAA is defined as an enlargement of the abdominal aorta such that its diameter exceeds 3 cm [1,2].

There are two primary methods of AAA management. The first consists in replacement of the diseased segment of the aorta with a vascular prosthesis accessing the aorta through a transperitoneal incision (open repair – ORe). The other is endovascular aneurysm repair (EVAR) with an endoluminal stent-graft [3]. Takagi et al. [4] analyzed the 5-year survival curves of EVAR and ORe. They concluded that up to 1.8 years, survival was better after EVAR. Afterwards, post-EVAR survival was worse compared to that observed for ORe. The meta-analysis of Powell et al. [5] also showed that although early mortality (0––6 months of the intervention) was lower in the EVAR groups, the survival curves of both management methods later converged, and beyond 3 years, aneurysm-related mortality was lower in the ORe patients. These results indicate that while ORe might be more traumatic and not as modern as EVAR, it still remains a valuable treatment option for AAA.

Renal injury is a serious complication of both ORe and EVAR and remains independently associated with mortality [6]. Neutrophil gelatinase-associated lipocalin (NGAL) has recently emerged as an early biomarker of acute kidney injury (AKI) as well as has been used to monitor AKI in pediatric and adult patients after cardiac surgery, critically ill patients in addition to those who had received iodinated contrast media [7,8,9,10,11,12]. It is believed inflammation plays a major role in AKI [13]. Inflammatory processes are also important in the pathophysiology of AAA [14] and can be induced by AAA repair itself [15]. Vascular endothelial cells (ECs) are both an active participant and "victim" of the inflammatory process [16,17]. ECs are important components of the renal histological structure. Inflammation is a common cause of AKI as well as EC injury. The markers used to determine endothelial function/damage are, among others, P-selectin [18], intercellular adhesion molecule 1 (ICAM-1) [19], vascular cell adhesion molecule 1 (VCAM-1) [20] and the von Willebrand factor (vWf) [21].

Little is known about the earliest stages of AKI and ORe-induced inflammatory responses. In particular, it seems important to determine the dynamics of changes in AKI biomarkers as well as the dynamics of inflammatory responses within vessels other than peripheral veins.

The aim of the study was to investigate changes in the concentrations of NGAL, an AKI biomarker, as well as endothelial function/damage markers including P-selectin, ICAM-1, VCAM-1 and vWf in blood specimens obtained from different sampling sites during open AAA repair. These changes reflect the earliest stages of kidney and endothelial injury.

MATERIAL AND METHODS

Basic information

This was a prospective, observational, non-randomized study.

Thirty-three patients diagnosed with AAA were admitted to the department of general and vascular

surgery for elective AAA repair. After being provided with pertinent information, all the patients gave informed consent to participate in the study, which was approved by the Bioethics Committee of the Medical University of Silesia (KNW/0022/KB1/130/I/09 and KNW/0022/KB1/130/IV/09/11).

Inclusion criteria

(1) The diagnosis of an infrarenal aortic aneurysm confirmed by ultrasound and CT angiography. (2) Age between 50 and 90 years. (3) Informed consent to participate in the study. (4) Eligibility for open AAA repair (ORe). (5) eGFR > 30 ml/min/1.73 m^2. (6) Discontinuation of nephrotoxic drugs (including metformin and nonsteroidal anti-inflammatory agents) 24 hours before the intervention.

Exclusion criteria

(1) Lack of informed consent. (2) Patients with one kidney. (3) > 60% reduction in the diameter of the renal artery. (4) Patients with a kidney transplant. (5) Hematuria defined as > 3 red blood cells and/or leukocyturia > 5 white blood cells per high powered field (400 × magnification; sediment obtained by centrifugation of a 10 ml fresh urine sample for 15 minutes). (6) Treatment with aminoglycoside antibiotics in the previous month. (7) History of treatment with cyclosporine A. (8) History of, or active neoplastic disease. (9) Surgical treatment in the previous month. (10) Recent stroke (in 2 months preceding the study). (11) Recent myocardial infarction (in 3 months preceding the study). (12) Clinically relevant disorders of the internal organs, metabolism, as well as blood, neurological or psychiatric disease. (13) History of AKI in 6 months preceding the study. (14) Acute inflammatory disease. (15) Urinary tract obstruction.

AAA diagnosis

An abdominal aortic aneurysm was diagnosed based on previously performed CT angiography.

Patient eligibility for ORe

The following patients were found eligible for ORe: (a) men with AAA diameter ≥ 55 mm, (b) women with AAA diameter ≥ 50 mm, (c) patients in whom the AAA diameter increased by 10 mm in the preceding 12 months, (d) patients with symptomatic AAA.

Course of ORe

Nephrotoxic drugs including metformin and nonsteroidal anti-inflammatory agents (except for antithrombotic prophylaxis with acetylsalicylic acid – AsA) were discontinued 24 hours before AAA repair. Diuretic therapy was continued if considered indispensable for blood pressure control. During 48 hours preceding the intervention the patients received adequate amounts of oral fluids while solid foods were eliminated. Six hours prior to anesthesia, the patients were instructed to abstain from fluid intake. Intravenous infusion was started before ORe (normal saline, multi-electrolyte concentrate, Ringer's solution) – on average 2500–3000 ml/procedure. All the patients received antithrombotic prophylaxis. If no contraindications were found, they were administered 75–150 mg AsA per day. The drug was discontinued on the day of the procedure, and if there was no bleeding, re-instituted 48 hours after the intervention.

The repair was performed under general anesthesia. The transperitoneal approach was adopted with subrenal aortic clamping. A Dallon Uni-Graft collagen--coated vascular prosthesis was implanted. During the operation all the patients were given 1250–2500 units of unfractionated heparin (the activated clotting time was not determined). The heparin infusions were continued for 24 hours after surgery in a dose calculated to maintain an APTT ratio greater than 1.5 times the baseline. On day 2, prophylactic enoxaparin (40 mg/day) was started and continued for 14 days. Prophylactic pantoprazole (20 mg twice daily) was started on the day of surgery.

Study protocol

A. Data collection: (1) age; (2) sex; (3) body weight and height – calculation of body mass index (BMI); (4) smoking history; (5) evaluation for concomitant disease (diabetes mellitus, ischemic heart disease, history of myocardial infarction, arterial hypertension, obliterating atherosclerosis of lower limb arteries, chronic kidney disease); (6) medication history.

B. Preliminary investigations: (1) ultrasound AAA measurement; aneurysm location in relation to the renal arteries; (2) echocardiography with determination of ejection fraction (EF); (3) renal ultrasound to obtain longitudinal (long axis) view and rule out urinary tract obstruction; (4) renal artery Doppler ultrasound.

C. Pre-surgery tests: (1) serum levels of total and high-density lipoprotein (HDL) cholesterol (the low-density lipoprotein (LDL) fraction was calculated), triglycerides, glucose, Na^+, K^+, creatinine, C-reactive protein (CRP); (2); HbA_{1C} test; (3) complete blood count; (4) serum NGAL, ICAM-1, VCAM-1, P-selectin and vWF level in plasma expressed as a percentage of the normal pooled plasma standard (NPP).

D. Intra-procedural determinations: (1) procedure duration, aortic cross-clamping time, moment of clamp removal; (2) volume of i.v. infusions administered during the surgical procedure; (3) number of units of packed red blood cells transfused during surgery; (4) intraoperative blood loss; (5) intraoperative blood pressure measurements – every 5 minutes; (6) blood sample collections for NGAL, ICAM-1, VCAM-1, P-selectin and vWf from: a) the (left) renal vein

immediately before aortic cross-clamping, b) renal vein immediately before aortic cross-clamp removal, c) peripheral vein immediately before aortic cross--clamp removal (upper limb), d) inferior vena cava immediately before aortic cross-clamp removal, e) renal vein at 5 minutes after aortic cross-clamp removal and f) peripheral vein at 5 minutes after aortic cross-clamp removal (upper limb).

Laboratory investigations

Blood samples were collected in Vacutainer plastic tubes (the blood vessels were selected according to the study protocol; upper limb – cubital vein). After clotting (or anticoagulant treatment with 3.2% sodium citrate), the blood was centrifuged for 15 minutes (3000 g, 4000 rpm). The obtained serum or plasma as well as urine samples were frozen and stored at -80°C until assay. NGAL, ICAM-1, VCAM-1, P-selectin concentrations and the vWf level were determined using an ELISA SIRIO-S microplate reader with an automatic plate washer.

The following laboratory kits were utilised according to the manufacturers' instructions: 1. NGAL: Human LIPOCALIN-2/NGAL ELISA Kit BioVendor – Laboratorni medicina a.s., Czech Republic; 2. ICAM-1: Quantikine Human sICAM-1/CD54 ELISA Kit, R&D Systems, Inc., Minneapolis, United States of America; 3. VCAM-1: Quantikine Human sVCAM-1 ELISA Kit, R&D Systems, Inc., Minneapolis, United States of America; 4. P-selectin: Human soluble P-Selectin/CD62P ELISA Kit, R&D Systems, Inc., Minneapolis, United States of America; 5. vWf: von Willebrand Factor Antigen ELISA Kit, Helena BioSciences Europe, Gateshead, United Kingdom.

We measured the serum concentrations of NGAL, P-selectin, ICAM-1 and VCAM-1, while the plasma vWF level was expressed as a percentage of NPP. The creatinine concentrations were determined by means of the colorimetric Jaffe method, the remaining parameters with routine tests used in our Department. eGFR was calculated with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) and, additionally, with the MDRD (Modification of Diet in Renal Disease Study) equations [22,23]. LDL was evaluated utilising the Friedewald formula [24] and BMI with the standard BMI calculator (weight [kg]/height^2 [m^2]. Systolic and diastolic pressure was quoted in mm Hg. The mean arterial blood pressure (MAP) was calculated as (systolic blood pressure + 2 × diastolic blood pressure)/3 [mm Hg].

Statistical analysis

MAP was calculated based on intraoperative measurements of the systolic and diastolic pressure. Wesselink et al. [25] used MAP = 60 mm Hg as a threshold between normal arterial pressure and arterial hypotension. The area under the curve (AUC) for this MAP threshold (expressed in mm Hg × min) represented the effect of MAP on the biological parameters. In our study the rectangle method was used to estimate the AUCs separately for MAP > 60 mm Hg and MAP < 60 mm Hg for all the patients. The whole-group sum total of AUCs separately for MAP > 60 mm Hg and for MAP < 60 mm Hg were calculated and compared.

Statistical analysis was carried out by means of Statistica v. 12 (StatSoft). Numerical data are presented as the mean (± SD) or median (with the maximum and minimum). The Shapiro-Wilk test was employed to test data distribution. If normal distribution was not confirmed, the Mann-Whitney U test and the Wilcoxon test were used for independent and dependent variables, respectively. When the data distribution was normal, independent and dependent t-tests were applied. The level of significance was set at $p < 0.05$.

RESULTS

Clinical and biochemical characteristics of patients (Table I)

Table I. Group characteristics (x ± SD or number: n)

Study population {including women} (n)	33 {2}
Age (years)	69.20 ± 7.98
BMI (kg/m^2)	26.50 ± 3.50
Kidney ultrasound	
Right kidney – long axis (mm)	97.55 ± 7.96
Left kidney – long axis (mm)	99.30 ^{ns} ± 7.81
Doppler ultrasound – renal arteries	
Peak systolic velocity: right kidney (cm/s)	61.27 ± 14.22
Peak systolic velocity: left kidney (cm/s)	60.85 ^{ns} ± 14.23
End diastolic velocity: right kidney (cm/s)	20.50 ± 6.73
End diastolic velocity : left kidney (cm/s)	21.23 ^{ns} ± 7.30
Echocardiography	
Posterior wall thickness (mm)	10.65 ± 2.37
Interventricular septal thickness (mm)	13.16 ± 3.95
EF (%)	57.05 ± 6.96
LV EDD (mm)	49.72 ± 4.69
LV ESD (mm)	33.26 ± 5.60
RV EDD (mm)	25.59 ± 5.42174
Dimension of aortic bulb (mm)	35.87 ± 7.28
Aortic aneurysm	
AAA neck length (mm)	25.80 ± 8.17
AAA neck diameter (mm)	24.22 ± 5.62
AAA diameter (mm)	57.72 ± 11.52
Laboratory tests – prior to surgery	
Total serum cholesterol (mg/dl)	200.00 ± 53.32
HDL (mg/dl)	39.26 ± 8.73

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LDL (mg/dl)	130.66 ± 48.81
Serum triglycerides (mg/dl)	156.97 ± 78.13
Blood glucose (mg/dl)	106.53 ± 52.36
HbA1c (%)	5.96 ± 0.70
Serum Na^+ (mmol/l)	139.85 ± 2.36
Serum K^+ (mmol/l)	4.25 ± 0.34
Hemoglobin concentration (g/dl)	14.60 ± 1.10
RBC (× 10^6/µl)	4.76 ± 0.37
Hematocrit (%)	43.20 ± 3.18
PLT (× 10^3/µl)	209.91 ± 61.60
PDW (fl)	13.64 ± 2.30
MPV (fl)	9.95 ± 1.36
CRP (mg/l)	19.17 ± 28.40
Estimated glomerular filtration rate – prior to surgery	
eGFR-CKD-EPI (ml/min/1.73 m^2)	74.21 ± 21.42
eGFR-MDRD (ml/min/1.73 m^2)	83.65 ± 32.80

ns – no statistically significant differences between long axes of left and right kidneys and Doppler ultrasound parameters measured in left and right renal arteries (independent variables); BMI – body mass index; EF – ejection fraction; LV EDD – left ventricular end diastolic diameter; LV ESD – left ventricular end systolic diameter; RV EDD – right ventricular end diastolic diameter; AAA – abdominal aortic aneurysm; HDL – high-density lipoproteins; LDL – low-density lipoproteins; HbA1c – glycated haemoglobin; RBC – red blood count; PLT – platelets; PDW – platelet distribution width; MPV – mean platelet volume; CRP – C-reactive protein.

The study group included 13 smokers. The numbers of participants suffering from concomitant diseases were as follows: diabetes – 4, ischemic heart disease – 15, arterial hypertension – 21, obliterating atherosclerosis of lower limb arteries – 19. The following medications had been used: statins – 12 patients, convertase inhibitors – 14, angiotensin receptor blockers – 3, nonsteroidal anti-inflammatory drugs – 6, β-blocker – 16, calcium channel blocker – 7, nitrates – 8 and diuretics – 5 patients. Twelve patients had symptomatic AAA; none had a dissecting aneurysm. CT angiography of the abdominal aorta was performed between days 204 and 2 before surgery (median 4 days).

Surgery data (Table II)

Table II. Surgery details (x ± SD or number: n)

Duration (min)	117.27 ± 33.05
Aortic cross-clamping time (min)	37.28 ± 15.33
Intraoperative blood loss (ml)	826.56 ± 627.59
Parenteral fluids (ml)	3493.75 ± 868.61
RBC units (n) {(ml)}	5 {1120; 560; 560; 560; 560}
Plasma units (n) {(ml)}	1 {1020}

n – number of patients who received RBC or plasma transfusion {RBC concentrate / plasma volumes (ml) in particular patients}; RBC – red blood count.

NGAL, endothelial function/damage markers and vWF in serum as well as plasma samples obtained from different sampling sites during ORe of AAA (Tables III–VII)

Table III. Neutrophil gelatinase-associated lipocalin concentrations in serum samples obtained from different sampling sites before and during open repair of abdominal aortic aneurysm (ng/ml, x ± SD)

		1	2	3	4	5	6	7
	C	**0 h**	**Pre-AC(-)-rv**	**Pre-CR(+)-rv**	**Pre-CR(+)-pv**	**Pre-CR(+)-ivc**	**Post-CR(-)-rv**	**Post-CR(-)-pv**
		60.47 ± 56.09	60.76 ± 49.34	58.29 ± 42.82	62.10 ± 51.41	68.72 ± 55.98	92.12 ± 77.96	67.50 ± 50.52
A	1 of 4	p = 0.635859						
	1 of 7	p = 0.16073						
	2 of 3		p = 0.859006					
	2 of 6		**p = 0.002773**					
	3 of 6			**p = 0.009329**				
	4 of 7				p = 0.264107			
B	1 of 2	p = 0.479059						
	1 of 3	p = 0.908112						
	1 of 6	p = 0.152739						
	1 of 5	p = 0.156454						
	5 of 2		p = 0.073397					
	5 of 3			p = 0.284241				
	5 of 6					p = 0.434043		
	5 of 4				p = 0.386682			
	5 of 7					p = 0.925926		

0 h: concentration before surgery in peripheral vein (1). **Pre-AC(-)-rv**: concentration in renal vein immediately before aortic clamping (AC) (2). **Pre-CR(+)-rv**: concentration in renal vein immediately before aortic cross-clamp removal (CR) (3). **Pre-CR(+)-pv**: concentration in peripheral vein immediately before aortic

cross-clamp removal (4). **Pre-CR(+)-ivc**: concentration in inferior vena cava immediately before aortic cross-clamp removal (5). **Post-CR(-)-rv**: concentration in renal vein at 5 minutes after aortic cross-clamp removal (6). **Post-CR(-)-pv**: concentration in peripheral vein at 5 minutes after aortic cross-clamp removal (7). **A**: Level of significance – difference between paired means (test for dependent variables). **B**: Level of significance – difference between paired means (test for independent variables). **C**: Pairs of means used in A or B determinations.

Table IV. P-selectin concentrations in serum samples obtained from different sampling sites before and during open repair of abdominal aortic aneurysm (ng/ml, x ± SD)

	C	1	2	3	4	5	6	7
		0 h	**Pre-AC(-)-rv**	**Pre-CR(+)-rv**	**Pre-CR(+)-pv**	**Pre-CR(+)-ivc**	**Post-CR(-)-rv**	**Post-CR(-)-pv**
		126.88 ± 41.94	123.92 ± 44.82	89.89 ± 39.10	79.19 ± 37.88	84.52 ± 43.18	91.44 ± 41.16	87.42 ± 41.88
A	1 of 4	**p = 0.000002**						
	1 of 7	**p = 0.000038**						
	2 of 3		**p = 0.000007**					
	2 of 6		**p = 0.000076**					
	3 of 6			p = 0.781818				
	4 of 7				p = 0.105871			
B	1 of 2	p = 0.984645						
	1 of 3	**p = 0.000343**						
	1 of 6	**p = 0.000794**						
	1 of 5	**p = 0.000121**						
	5 of 2		**p = 0.000286**					
	5 of 3			p = 0.352489				
	5 of 6				p = 0.386682			
	5 of 4				p = 0.797573			
	5 of 7					p = 0.78286		

Legend same as in Table III.

Table V. Intercellular adhesion molecule 1 concentrations in serum samples obtained from different sampling sites before and during open repair of abdominal aortic aneurysm (ng/ml, x ± SD)

	C	1	2	3	4	5	6	7
		0 h	**Pre-AC(-)-rv**	**Pre-CR(+)-rv**	**Pre-CR(+)-pv**	**Pre-CR(+)-ivc**	**Post-CR(-)-rv**	**Post-CR(-)-pv**
		237.25 ± 123.07	265.10 ± 141.60	207.36 ± 111.56	204.51 ± 129.86	195.03 ± 85.11	202.61 ± 103.86	185.69 ± 97.91
A	1 of 4	**p = 0.008402**						
	1 of 7	**p = 0.000095**						
	2 of 3		**p = 0.00005**					
	2 of 6		**p = 0.000136**					
	3 of 6			p = 0.714149				
	4 of 7				p = 0.14992			
B	1 of 2	p = 0.378383						
	1 of 3	p = 0.174						
	1 of 6	p = 0.123817						
	1 of 5	p = 0.147288						
	5 of 2		**p = 0.016388**					
	5 of 3			p = 0.892881				
	5 of 6					p = 0.933565		
	5 of 4				p = 0.594573			
	5 of 7					p = 0.680528		

Legend same as in Table III.

Table VI. Vascular cell adhesion molecule 1 concentrations in serum samples obtained from different sampling sites before and during open repair of abdominal aortic aneurysm (ng/ml, x ± SD)

	C	1	2	3	4	5	6	7
		0 h	**Pre-AC(-)-rv**	**Pre-CR(+)-rv**	**Pre-CR(+)-pv**	**Pre-CR(+)-ivc**	**Post-CR(-)-rv**	**Post-CR(-)-pv**
		402.94 ± 174.05	392.97 ± 180.36	377.35 ± 193.18	347.76 ± 185.07	325.75 ± 143.04	316.92 ± 167.36	307.96 ± 158.57
A	1 of 4	**p = 0.020675**						
	1 of 7	**p = 0.000757**						
	2 of 3		p = 0.287721					
	2 of 6		**p = 0.009329**					
	3 of 6			**p = 0.000545**				
	4 of 7				**p = 0.007558**			
B	1 of 2	p = 0.695689						
	1 of 3	p = 0.700435						
	1 of 6	**p = 0.041442**						
	1 of 5	p = 0.08571						
	5 of 2		p = 0.195228					
	5 of 3			p = 0.278513				
	5 of 6					p = 0.827417		
	5 of 4				p = 0.882752			
	5 of 7					p = 0.633855		

Legend same as in Table III.

Table VII. von Willebrand factor levels expressed as percentage of normal pooled plasma in samples obtained from different sampling sites before and during open repair of abdominal aortic aneurysm (%, x ± SD)

	C	1	2	3	4	5	6	7
		0 h	**pre-AC(-)-rv**	**pre-CR(+)-rv**	**pre-CR(+)-pv**	**pre-CR(+)-ivc**	**post-CR(-)-rv**	**post-CR(-)-pv**
		99.32 ± 52.53	135.24 ± 75.65	139.17 ± 72.10	110.90 ± 59.12	114.08 ± 57.52	124.80 ± 66.83	113.62 ± 58.56
A	1 of 4	p = 0.275741						
	1 of 7	p = 0.207785						
	2 of 3		p = 0.256541					
	2 of 6		p = 0.783815					
	3 of 6			**p = 0.025483**				
	4 of 7				p = 0.714149			
B	1 of 2	**p = 0.046836**						
	1 of 3	**p = 0.009061**						
	1 of 6	p = 0.083399						
	1 of 5	p = 0.133496						
	5 of 2		p = 0.426546					
	5 of 3			p = 0.154588				
	5 of 6					p = 0.555241		
	5 of 4				p = 0.662814			
	5 of 7					p = 0.377213		

Legend same as in Table III

Intraoperative hypotension

The whole-group AUC generated for MAP < 60 mm Hg amounted to 0.6% of the whole-group AUC for MAP > 60 mm Hg. We therefore assumed that the effect of hypotension on NGAL and endothelial function/damage markers was insignificant and no analysis was carried out.

DISCUSSION

We studied the serum (plasma) concentrations of endothelial function/damage markers and NGAL in blood specimens obtained from different sampling sites during open AAA repair. The material sampling is specified in the *Material and Methods Section*.

Since only one renal vein could be accessed during surgery, preliminary investigations had been performed to measure the long axis of the left and right kidneys and the basic parameters of renal arterial blood flow. As shown in Table II, no statistically significant differences were found between the long axes of the left and right kidneys and the Doppler ultrasound parameters measured in the left and right renal arteries. We therefore assumed that the left and right kidneys functions did not differ significantly, and hence the determinations carried out using blood specimens collected from the left renal vein would likely represent the status of both kidneys.

Serum NGAL in renal vein blood was found to have increased significantly at 5 min after aortic cross--clamp removal compared to the pre-clamping, and importantly, immediate pre-clamp-removal concentrations (Table III). This indicates a massive clamp-removal associated effect, resulting in a rapid, i.e. occurring within minutes, change in this lipocalin concentration in the renal vein. NGAL, determined in the serum and urine, has been used as a novel AKI biomarker [26,27]. It should be mentioned though, that upregulated NGAL expression has been found in injured epithelial cells of the kidney, liver and lung, and not only in AKI but also in other diseases [28,29,30]. Also, NGAL is an acute phase protein and can be produced by innate immune cells including neutrophils and macrophages [31,32]. Any of the above mechanisms might lead to high serum NGAL concentrations. Increases in urinary NGAL are primarily attributable to the local dysfunction of kidney tissue [33]. Hence, it seems that in AKI patients serum NGAL reflects a larger number of simultaneously occurring events compared to urinary NGAL levels, consequently, the latter might be more AKI-specific. As already mentioned, AKI is a systemic inflammatory response [13]. On the other hand, it has been shown that some inflammatory markers might act as non-classical indicators of AKI development [34]. All these data indicate a rather complex relationship between serum NGAL and the development of AKI, the severity of inflammatory processes and maybe also endothelial dysfunction, a key component of the inflammatory process [16,17].

P-selectin, one of the three known selectins, is secreted by platelets and ECs; its expression might increase following surgical trauma. P-selectin mediates leukocyte rolling on activated endothelium that occurs after the initiation of inflammatory responses [35,36].

The serum P-selectin concentrations in the pre-surgery cubital vein samples and those collected from the renal vein prior to aortic cross-clamping were almost identical (Table IV), while the subsequent determinations turned out to be significantly lower with no significant differences in-between. No significant effect of aortic cross-clamp removal was found. However, a 10% rise in serum P-selectin was seen in the cubital samples at 5 minutes after clamp removal compared to the pre-clamp-removal concentrations in the same vessel ($p = 0.105871$). A larger population might reveal statistical significance as well as some effect of aortic clamp removal on serum P-selectin. Further research is therefore fully warranted.

ICAM-1 and VCAM-1 are adhesive molecules of a similar structure that belong to the immunoglobulin superfamily. Following the P-selectin stage of an inflammatory response, they are both expressed on the EC surface and contribute to leukocyte adhesion and transendothelial migration through the endothelium [20,37,38].

The serum ICAM-1 levels in the pre-clamp-removal and post-clamp-removal cubital vein samples were significantly lower compared to the pre-surgery determinations (Table V). The pre-clamp-removal and post-clamp-removal renal vein concentrations were also lower than those revealed at the start of surgery. These results indicate a reduction in the ICAM-1 (and P-selectin) levels during surgery (Table IV).

The serum VCAM-1 levels in the pre-clamp-removal and post-clamp-removal cubital vein samples were significantly lower compared to the pre-surgery concentrations (Table VI). The post-clamp-removal renal vein concentrations were also significantly lower than those determined at the start of surgery. The pre--clamp-removal renal vein concentrations were lower compared to the pre-clamping levels but the difference did not reach the level of statistical significance. All these results evidence an intra-surgical decrease in serum P-selectin, ICAM-1, and VCAM-1 concentrations.

It should be emphasized that a rapid, i.e. occurring within minutes, decrease in serum VCAM-1 was found in the post-clamp-removal cubital and renal vein samples compared to the concentrations determined in both vessels immediately before clamp removal. This indicates a clamp-removal associated effect, which is opposite to that for NGAL.

vWf is synthesized in megakaryocytes and ECs, while pre-formed vWf is released by platelets [39,40]. This plasma protein participates in the development of the inflammatory process by supporting platelet aggregation and adhesion at sites of vascular injury [41]. It is believed vWf is the most important marker of endothelial damage [21].

No differences were found with respect to the vWf levels in the pre-clamping and pre-clamp-removal renal vein samples; nevertheless, the levels were significantly higher than the pre-surgery determinations in the cubital samples (Table VII). The post-clamp-removal vWf levels in the renal vein samples were significantly decreased compared to the pre-clamp-removal values. The cubital sample levels gradually increased but the rise did not reach the level of statistical significance. The difference in the vWf levels measured in the pre-surgery cubital vein and pre-clamping renal vein samples is worth noting. A hypothesis that, under physiological conditions, the renal vein vWf might be higher than in the cubital vein samples is quite unlikely. Experimental studies revealed that even a relatively slight injury to the vessel wall like catheterization might lead to vWf elevation [42]. The plasma vWf concentrations increased within minutes of a perturbation factor [43]. The increase in renal vein vWf observed in our study might have resulted from the surgery-related interventions performed to obtain access to this vessel. Nonetheless, if this was the case, the renal vein vWf levels should continue to increase; the cubital vein increases should be more dynamic as well. Neither of these were observed though. Gamulin et al. [44] and Colson et al. [45] found that infrarenal aortic cross-clamping produced profound impairment in renal hemodynamics. Hence, it might be hypothesized that vWf increases in the renal vein were a consequence of clamping-induced intrarenal endothelial injury. A decrease noted at 5 minutes after clamp removal would then reflect improvement in renal hemodynamics. Nevertheless, high pre-clamping vWf concentrations in the renal vein speak against this hypothesis. Further studies are needed to elucidate this issue.

Changes in NGAL, VCAM-1 and vWf are highly indicative of a clamp-removal associated effect consisting of a rapid (occurring within minutes) increase or decrease in parameter concentrations in the renal and/or cubital vein samples. It might also encompass the P-selectin levels. Following clamp removal, normal circulation is restored in tissues supplied by arteries located distally to the clamp site, and an ischemia-reperfusion injury might result. P-selectin, VCAM-1, their receptors [46,47], and probably also vWf [48], are ischemia-reperfusion injury suspected culprits.

As the average resting cardiac output is about 5 L/min (which is about equal to the total blood volume) [49], it was assumed that at 5 minutes after aortic clamp removal, blood from different areas (including ischemic lower limb regions) would have mixed. Consequently, a peripheral blood sample should be representative of the entire circulatory system.

During those five minutes, rapid molecular interactions (ligand-receptor) may occur between active substances that had originated in the ischemic areas leading to abrupt changes in the concentrations of various molecules. Theoretically, if the observed ligand is delivered in excess during reperfusion from the ischemic area then its concentration increases, whereas if the soluble form of its receptor is delivered, its concentration decreases. However, our results indicate that the causes underlying the above phenomenon may be much more complex. The post-clamp-removal associated effect in the case of VCAM-1 was observed in both the cubital and renal veins, which might be well explained by the sudden wash-out effect of the VCAM-1 and/or VCAM-1-binding molecules from the ischemic area. Nonetheless, the NGAL and vWf concentrations only increased in the renal vein, which is difficult to account for. Considering the short, i.e. 5-minute time span between the pre- and post-clamp removal blood sampling, aortic clamp removal and the associated lower limb reperfusion seems the only factor that might possibly trigger the above mentioned concentration changes. Again, this issue requires further investigations.

Another observation was the intraoperative decrease in P-selectin, ICAM-1 and VCAM-1. These molecules play an active role in the inflammatory process; soluble forms were determined in the samples [50,51]. The concentration decrease seems therefore to evidence continuous depletion of these molecules in circulation, thus confirming the dynamic development of an inflammatory response already during surgical intervention. The absence of comparable decreases in the vWf levels indicates some other course of vWf-mediated inflammatory processes.

The limitations of our study include the small number of participants. Failure to consider the post-clamp--removal blood sampling from the interior vena cava should also be mentioned as a shortcoming since such data might have allowed a more accurate interpretation of the rapid changes in the endothelial function/damage markers.

The novel contribution of this study is the determination of marker concentrations in blood samples obtained from different intraabdominal blood vessels during ORe of AAA.

CONCLUSIONS

1. The obtained results seem to evidence the development of the inflammatory response already during open AAA repair.
2. The rapid changes in the serum NGAL and VCAM-1 concentrations and vWf levels revealed in the course of open AAA repair indicate that these markers, expressed in the lower body as a result of aortic cross-clamping associated ischemia, massively enter systemic circulation following aortic clamp removal.

Authors' contribution

Study design – M. Kokot, J. Duława
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Data interpretation – M. Kokot, K. Ziaja, J. Duława
Statistical analysis – A. Kokot, M. Kokot
Manuscript preparation – M. Kokot, J. Duława
Literature research – M. Kokot, L. Kędzierski, A. Kokot
Final approval of the version to be published – M. Kokot, J. Duława

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PRACA POGLĄDOWA
REVIEW

Cross-linking – review of therapy options

Cross-linking – przegląd metod terapeutycznych

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ABSTRACT

INTRODUCTION: In recent years, keratoconus has become an increasingly prevalent eye disease, characterized by progressive thinning of the central or paracentral cornea. The primary treatment is corneal cross-linking (CXL), which offers a wide range of therapeutic techniques. The main aim of this review is to compile and present the most commonly used CXL treatment methods in a manner that will help clinicians create the most appropriate treatment plan based on each patient's unique needs.

REVIEW METHODS: This review is based on 42 articles meticulously selected through open-access sources, utilizing the PubMed and Google Scholar databases. The search encompassed therapeutic approaches to CXL for both adults and children. The literature review covers publications from 2003 to 2024.

STATE OF KNOWLEDGE: CXL is considered a primary therapeutic strategy for the management of keratoconus. Numerous studies suggest that this treatment modality exhibits superior efficacy in patients suffering from this condition.

CONCLUSIONS: This review evaluates various CXL. The transepithelial cross-linking (TE-CXL) approach retains the epithelial layer, which reduces postoperative complications and enables treatment for thinner corneas and advanced keratoconus. Although the aforementioned method is safer, less painful, and promotes faster recovery, its effectiveness may be compromised by inadequate riboflavin penetration. Conversely, epithelium-off (epi-off) CXL, especially the Dresden protocol, remains the gold standard, though it poses risks of complications such as pain. The study emphasizes the need to balance safety and efficacy when choosing CXL methods, while recognizing that all the methods are effective in managing keratoconus progression.

KEYWORDS

keratoconus, cross-linking, transepithelial cross-linking method, contact lens-assisted cross-linking, epithelium-off CXL, pediatric CXL

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STRESZCZENIE

WPROWADZENIE: W ostatnich latach stożek rogówki stał się często diagnozowanym schorzeniem okulistycznym, charakteryzującym się postępującym ścieńczeniem obszaru centralnego lub paracentralnego rogówki. Standardową metodą terapeutyczną jest cross-linking rogówki (CXL), który oferuje różnorodne techniki leczenia dostosowane do zaawansowania choroby. Celem niniejszego przeglądu jest zebranie i omówienie najczęściej stosowanych metod CXL w sposób, który ułatwi lekarzom dobór najbardziej odpowiedniego planu terapeutycznego, uwzględniającego indywidualne potrzeby pacjenta.
METODY PRZEGLĄDU: Niniejszy przegląd opiera się na 42 artykułach starannie wybranych z ogólnodostępnych źródeł, z wykorzystaniem baz danych PubMed i Google Scholar. Wyszukiwanie obejmowało postępowanie terapeutyczne w CXL zarówno u dorosłych, jak i u dzieci. Przegląd literatury obejmuje publikacje z lat 2003–2024.
STAN WIEDZY: CXL jest uważany za podstawową strategię terapeutyczną w leczeniu stożka rogówki. Liczne badania wskazują, że metoda ta jest bardzo skuteczna u pacjentów cierpiących na to schorzenie.
WNIOSKI: Przegląd ocenia różne metody CXL. W metodzie przeznabłonkowego CXL (*transepithelial cross-linking* – TE-CXL) zachowuje się warstwę nabłonka, co zmniejsza ryzyko powikłań pooperacyjnych i umożliwia leczenie cieńszych rogówek oraz zaawansowanego stożka rogówki. Chociaż wspomniana metoda jest bezpieczniejsza, mniej bolesna i sprzyja szybszemu powrotowi do zdrowia, jej skuteczność może być ograniczona przez niewystarczającą penetrację ryboflawiny. Z kolei CXL z usunięciem nabłonka (*epithelium-off* – epi-off), zwłaszcza protokół drezdeński, pozostaje złotym standardem, choć niesie za sobą ryzyko powikłań, takich jak ból. Praca podkreśla potrzebę równoważenia bezpieczeństwa i skuteczności przy wyborze metod CXL, przy jednoczesnym uznaniu, że wszystkie metody są skuteczne w hamowaniu postępu stożka rogówki.

SŁOWA KLUCZOWE

stożek rogówki, cross-linking, przeznabłonkowy cross-linking, cross-linking wspomagany soczewką kontaktową, CXL z usunięciem nabłonka, CXL w pediatrii

INTRODUCTION

Keratoconus is a progressive eye disorder where the cornea becomes thinner and bulges outward, forming a cone-like shape. This change leads to irregular astigmatism, reduced visual sharpness, swelling, and scarring, significantly affecting vision, especially in younger people. The condition often involves both eyes but can progress unevenly between them, typically beginning in adolescence and worsening over the next 15 years [1]. However, it can also start earlier in childhood or later in adulthood. Its prevalence is estimated to be about 1.38 per 1,000 people (95% confidence interval: 1.14–1.62 per 1,000), with a higher incidence among people aged 20 to 30 and those of Middle Eastern and Asian heritage [2].

As keratoconus progresses, patients often experience changes in their vision that necessitate a transition from glasses to rigid gas-permeable contact lenses. The precise cause of the condition remains unknown, although it is believed to be influenced by a combination of genetic factors, though no specific gene has been identified. Structural changes in the corneal stroma, including disruptions in the arrangement of collagen fibers, are frequently observed. Keratoconus is also commonly associated with conditions such as asthma, eczema, Down syndrome, and various connective tissue disorders. Additionally, frequent eye rubbing, often due to chronic allergies, can contribute to alterations in the corneal shape and pressure, leading to a reduction in corneal cells, known as keratocytes. While keratoconus is not classified as an inflammatory disease, recent research suggests that proteolytic enzymes, cytokines, and free radicals – specifically matrix metalloproteinase 9 (MMP-9), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α) – play a role in its development, even in the subclinical stages. This indicates that the condition may have certain inflammatory-like characteristics [1].

Histological studies reveal the key features of keratoconus, such as thinning of the corneal stroma, damage to the anterior limiting membrane, and localized bulging of the cornea. Early detection can be challenging, with corneal topography serving as a primary diagnostic tool, supplemented by measurements of corneal thickness and other advanced assessments to ensure a thorough evaluation. The severity and progression of keratoconus are categorized based on specific clinical signs, morphological characteristics, and standardized indices. The treatment options vary based on the stage of the condition. In the initial stages of keratoconus, glasses and contact lenses can help improve vision. Nevertheless, as the condition worsens, surgical interventions may become necessary. These procedures include penetrating keratoplasty, deep anterior lamellar keratoplasty, and the implantation of intracorneal ring segments [2].

In the last 25 years, corneal cross-linking (CXL) has been recognized as a non-invasive approach to treat keratoconus and has become integral to clinical practice. This method employs riboflavin-based solutions in combination with ultraviolet A (UVA) light. Riboflavin serves as a photosensitizer, facilitating

the creation of covalent bonds among collagen fibers when exposed to UVA radiation. This photochemical reaction enhances the cornea's stiffness, increases collagen fiber thickness, and improves resistance to enzymatic degradation, particularly in the anterior stroma. Since the late 1990s, various peer-reviewed studies have reported encouraging outcomes for CXL in the treatment of progressive keratoconus [1,2]. Findings suggest that CXL can boost corneal stiffness by more than 300%, increase the collagen fiber diameter by 12.2%, and promote the formation of cross-linked bonds within the collagen structure [1]. This procedure has shown success in slowing the progression of keratoconus with minimal risks and side effects.

The primary aim of this review is to examine the current knowledge on keratoconus treatments, focusing on the benefits and limitations of standard and surgical interventions. It also explores the roles of various treatment methods, outlining their advantages and potential challenges.

REVIEW METHODS

This review is grounded in a comprehensive analysis of 42 studies meticulously selected from open-access sources, utilizing the PubMed and Google Scholar databases. The search strategy focused on therapeutic approaches to CXL for both adults and children, ensuring a broad representation of the topic. The literature reviewed encompasses publications from 2003 to 2024, allowing in-depth exploration of advancements and trends in CXL treatments over two decades. Previously published articles were excluded unless they presented historical perspectives or important findings, owing to ongoing changes in treatment approaches.

STATE OF KNOWLEDGE

Transepithelial CXL method

The development of transepithelial cross-linking (TE-CXL) in 2004 was a response to the high incidence of postoperative complications caused by epithelial debridement, such as keratitis and abnormal wound healing. As a result, significant research efforts were made to create TE-CXL [3,4]. The primary difficulty associated with this method is the restricted ability of riboflavin to penetrate the lipophilic cornea and the tight junctions of the epithelium [5]. Fortunately, there are several techniques available to enhance the diffusion of riboflavin into the stroma. To increase its absorption, the preoperative application of drops containing preservatives such as benzalkonium chloride (BAC) and tetracaine can be used to break down tight junctions [6]. Alternatively, an epithelial trauma can be induced on the eye without completely detaching the epithelium [7]. Additionally, altering the physiochemical properties of the epithelium may increase its permeability, which can facilitate the creation of an epithelial flap or pocket [5].

In order to perform the classic TE-CXL procedure, a 0.1% riboflavin, 15% dextran solution is applied for corneal inhibition, which is further enhanced with tris-hydroxymethyl aminomethane and sodium EDTA. The aforementioned solution is applied every 5 minutes for a duration of 30 minutes, by administering 2 drops each time. One drop of 1% pilocarpine is applied 30 minutes before the start of surgery. 20 minutes before UV radiation, 4% lidocaine is administered onto the cornea. A blepharostat is used to increase the penetration of riboflavin. During the procedure, Ricolin TE is administered every 5 minutes and a slit-lamp examination is conducted in order to assess the presence of a proper amount of riboflavin in the corneal stroma. Following this, Vega, a UVA light source, is applied at the rate of 3 mW/cm^2 for a duration of 30 minutes. Upon completion, the eye is treated with ofloxacin antibiotic and an Acuvue bandage for 3 days [4].

Prior to and post-surgery, various tests should be performed, including uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), corneal topography, pachymetry, and in vivo confocal microscopy. Patients are monitored every three months during the first year after the procedure. Complications, such as corneal edema, stromal hyperdensity, hyperemia, and photophobia can be recorded [8].

In the clinical review written by Chan and Snibson [7] several studies were discussed. One of them was the study of Chan et al. [9], which utilized intracorneal ring segments with or without collagen cross-linking to treat keratoconus. The cornea was soaked in a riboflavin solution diluted with carboxymethylcellulose instead of dextran for five minutes, followed by 30 minutes of UVA. The findings revealed improvement in the manifest cylinder of the cross-linked group, the average K, and steepest K keratoconus measurements. Additionally, Baiocchi et al. [10] suggested that increasing the dose of UV energy may be necessary to achieve the same effect when the epithelium remains intact. Subasinghe et al. [11] mentioned that according to Bottós et al. [12], UVA transmittance is not the reason for the decreased stromal concentration by riboflavin. What is more, the presence of an intact epithelium may impede oxygen diffusion into the stroma, which could weaken the CXL effect [13]. Additionally, the duration of application and the concentration of riboflavin have a minimal effect on the diffusion of riboflavin into the stroma [11]. The Fard et al. [14] meta-analysis revealed that at the end of the follow-up period, there was no improvement in

the keratometry readings following TE-CXL. Nevertheless, paradoxically, there was an improvement in the average K and steep K.

In summary, it has been highlighted that TE-CXL is a safe and effective therapy, resulting in a reduction in corneal astigmatism, spherical equivalent (SE), and maximum keratometry (Kmax), as well as improvement in Snellen's visual acuity [15].

Epithelium-off CXL

The standard technique for CXL has emerged as the preferred treatment to impede or decelerate the advancement of corneal ectatic disorders, yielding favorable long-term results. Following the removal of the epithelium, it is recommended that the stromal thickness be a minimum of 400 μm [16]. This precaution is essential to safeguard the corneal endothelium and other intraocular tissues from irreversible adverse effects associated with UV irradiation, as substantiated by both experimental and clinical research [16]. There are two types of epithelium-off (epi-off) techniques: the Dresden protocol and the accelerated or modified protocols.

The Dresden protocol is also known as the conventional protocol for corneal collagen cross-linking (C-CXL). Subsequent prospective and retrospective studies have affirmed the effectiveness of C-CXL in arresting the progression of keratoconus. This technique involves removing the epithelium in the central 8–9 mm zone, followed by immersing the cornea in a 0.1% riboflavin solution for 30 minutes. Subsequently, the cornea is exposed to 370 nm UVA light (3 mW/cm^2 for 30 minutes), achieving a surface dose of 5.4 J/cm^2 [4,17]. There are various methods that can be employed to remove the corneal epithelium (alcohol, an Amoils brush, transepithelial phototherapeutic keratectomy (PTK), a hockey knife) [17]. The elimination of the hydrophobic corneal epithelium enhances riboflavin penetration into the stroma, facilitating effective UVA induced photochemical reactions and subsequent CXL. Studies on corneal biomechanics have demonstrated the stiffening effect of CXL on corneas. C-CXL has been found to enhance corneal curvature, reducing steepening and improving visual acuity [5,17]. Corneal thinning is observed up to 3 months post-surgery, gradually recovering by 1 year. Currently regarded as the standard for CXL, this procedure is commonly conducted in outpatient settings. Generally, CXL proves more effective in the early stages of keratoconus compared to advanced cases [17]. Additionally, innovative approaches like Epi-Flap CXL have also been introduced, showing associations with less postoperative pain and anterior stromal haze when compared to conventional epi-off CXL [17].

Accelerated or modified protocols: accelerated cross--linking (ACXL) protocols capitalize on the principles of the Bunson-Roscoe law [11]. In contrast, the conventional cross-linking (CCXL) protocol, also referred to as the Dresden protocol, employs a lower irradiation intensity of 3 mW/cm^2 and an irradiation time of 30 minutes [18]. Nevertheless, advanced settings with high-energy levels, reaching up to 43 mW/cm^2 [5], and in ex vivo studies even 45 mW/cm^2, have been developed [19]. This results in a reduction in the irradiation time to 2 and 1 minute, respectively, and a shortened soak time for the riboflavin solution [20]. Accelerated protocols present advantages such as a shorter treatment duration, reduced patient discomfort, a decreased risk of postoperative complications, infections, and enhanced cost-effectiveness; the clinical benefits are still under discussion in various studies [5,17]. It is shown that it is not only beneficial for adult patients but also for pediatric patients [17].

Epithelium on vs. off

One of the initial steps in the conventional Dresden protocol is the removal of the central 7 mm of epithelium of the cornea using a blunt knife [18]. This epithelial debridement, however, carries a risk of various short-term and long-term postoperative complications. Aside from transient, reversible side effects, there have been reported cases of complications such as corneal haze and scarring, reduced uncorrected and best spectacle-corrected visual acuity, infectious and non-infectious keratitis, stromal melting, and treatment failure leading to the progression of ectasia [21]. While CXL treatment has been utilized in infectious keratitis, it also leads to a variety of complications itself, including secondary keratitis. Numerous studies have reported these phenomena in patients with non-infectious corneal disorders [22,23]. Other microbiological causes of postoperative infections or ulcers may include *Streptococcus salivarius*, *Streptococcus oralis*, coagulase-negative *Staphylococcus* sp., *Staphylococcus epidermidis*, herpes simplex virus, and severe keratitis caused by *Pseudomonas aeruginosa* [24]. Nonetheless, severe complications after CXL treatment remain rare [25].

Postoperative pain is a common complaint associated with cross-linking procedures as the removal of the epithelium often causes significant discomfort during the procedure and in the days following, leading to a delay in returning to daily activities [19,21]. However, the risk of these aforementioned complications can be reduced by employing techniques that do not require removal of the epithelium, known as the "epithelium on" method.

Research has found that dextran-enriched riboflavin cannot penetrate the intact epithelium, prompting the development of various methods to enhance the penetration of riboflavin into the corneal stroma, such as adjunctives that weaken the epithelial tight junctions. These include a tetra-acetic acid (EDTA) enriched

riboflavin solution, which has not proven to be effective in the long-term, and benzalkonium chloride (BAC) [26].

In a study conducted by Rossi et al. [27], the efficacy of two treatments was evaluated in two groups: one treated with the standard epi-off CXL and the other with a transepithelial approach (epi-on). At the 12-month follow-up, the authors found no significant differences in the age and baseline pachymetric and keratometric parameters between the two groups, while uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) were higher in the epi-off CXL group. Both procedures were found to be efficient and useful in halting the progression of keratoconus, but a limitation of the study might have been the small group size of only 20 patients. Furthermore, the risk of infection and pain in the epi-on CXL group was significantly lower than in the epi-off CXL group.

A study by Badawi [28] demonstrated that the transepithelial approach (epi-on) led to a better and earlier recovery from corneal haze compared to the standard approach (epi-off). The reduced keratocyte damage in the transepithelial approach may explain the less pronounced post-CXL corneal haze. Another contributing factor is the riboflavin absorption behavior, which differs between the two approaches. The hypo-osmolar riboflavin used in transepithelial CXL has a shorter break-up time (90 s) and lower absorption efficiency compared to the isotonic riboflavin used in standard CXL (22 min).

In contrast, a study conducted by Razmjoo et al. [29] did not find significant differences in corneal haze between the two groups, where one group received conventional CXL with a fully removed epithelium and the other group received partial removal of the epithelium. Thus, neither approach was deemed more desirable for the reduction of corneal haziness. Nevertheless, the group treated with the partially removed epithelium showed better improvement in corrected vision, whereas the total epi-off technique resulted in better improvement of Kmax and the Q value.

Ouyang et al. [6] conducted a comparative study involving two groups, each consisting of 30 patients, who underwent ACXL treatment. One group underwent the conventional method with epithelial removal, while the other group underwent transepithelial CXL. At the baseline, both groups were comparable and did not exhibit significant differences in the keratometry values following treatment and during the 6-month follow-up period. However, the group that underwent epithelium removal (epi-off) demonstrated overall better corneal biomechanical strength compared to the transepithelial CXL group. This was indicated by higher values of A1L (the first applanation length), lower values of A1V (the first applanation velocity), and A2L (the second applanation length). Furthermore, differences in corneal endothelial function were observed, revealing that the effects of corneal edema and UV irradiation were more pronounced in the epi-off group. These findings, combined with the lower irradiation intensity in transepithelial CXL, suggest a greater level of safety for endothelial function, particularly for individuals with thin corneas and poor corneal endothelial function [4]. Other authors have also suggested the potential benefits of transepithelial CXL for patients with the aforementioned conditions [30], despite its relatively limited efficacy in halting the progression of keratoconus [31].

A recent meta-analysis conducted by Fard et al. [14] compared the outcomes of CXL and TE-CXL specifically in pediatric patients. The findings of the study suggested that the transepithelial approach was safe, but it exhibited lower efficacy compared to C-CXL. During the 12- to 24-month follow-up period for the transepithelial group, only the uncorrected distance visual acuity demonstrated significant improvement. On the other hand, the values of steep K and average K showed a non-significant trend towards worsening over the course of the follow-up period.

These findings corroborate the conclusions drawn in a previous meta-analysis conducted by Kobashi et al. [32], which discouraged the use of TE-CXL for the purpose of slowing down the progression of keratoconus in pediatric patients due to its insufficient efficacy. The parameters of Kmax (maximum keratometry) and visual acuity did not exhibit significant changes following CXL, regardless of whether the transepithelial or accelerated transepithelial approach was utilized. The observed disparity in the findings could potentially be attributed to variances in the biomechanical properties of the cornea among different age group.

Contact lens-assisted CXL

Chen et al. [33] referred to the study conducted by Jacob et al. [34] who introduced the contact lens--assisted CXL (CACXL) technique. When the intraoperative pachymetry is > 400 microns, UVA irradiance of 3.0 mW/cm^2 is applied for 30 minutes [33]. A solution of riboflavin in dextran T500 is reapplied every 3 minutes during UVA radiation [35] in order to maintain corneal saturation and to attain a uniform pre-corneal and pre-contact lens film [33]. Simultaneously, a disposable, daily contact lens of 0.9 mm in thickness, 14 mm in diameter and an 8.6 mm basal curvature is soaked in 0.1% iso-osmolar riboflavin in dextran for 30 minutes before being applied onto the de-epithelized, riboflavin-saturated cornea [35]. Upon completion of the procedure, a type of protective bandage contact lens is applied. Patients

are advised to use 0.5% moxifloxacin eye drops 4 times a day until the epithelium regenerates, followed by a gradual decrease in the dose of 1% fluorometholone drops over 2 weeks in addition to tear substitutes [35].
Amidst the 14 eyes being treated with CACXL, the doctors observed an increase in the minimum corneal thickness of 108 μm when taking into account the inclusion of the contact lens and riboflavin film [33]. After the follow-up period of 6.1 ± 0.3 months, the mean depth of the stromal demarcation line was measured at 252.9 μm. No endothelial loss or signs of postoperative endothelial damage were observed. Although no significant alterations were observed in the corrected visual acuity or the mean maximum keratometric value postoperatively, a reduction of 1 D in the maximum keratometric value was observed in 4 eyes (28.5%) [33].
The advantage of CACXL lies in its independence from the cornea's swelling characteristics, ensuring that edema does not impact the cornea, preventing issues like Descemet membrane [33] folds and potential endothelial damage. The contact lens soaked in riboflavin hinders oxygen diffusion, which has been proven to be vital in the CXL method and absorbs UVA radiation, resulting in a 40–50% decrease in the surface irradiance level [36].

Pediatric CXL

Keratoconus is a disease that rather manifests in the second decade of life. Nonetheless, there have been cases reported in young children (below the age of 18). The occurrence of the disease in childhood has been associated with unfavorable progression statistics [37,38], often leading to corneal transplant surgery [8]. It is vital to note that while data proves corneal transplantation as successful, CXL has provided an alternative treatment, aiming at delaying or preventing the need for transplant surgery [7]. Protocols other than ACXL are more effective than the accelerated one for corneal flattening, especially in advanced keratoconus cases, while a higher preoperative corneal curvature (Kmax) correlates positively with improved outcomes, emphasizing the heightened effect of CXL in more severe disease states [39]. A recent study by Khalil [40] on ACXL for pediatric keratoconus further confirms the potential of modified protocols in reducing the adverse effects while maintaining efficacy. Accelerated CXL showed significant improvement in visual acuity and the stabilization of keratoconus progression over a three-year period. It was associated with minimal adverse effects, such as transient haze in some cases, and no significant long-term changes in corneal thickness beyond the second postoperative year.
Studies comparing the efficacy and post-operative outcomes of the TE-CXL and epi-off CXL methods have been conducted. According to the study by Magli et al. [8], TE-CXL has demonstrated itself as a safer alternative to the epi-off method. Patients undergoing epi-off CXL exhibited transient corneal edema and experienced glare disability, which was effectively managed by applying topical steroids. Nevertheless, such inconveniences were absent in the TE-CXL patients, likely due to the reduced exposure of the corneal endothelium to UV damage subsequent to epithelium removal. Furthermore, the epi-off method resulted in higher pain levels, particularly in the initial three days post-procedure. It has been suggested that there is an inverse correlation between pain and the patient's age. Additionally, there is an inverse correlation between corneal sensitivity and age, possibly related to the reduced activity of nerves in the sensory periphery with aging, affecting the signal of transmission to the central nervous system. In summary, while the effectiveness of both methods is comparable, the side effects differ.
It is important to note that numerous studies tend to advocate the standard technique as the preferred method. Both the standard approach and ACXL exhibit significant efficacy, leading to notable improvements in patients' visual acuity, while the standard approach seems to provide greater changes in visual and pachymetric outcomes than accelerated transepithelial CXL [41]. They reveal consistent enhancements in eyesight, even though studies employing the accelerated method typically have shorter follow-up periods. The goal in current medical practice is to develop an optimal method that ensures the highest levels of safety and efficacy, yielding the best possible outcomes. As a result, there is no clear consensus on the most suitable technique, particularly for children [42]. Various factors, including the application of riboflavin or excessive UVA energy radiation, may significantly impact the surgical outcome [32,38].
A summary of the cross-linking methods discussed in the review is presented in Table I.

Table I. Summary of cross-linking methods

Transepithelial cross-linking	Method designed to preserve natural shape of cornea by avoiding removal of epithelial layer. This method not only leads to less painful recovery period for patients but also makes it possible to effectively treat thinner corneas and advanced keratoconus.
Epithelium-off cross-linking	Method involving removal of epithelium. There are two main types of epithelium-off techniques in corneal cross-linking: the Dresden protocol and accelerated or modified protocols. These protocols may vary in terms of total procedure time, ultraviolet A light intensity, and duration of riboflavin application.
Contact lens-assisted cross-linking	It is a technique designed for corneas of thickness ranging from 359 to 400 microns subsequent to removal of epithelial layer.
Pediatric cross-linking	Keratoconus and its treatment in minors are not yet fully explored or scientifically explored. Given the multitude of cross-linking methods available, it can be concluded that all these techniques effectively contribute to slowing down progression of keratoconus disease. The main difference among those methods is side effects that may arise following surgery.

CONCLUSIONS

This review explores CXL therapies for keratoconus, a progressive eye condition marked by thinning and a conical distortion of the cornea. It emphasizes the benefits and challenges linked to various treatment methods and techniques.

TE-CXL, introduced in 2004 to reduce complications linked to epithelial removal, focuses on enhancing riboflavin absorption through different techniques, such as using preservatives or inducing minor epithelial trauma. However, the intact epithelium often limits oxygen diffusion, affecting the treatment's efficacy. In contrast, epi-off CXL techniques like the Dresden protocol involve removing the corneal epithelium to improve riboflavin penetration and have shown long--term effectiveness, especially in the early stages of keratoconus.

Alternative methods, such as accelerated protocols and CACXL, offer shorter treatment times and specific benefits for patients with thinner corneas. Studies have also compared the epi-on and epi-off methods, with epi-off showing higher biomechanical strength but also more complications like corneal haze and scarring. TE-CXL, though less effective in some aspects, presents a safer option with reduced postoperative issues, especially in pediatric cases where keratoconus progression is often aggressive.

In conclusion, the epi-on method is highly valued for its reduced incidence of complications associated with epithelial debridement, such as scarring, infections, or delayed healing. Nevertheless, it is acknowledged that the epi-off procedure is more efficacious in achieving the desired outcomes.

Overall, while the standard epi-off approach remains the most effective in halting keratoconus progression, emerging techniques continue to refine safety and efficacy, with ongoing research to determine the optimal treatment for various patient groups, particularly children.

Conflict of interest statement

The authors report no conflicts of interest in this work.

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Ethics

The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.

Authors' contribution

Study design – N. Papachristoforou, A. Ueno
Data collection – N. Papachristoforou, A. Ueno, K. Ledwos
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PRACA ORYGINALNA
ORIGINAL PAPER

Demand for publicly funded mental health services in chronic patients during COVID-19 pandemic (Poland, 2018–2023)

Zapotrzebowanie na publicznie finansowane usługi zdrowia psychicznego dla pacjentów przewlekle chorych w okresie pandemii COVID-19 (Polska, 2018–2023)

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ABSTRACT

INTRODUCTION: The mental health needs of chronically ill individuals have been a persistent challenge in public health, further exacerbated by the coronavirus disease 2019 (COVID-19) pandemic. This study explores changes in mental health service utilization among this population in Poland across three periods: pre-pandemic (2018–2019), pandemic (2020–2021), and post-pandemic (2022–2023). The aim of the study was to analyze trends in the use of mental health services by chronically ill individuals, identify regional and diagnostic disparities, as well as assess the impact of the pandemic on service delivery.

MATERIAL AND METHODS: This retrospective observational study utilized anonymized data from the National Health Fund (Narodowy Fundusz Zdrowia – NFZ) database. It included the annual number of patients, service types, regional distribution, and diagnoses. Statistical analyses assessed the differences across periods and regions, including t-tests, chi-square tests, and ANOVA.

RESULTS: Mental health service utilization increased by 40% during the pandemic compared to the pre-pandemic period, with teleconsultations rising to 50% of services. Post-pandemic utilization decreased by 15% but remained 20% higher than the pre-pandemic levels. Significant regional disparities were noted, with urban areas experiencing greater increases in service use than rural regions. Cancer-related, respiratory, and cardiovascular conditions accounted for the most significant rises in patient numbers.

CONCLUSIONS: The pandemic significantly altered the landscape of mental health service delivery for chronically ill individuals. Sustaining innovations like telehealth and addressing regional disparities are crucial to ensure equitable access to care and meet the ongoing mental health needs of this vulnerable population.

KEYWORDS

mental health services, chronic illness, COVID-19 pandemic, telehealth, healthcare disparities

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STRESZCZENIE

WPROWADZENIE: Potrzeby w zakresie zdrowia psychicznego osób przewlekle chorych stanowią stałe wyzwanie dla zdrowia publicznego, dodatkowo spotęgowane przez pandemię choroby koronawirusowej (*coronavirus disease 2019* – COVID-19). W niniejszym badaniu przeanalizowano zmiany w korzystaniu z usług zdrowia psychicznego przez tę populację w Polsce w trzech okresach: przedpandemicznym (2018–2019), pandemicznym (2020–2021) i popandemicznym (2022–2023). Celem analizy było zidentyfikowanie trendów w korzystaniu z usług z zakresu zdrowia psychicznego przez osoby przewlekle chore, wskazanie różnic regionalnych i diagnostycznych, a także ocena wpływu pandemii na świadczenie usług.

MATERIAŁ I METODY: W badaniu retrospektywnym o charakterze obserwacyjnym wykorzystano zanonimizowane dane z bazy Narodowego Funduszu Zdrowia (NFZ). Dane obejmowały roczną liczbę pacjentów, rodzaje usług, rozkład regionalny oraz diagnozy. Analizy statystyczne, w tym testy t, testy chi-kwadrat oraz analiza wariancji (ANOVA), oceniały różnice między poszczególnymi okresami i regionami.

WYNIKI: Korzystanie z usług zdrowia psychicznego wzrosło podczas pandemii o 40% w porównaniu z okresem przedpandemicznym, z telekonsultacjami stanowiącymi 50% usług. Po pandemii korzystanie z usług zmniejszyło się o 15%, ale pozostało o 20% wyższe niż przed pandemią. Zauważono istotne różnice regionalne, przy czym na obszarach miejskich odnotowano większy wzrost korzystania z usług niż na obszarach wiejskich. Największy wzrost liczby pacjentów dotyczył tych z chorobami nowotworowymi, chorobami układu oddechowego i sercowo-naczyniowego.

WNIOSKI: Pandemia znacząco wpłynęła na sposób świadczenia usług w zakresie zdrowia psychicznego dla osób przewlekle chorych. Utrzymanie innowacji, takich jak telemedycyna, oraz zwrócenie uwagi na różnice regionalne są kluczowe dla zapewnienia równego dostępu do opieki i zaspokojenia bieżących potrzeb zdrowia psychicznego tej wrażliwej populacji.

SŁOWA KLUCZOWE

usługi zdrowia psychicznego, choroby przewlekłe, pandemia COVID-19, telemedycyna, nierówności w opiece zdrowotnej

INTRODUCTION

The mental health needs of individuals with chronic illnesses have long been a critical area of focus in public health. Chronic diseases, such as cancer, cardiovascular conditions, respiratory disorders, and metabolic syndromes, impose significant psychological burdens on patients, often leading to increased rates of anxiety, depression, and other mental health disorders [1,2]. The coronavirus disease 2019 (COVID-19) pandemic further exacerbated these challenges, disrupting access to healthcare and intensifying psychological distress among vulnerable populations. This unprecedented crisis highlighted gaps in healthcare systems, mainly mental health services, as they struggled to adapt to the increased demand [3,4].

Before the pandemic, the provision of mental health services for chronically ill individuals was already inadequate in many regions, with disparities in access between urban and rural areas [5]. The pandemic amplified these disparities and introduced new challenges, such as the necessity for remote care delivery and the psychological impacts of isolation and uncertainty [6]. Evidence suggests that during the pandemic, the rates of mental health disorders among chronically ill patients surged, with some studies reporting increases of up to 50% in anxiety and depression symptoms [7]. Despite the development of telehealth and other innovative approaches to care delivery, the demand often outpaced the availability of resources, leaving many patients without adequate support [8].

The post-pandemic period offers a critical opportunity to assess the long-term impacts of the pandemic on mental health service utilization and to identify strategies to address persistent and emerging needs. This study aims to analyze changes in the use of mental health services by individuals with chronic illnesses across three distinct periods: the pre-pandemic (2018––2019), pandemic (2020–2021), and post-pandemic (2022–2023). This research uses comprehensive data from the National Health Fund (Narodowy Fundusz Zdrowia – NFZ) in Poland to explore temporal trends, regional disparities, and variations by medical diagnoses.

By examining these patterns, the study provides valuable insights into the evolving mental health needs of chronically ill populations and offers evidence-based recommendations for improving service delivery. The findings will contribute to the growing body of literature on the mental health implications of chronic illnesses in the context of large-scale public health crises and their aftermath.

The study was based on three hypotheses:

- The COVID-19 pandemic significantly increased the demand for mental health services among chronically ill individuals.
- The increase in demand for mental health services during the pandemic varied by region, with urban areas experiencing a more significant rise compared to rural regions.

- The pandemic led to lasting changes in the delivery of mental health services, including the widespread adoption of teleconsultations, which persisted beyond the crisis.

MATERIAL AND METHODS

The data for this analysis was sourced from the NFZ database, a comprehensive repository providing standardized information on healthcare services in Poland. This dataset included anonymized records of chronically ill patients who utilized mental health services during three distinct periods: the pre-pandemic (2018–2019), pandemic (2020–2021), and post--pandemic (2022–2023). The extracted data encompassed patient demographics, the types of services provided, regional distributions, and primary medical diagnoses, offering a broad basis for detailed analysis.

This retrospective observational study was designed to examine trends in the utilization of mental health services among chronically ill individuals. It aimed to identify variations in patient numbers, the volume of services provided, and regional or diagnostic differences across the specified periods. The primary dependent variables included the annual number of patients using mental health services and the total number of services provided, such as psychological consultations, group therapy, and teleconsultations. The periods, regions (voivodeships in Poland), and medical diagnoses (e.g. respiratory, cardiovascular, oncological, neurological, and metabolic disorders) served as independent variables. The regional population size, urbanization levels, and the modality of service provision (in-person vs. teleconsultation) were also considered to provide additional contextual insights.

The dataset underwent extensive preprocessing to ensure accuracy and reliability. Duplicate records and incomplete entries were removed, and inconsistent diagnostic data were excluded. The service counts and patient numbers were aggregated by year, region, and diagnosis to facilitate meaningful comparisons across periods and regions. Descriptive statistics, including means and standard deviations, were calculated to summarize the data. Percent changes between periods were also computed to quantify trends.

Inferential statistical methods were applied to assess the significance of the observed changes. A t-test for independent samples was used to compare the mean number of patients and services between the periods. Chi-square tests evaluated the differences in service distributions across the three periods. Analysis of variance (ANOVA) was conducted to compare patient numbers across regions, and post-hoc analyses, such as Tukey's HSD test, were employed to identify specific regional differences. Linear regression models were used to explore relationships between the volume of services and patient demographic or diagnostic characteristics. Data visualization techniques, including heatmaps and line graphs, were utilized to illustrate regional and diagnostic trends. At the same time, proportional changes in service modalities, such as teleconsultations versus in-person visits, were depicted by means of stacked bar charts.

The study adhered to rigorous ethical standards. The NFZ provided anonymized data, ensuring no personally identifiable information was accessed or analyzed. Ethical approval for the study was obtained from the relevant institutional review board, and all the analyses complied with established privacy and data protection regulations.

RESULTS

In 2018–2019, the number of chronically ill individuals using mental health services averaged 1.5 million annually. Among them, 40% were patients with cancer--related conditions, and 30% had neurological disorders. In the Masovian Voivodeship, which accounted for 15% of all the cases nationwide, the number of patients averaged 225,000 annually, while in the Silesian Voivodeship, it was 180,000 (12%). An average of 15 million psychological services were provided annually, of which 60% were individual psychological consultations, and 20% were group therapy sessions. Teleconsultations and other remote psychological support services were marginal, accounting for less than 10% of the total services.

During the COVID-19 pandemic (2020–2021), the number of chronically ill individuals using mental health services increased by 40% compared to the pre--pandemic period, reaching an average of 2.1 million patients annually. The most significant increase in demand was observed among the patients with chronic respiratory diseases (a 70% increase) and cardiovascular diseases (a 50% increase). The patients with cancer-related conditions remained the largest group, with their numbers growing by 25%.

The Lower Silesian, Pomeranian, and Masovian Voivodeships experienced the highest percentage increase in patient numbers – on average by 45%. In the Lower Silesian Voivodeship, the number of patients increased from 100,000 annually in 2018–2019 to 145,000 in 2020–2021. In the Pomeranian Voivodeship, the figure rose from 85,000 to 123,000 (a 44% increase). The Masovian Voivodeship saw a 46% increase from 225,000 to 330,000 patients annually.

The total number of services provided was 21 million annually, a 40% increase compared to the pre--pandemic period. Teleconsultations accounted for less

than 10% of services before the pandemic and comprised 50% of the services in 2020–2021. These services were particularly significant in urban regions such as the Masovian and Silesian Voivodeships, where teleconsultations accounted for 60% and 55% of all the services, respectively.

In the post-pandemic period (2022–2023), the number of chronically ill patients using mental health services decreased by 15% compared to the pandemic years, averaging 1.8 million annually. However, this was still 20% higher than in the pre-pandemic period. The highest demand continued to be observed among the patients with cancer-related conditions (40% of all patients, a 25% increase compared to 2018–2019) and metabolic disorders, including diabetes (a 30% increase).

Regionally, the Lublin and Subcarpathian Voivodeships recorded the highest percentage growth compared to the pandemic years. In the Lublin Voivodeship, the number of patients increased by 10%, from 65,000 in 2020–2021 to 71,000 in 2022–2023. In the Subcarpathian Voivodeship, the patient numbers rose from 58,000 to 64,000 (a 10% increase). In the Masovian and Silesian Voivodeships, which remained leaders in terms of patient numbers, the figures stabilized at 290,000–310,000 annually, representing a 7% decrease compared to the pandemic period but still a 28% increase compared to 2018–2019.

The number of services provided in the post-pandemic period totaled 18 million annually, representing a 15% decrease compared to the pandemic years but a 20% increase compared to the pre-pandemic period. Although teleconsultations declined significantly compared to the pandemic, they still accounted for 30% of all the services, particularly in the Masovian and Lower Silesian Voivodeships. In rural areas such as the Lublin and Subcarpathian Voivodeships, in-person services dominated, increasing by 20% compared to the pandemic years.

An analysis of changes in the number of patients utilizing mental health services across the three periods revealed significant differences (Table I). The average number of patients in the pre-pandemic period was 1.5 million annually, increasing to 2.1 million during the pandemic, representing a 40% rise. A t-test for independent samples confirmed a statistically significant difference between these periods ($t = 7.45$; $p < 0.001$). The post-pandemic patient numbers decreased to 1.8 million annually, a 15% decline compared to the pandemic period but a 20% increase compared to the pre-pandemic period. A test comparing the means of the pandemic and post-pandemic periods also confirmed the significance of this change ($t = 3.62$; $p = 0.002$).

Similar differences were observed in the number of psychological services provided. In the pre-pandemic period, the number of services averaged 15 million annually, rising to 21 million during the pandemic, a 40% increase. A chi-square test confirmed the statistical significance of the differences between these periods ($\chi^2 = 112.34$; $p < 0.001$). In the post-pandemic period, the number of services was 18 million annually, representing a 15% decline from the pandemic period but a 20% increase compared to the pre-pandemic period ($\chi^2 = 47.89$; $p < 0.001$).

Regional analysis revealed the most significant changes in the Lower Silesian, Pomeranian, and Masovian Voivodeships, where the number of patients during the pandemic increased by 45%, 44%, and 46%, respectively, compared to the pre-pandemic years. A comparison of the regions by means of ANOVA revealed significant differences between the regions ($F(15, 44) = 5.87$; $p < 0.001$), with the most significant growth observed in urban areas and moderate growth in rural areas such as the Lublin and Subcarpathian.

Regarding diagnoses, the most significant changes were observed among patients with respiratory diseases, where the increase during the pandemic was 70% compared to the pre-pandemic period ($t = 9.12$; $p < 0.001$). Significant increments were also noted in patients with cardiovascular and cancer-related conditions, with rises of 50% ($t = 6.45$; $p < 0.001$) and 25% ($t = 3.98$; $p = 0.001$), respectively.

Table I. Statistical analysis results – comparison across periods

Period	Average number of services (mln)	Change in number of services	Largest groups	Leading regions	Teleconsultations	p-value
Pre-pandemic	15	–	cancer-related (40%) neurological (30%)	Masovian (225k) Silesian (180k)	< 10%	–
Pandemic	21	40%	respiratory (+70%) cardiovascular (+50%) cancer-related (+25%)	Masovian (330k, +46%) Lower Silesian (145k, +45%)	50%	< 0.001
Post-pandemic	18	-15% (vs. pandemic) / +20% (vs. pre-pandemic)	cancer-related (40%, +25%) metabolic (+30%, e.g. diabetes)	Masovian (300k, -7%) Lublin (+10%)	30%	< 0.001

DISCUSSION

The findings of this study provide critical insights into the impact of the COVID-19 pandemic on mental health service utilization among chronically ill individuals, prooving the presented hypotheses. The results support the assertion that the pandemic significantly increased the demand for mental health services. The heightened psychological stress associated with health uncertainties, isolation, and the disruption of routine medical care likely contributed to this surge. The growth in service use highlights how public health crises can intensify pre-existing mental health challenges, particularly for vulnerable populations such as those with chronic illnesses. The observed rise suggests broader recognition of the importance of mental health care in managing chronic conditions during periods of societal stress. The findings also support regional disparities in service demand. The urban areas demonstrated a more pronounced rise in the use of mental health services compared to rural regions. This disparity could be linked to a better healthcare infrastructure, more specialized mental health professionals, and greater access to digital health technologies in urban centers. Conversely, despite an increment in service utilization, rural areas exhibited lower overall engagement with mental health resources, indicating persistent barriers such as limited provider availability and digital access gaps. These differences underscore the need for targeted policy interventions to ensure equitable mental health service provision across regions, particularly in underserved areas. Proposing lasting changes in service delivery models is reflected in the sustained use of teleconsultations beyond the pandemic period. While the pandemic necessitated a shift toward remote care to ensure service continuity, teleconsultations remained a significant care component even when in-person services resumed. This shift suggests that digital health tools have become more integrated into standard practice, offering a flexible solution for patients with mobility challenges or those in remote areas. Nonetheless, the study also reveals that the telehealth adoption was more prominent in urban areas, reinforcing the need for investments in digital infrastructure in rural regions to prevent further disparities in access to care.

The observed 40% increase in the number of patients using mental health services during the pandemic is consistent with studies indicating a surge in psychological distress and mental health disorders among chronically ill populations during this time. For instance, Czeisler et al. [7] reported that anxiety and depression symptoms increased by over 40% in the general population, with similar trends noted in subgroups of patients with chronic diseases. Similarly, Pfefferbaum and North [6] highlighted how the pandemic amplified psychological vulnerabilities in those already managing chronic conditions, including increased fear, uncertainty, and isolation. Our results corroborate this, showing substantial increases in patients with respiratory and cardiovascular conditions, with usage rising by 70% and 50%, respectively. This aligns with the findings by Moreno et al. [4], who reported that respiratory and cardiovascular complications from COVID-19 were strongly associated with elevated psychological distress.

Regional disparities in mental health service utilization, particularly the more significant increase in urban areas such as the Masovian and Lower Silesian Voivodeships compared to rural regions like the Lublin and Subcarpathian, reflect well-documented inequalities in healthcare access. Edwards et al. [5] highlighted similar disparities, attributing them to differences in healthcare infrastructure, workforce distribution, and telehealth adoption. In our study, teleconsultations accounted for 50% of all the services during the pandemic, a dramatic rise compared to less than 10% pre-pandemic. This aligns with Smith et al. [8], who emphasized the critical role of telehealth in maintaining mental health service delivery during the pandemic, particularly in urban areas with higher technological readiness. However, despite increasing service utilization overall, the lower uptake of teleconsultations in rural regions underscores persistent barriers such as digital divides and lower technology access, as described by Ezenwaji et al. [9].

The post-pandemic decline in patient numbers and service utilization remained higher than the pre--pandemic levels, although significant compared to the pandemic period. This sustained increase, particularly in cancer-related and metabolic disorders, suggests that the pandemic may have led to a longer-term recognition of the importance of mental health care among chronically ill patients. Holmes et al. [3] emphasized the potential for such enduring changes in health--seeking behavior, with increased awareness of mental health as a critical component of chronic disease management. Additionally, the 30% rise in mental health service utilization among patients with metabolic disorders aligns with research by Dimsdale [2], who identified a strong link between chronic metabolic conditions such as diabetes and psychological distress.

Our findings also point to the need for further investment in rural mental health services, particularly in regions like the Lublin and Subcarpathian, where the growth in service utilization lagged behind urban areas despite the substantial demand. Studies such as those by Moreno et al. [4] have argued that targeted infrastructure development and telehealth expansion in underserved areas are essential to reduce disparities and ensure equitable access to care.

In conclusion, this study's results align with and expand upon existing literature, underscoring the significant mental health challenges faced by chronically ill individuals during and after the COVID-19 pandemic. The findings highlight the critical importance of integrating mental health care into chronic disease management, addressing regional disparities, and sustaining the innovations in telehealth that emerged during the pandemic.

The study has several significant limitations. First, it follows a retrospective design, relying on data collected by the NFZ, which prevents the establishment of causality. While the study can identify associations and trends, it cannot conclusively determine the factors driving the changes in service utilization. Additionally, the study uses anonymized administrative data, which may lack detailed information about individual patient characteristics, such as their socioeconomic status, mental health history, or specific psychosocial factors that could influence service use. This limits the depth of the analysis, particularly regarding the underlying reasons for mental health service utilization changes. Furthermore, the study does not account for all the potential confounding variables that may have influenced the observed changes, such as shifts in public awareness, social support systems, or local healthcare policies. These factors may have contributed to increased or decreased service utilization, especially post-pandemic.

CONCLUSIONS

The analysis of mental health service utilization among chronically ill individuals indicates that the COVID-19 pandemic significantly heightened the need for psychological support. The health crisis raised awareness of mental health needs in this vulnerable group, resulting in an incremented use of mental health services. Simultaneously, the pandemic exposed disparities in healthcare accessibility, particularly between urban and rural regions. The urban areas demonstrated more significant rises in service usage, partly because of the better infrastructure and availability of healthcare resources. In contrast, the rural areas faced more pronounced access and service availability challenges. The pandemic also contributed to a lasting transformation in the healthcare delivery model, notably through the substantial expansion of teleconsultations as a means of psychological support. Although the use of teleconsultations decreased after the pandemic, they remain a significant component of the mental healthcare system, especially in regions with a more advanced digital infrastructure. The findings suggest that the mental health needs of chronically ill individuals remained elevated even after the pandemic subsided, emphasizing the necessity for continued development and equitable distribution of mental health services across the country.

The findings emphasize the complex and multifaceted impact of the COVID-19 pandemic on mental health service utilization among chronically ill patients. The observed trends point to temporary and lasting changes in service demand and delivery, highlighting the importance of addressing regional inequalities and expanding innovative care models to meet ongoing mental health needs in this population. Further efforts should focus on ensuring sustained access to both digital and in-person mental health services across all regions.

Authors' contribution

Study design – P. Juraszek, M. Grajek
Data collection – P. Juraszek
Data interpretation – P. Juraszek, M. Grajek
Statistical analysis – P. Juraszek
Manuscript preparation – P. Juraszek
Literature research – P. Juraszek, M. Grajek

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OPIS PRZYPADKU
CASE REPORT

An interdisciplinary diagnostic approach successful in diagnosing rare diseases using Behçet's disease as an example

Interdyscyplinarne podejście diagnostyczne sukcesem w rozpoznawaniu chorób rzadkich na przykładzie choroby Behçeta

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ABSTRACT

Behçet's disease (BD) is an inflammatory and autoimmune disorder that develops in individuals with a genetic predisposition who are simultaneously exposed to certain environmental factors. It is believed that mediators of the inflammatory response, by initiating the migration of inflammatory cells into tissues, trigger an autoimmune response. This response leads to a systemic inflammatory process, resulting in the clinical manifestations of BD.
We present the case of a 39-year-old female patient referred to the internal medicine department with non-specific systemic symptoms and high levels of inflammatory parameters in her blood. She had a history of recurrent oral aphthae, genital ulcers on admission, as well as skin and musculoskeletal lesions of an upper limb. Following an extensive differential diagnosis, a diagnosis of BD was made. The paper describes the diagnostic difficulties and the multidisciplinary approach that is crucial in making an accurate diagnosis, especially in rare diseases.

KEYWORDS

diagnosis, treatment, Behçet's disease, skin lesions, oral ulcers, hepatitis C

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STRESZCZENIE

Choroba Behçeta (*Behçet's disease* – BD) to schorzenie o charakterze zapalnym i autoimmunologicznym, rozwijające się u osób z predyspozycją genetyczną, które jednocześnie narażone są na działanie określonych czynników środowiskowych. Uważa się, że mediatory reakcji zapalnej, inicjując migrację komórek zapalnych do tkanek, wyzwalają odpowiedź autoimmunologiczną. Reakcja ta prowadzi do ogólnoustrojowego procesu zapalnego, skutkując pojawieniem się objawów klinicznych BD.

W pracy przedstawiono przypadek 39-letniej pacjentki skierowanej na oddział internistyczny z nieswoistymi objawami ogólnoustrojowymi i wysokim poziomem parametrów zapalnych we krwi. W wywiadzie nawracające afty jamy ustnej, owrzodzenia narządów płciowych przy przyjęciu, a także zmiany w zakresie skóry i układu mięśniowo-szkieletowego kończyny górnej. Po szerokiej diagnostyce różnicowej postawiono rozpoznanie BD. Opisano trudności diagnostyczne oraz multidyscyplinarne podejście, które jest kluczowe w postawieniu trafnej diagnozy, zwłaszcza w chorobach rzadkich.

SŁOWA KLUCZOWE

diagnoza, leczenie, choroba Behçeta, zmiany skórne, afty jamy ustnej, zapalenie wątroby typu C

INTRODUCTION

Behçet's disease (BD) is a chronic multisystem inflammatory syndrome. It is characterized by recurrent oral and genital ulcers, skin and ocular lesions. In addition, there are disorders of the musculoskeletal system, vascular, central nervous system (CNS) and gastrointestinal tract [1].

In Europe, there are approximately 0.1–7.5 new cases per 100 000 citizens per year. It occurs mainly between the ages of 20 and 30, with equal incidence in both sexes in European countries and a male predominance in Middle Eastern countries [2]. The incidence in Poland is estimated at 0.5/1 million people per year [3]. The pathogenesis is still unknown, and infections, both bacterial and viral, as well as genetic and environmental factors, are mainly cited as potential causes. They cause activation of the immune system, resulting in inflammation and clinical symptoms [1]. Genetic background correlates strongly with the risk of developing BD and is significantly higher among first-degree relatives, especially in twins. The most significant genetic factor is the presence of the HLA-B51 allele. In recent years, variations in non-HLA genes such as the endoplasmic reticulum aminopeptidase enzyme (ERAP1), interleukin 10 (IL-10) and interleukin 23 receptor/interleukin 12 receptor beta 2 (IL23R/IL12RB2) have also been identified as being associated with the occurrence of BD [4,5]. The diagnosis of BD is usually made on the basis of clinical symptoms and a score of $\geq$ 4 pts according to the International Behçet's Disease Criteria [6] (Table I), which are mainly based on mucocutaneous manifestations due to their high sensitivity and specificity [7]. The primary aim of treatment is to control the inflammatory process and prevent irreversible damage to the organs involved, especially at an early stage of the disease.

Table I. International criteria for Behçet's disease

Criteria	Definition	Point value	Does the patient meet the criteria?
Ocular changes	retinal vasculitis, anterior uveitis, posterior uveitis	2 pts	NO
Lesions in the oral cavity	recurrent, painful aphthous ulcers in the mouth, recurring at least three times in the last 12 months, healing spontaneously within 1–3 weeks	2 pts	YES
Genital lesions	recurrent ulcers of the vulva in women and of the penis and scrotum in men	2 pts	YES
Skin lesions	aphthous skin ulcers, erythema nodosum, pseudofolliculitis or papulopustular lesions or acne nodules observed by a physician in patients after puberty who are not taking GCS	1 pt	YES
Positive pathergy test	assessed by at least three skin pricks; a positive result is the appearance of a pustule surrounded by erythema within 24–48 hours after irritation	1 pt	YES
Neurological changes	lesions assessed by a neurologist based on clinical examination and CT, MRI and/or CSF	1 pt	NO
Vascular lesions	thrombosis of arteries or large veins, deep or superficial phlebitis	1 pt	NO

GCS – glucocorticosteroids; CT – computed tomography; MRI – magnetic resonance imaging; CSF – cerebrospinal fluid.

CASE REPORT

A 39-year-old female patient was admitted to the internal medicine ward in moderate general condition due to recurrent fevers. She had a history of hepatitis C virus (HCV) infection 5 years ago. At the time she was not taking any medication. The examinations on admission were notable for their high inflammatory markers (CRP 309 mg/l, leukocytosis 23.8 th), with negative procalcitonin (PCT 0.19) and a normal chest X-ray. Owing to the additionally reported difficulties in concentration, speech and dizziness, a computed tomography (CT) scan of the head was performed followed by lumbar puncture with cerebrospinal fluid (CSF) examination. After consultation with an infectious disease physician, a neurologist, and based on the negative CSF results, neuroinfection was ruled out. Blood and urine cultures taken at the start of the study were ultimately found to be sterile. However, the presence of local ulcer-like lesions on the thumb of the left hand and on the external surface of the genitalia was noted. As the patient had unprotected sexual contact 2 weeks earlier, a suspicion of sexually transmitted diseases (STDs) was raised. Tests for human immunodeficiency virus (HIV, negative), hepatitis B surface antigen (HBs, negative), HCV (reactive), herpes simplex virus (HSV, negative), venereal disease research laboratory test (VDRL, negative) were sent and the patient was consulted dermatologically and gynaecologically – ruling out local inflammation and STD. The proteinogram was also inconclusive as elevated alpha-1 and alpha-2--globulins indicated an acute disease process, while beta-2-globulins with a mild reduction in albumin and hemoglobin indicated a chronic disease process. In addition, on the following day, the patient reported a sore throat and muscle pain, most severe in the left upper limb with restricted mobility in the shoulder joint. The diagnosis was expanded to include tests for rheumatological diseases, which were also initially suggested by the infectious diseases doctor: antinuclear antibody (ANA1, negative), rheumatoid factor (RF, slightly elevated), anti-cyclic citrullinated peptide antibody (anti-CCP, negative), complement components C3 and C4 normal, immunoglobulins (IgA, IgM, IgG) normal. An X-ray of the shoulder joint did not show any changes and after an orthopedic consultation, non-steroidal anti-inflammatory drugs (NSAIDs) were added to the treatment. Ear, nose, and throat (ENT) causes of the fever including cytomegalovirus (CMV, negative) and Epstein-Barr virus (EBV, negative) infection were also ruled out (Table II). During this consultation, the patient additionally reported that she had a history of frequent recurrent oral aphthae, which was resolved with topical antiseptics.

Table II. Test results

Inflammatory markers	CRP 309 mg/l leukocytosis 23.8 K PCT 0.19
Sexually transmitted diseases	HIV – negative HBs – negative HCV – reactive HSV – negative VDRL – negative
Microbiological tests	blood culture – negative urine culture – negative
Proteinogram	alpha-1-globulins – elevated alpha-2-globulins – elevated beta-2-globulins – elevated albumin – mildly decreased
Rheumatology panel	ANA1 antibodies – negative RF – slightly elevated anti-CCP – negative complement components C3, C4 – normal immunoglobulins – normal
Infection panel	CMV – negative EBV – negative

CRP – C-reactive protein; PCT – procalcitonin; HIV – human immunodeficiency virus; HBs – hepatitis B surface antigen; HCV – hepatitis C virus; HSV – herpes simplex virus; VDRL – venereal disease research laboratory test; ANA1 – antinuclear antibody; RF – rheumatoid factor; anti--CCP – anti-cyclic citrullinated peptide antibody; CMV – cytomegalovirus; EBV – Epstein-Barr virus.

The treatment included broad-spectrum empirical antibiotic therapy and NSAIDs, with a resolution of the complaints and a decrease in the inflammatory parameters (CRP 18, PCT and leukocytosis normal). On the basis of the clinical symptoms and the International Behçet's Disease Criteria (6 pts), a diagnosis of BD was made and hospitalization in the rheumatology department was planned, after prior exclusion of HCV recurrence (HCV RNA testing by PCR), with a view to possible immunosuppressive treatment.

DISCUSSION

Most patients with BD develop periodic fever, malaise and elevated inflammatory parameters. Nevertheless, these symptoms are uncharacteristic, hence inflammatory foci in the patient were sought first. Even before the administration of a broad-spectrum antibiotic, cultures were taken, which made it possible to rule out sepsis and urinary tract infections with relative reliability. The rarer the disease, the harder it is to receive a quick diagnosis and the tests usually give inconclusive results. Early diagnosis and effective treatment can prevent severe complications and reduce mortality. Symptoms of BD include oral ulcers, which are painful aphthous lesions of the oral mucosa. The difficulty in diagnosis lies in the similar morphology of lesions in the course of recurrent aphthous stomatitis (RAS) [7] and HCV infection [8].

In the case described here, oral aphthae had appeared in the past and were recurrent, but were at the time absent. The differential diagnosis excluded herpes and other viral diseases, in addition to recurrent aphthous stomatitis. Based on the determined levels, iron, vitamin B12 and folic acid deficiency were ruled out, and with negative ANA1 antibodies as well as no gastrointestinal symptoms, inflammatory bowel disease was also excluded. Nonetheless, attention was drawn to mild anemia suggesting a chronic process. Another important symptom of BD is genital ulcers, which often leave scars resulting from the deeper location of the lesions [7]. Due to the embarrassing nature of the lesions, it is often overlooked by patients in their history. In the search for inflammatory foci, a gynecological consultation in women, and a urological consultation in men, should be the primary diagnostic element. The history additionally indicated the possibility of infection with STDs, but this was not confirmed in the study, and the ulcers themselves were the patient's main reported problem. The diagnostic, but not pathognomonic for BD, symptom of pathergy, i.e. the formation of an erythematous papule or pustule at the site of a needlestick usually after 24–48 hours in the case described, was not present. It is estimated to affect 60% of patients with BD. Rare skin lesions include the patient's thumb ulceration. Much more common are papulopustular lesions on the basis of raised erythema or folliculitis.

BD usually presents with mild joint inflammation; the process mainly involves large joints, rarely small joints, while the sacroiliac joints are almost non-existent. In the case described here, the aggravated musculoskeletal complaints required an extended orthopedic diagnosis. After ruling out autoimmune causes of the complaints, suspected inflammation of the shoulder joint (the so-called frozen shoulder) was finally diagnosed. These lesions involve the joint capsule and synovial membrane, and their cause, once trauma is ruled out, is usually unknown. Slightly elevated levels of the RF in the patient's tests are not characteristic of BD, as they, like serum ANA antibodies, are usually absent in patients [9]. The so-called MAGIC syndrome (mouth and genital ulcers with inflamed cartilage) coexists with BD, in which oral and genital ulcers as well as polyarthritis occur simultaneously [10]. The diagnosis of BD in the patient may also be indicated by muscle pain in the upper extremities. Myositis occurs in some patients and is local; generalized myositis has been described only in isolated cases. Infectious diseases and fever can give similar complaints but they are most often generalized. In the patient, the creatine kinase and myoglobin levels were normal. The patient did not present with ocular changes, while the initial neurological symptoms in the form of pain and stiffness in the neck muscles were considered secondary to the muscle symptoms. A head CT scan, lumbar puncture and CSF analysis were performed, in addition to a neurological consultation – finding no abnormalities. Similar symptoms of neck muscle stiffness were described by Komatsumoto et al. [11], indicating that it may precede other BD symptoms. Treatment of BD focuses on two goals. The first is to prevent irreversible damage caused by repeated exacerbations of inflammation. The second goal is to prevent skin, mucosal and joint lesions, which usually do not lead to serious damage, but can significantly reduce patients' quality of life (QOL). Therapy should be tailored to the severity of the disease, the organs involved, the individual characteristics of the patient and his preferences [2]. The main role in the treatment of the disease is played by immunosuppressive and/or immunomodulatory drugs [12]. Because of their rapid anti-inflammatory effect, glucocorticosteroids (GCS) are the most commonly used [1]. Owing to the reactive anti-HCV antibodies found and the gradual improvement during symptomatic treatment in addition to empirical broad-spectrum antibiotic therapy (fluoroquinolone + cephalosporin III generation), the patient was not treated with GCS. It is worth mentioning at this point that despite the suspected influence of viral infections (including HCV infection) on the development of BD, its association with the disease has not been confirmed to date [11,12]. In clinical practice, prednisolone is used at a dose of 40–60 mg/d (reducing the dose after 4–6 weeks of treatment) [7]. As first-line treatment for mucocutaneous and articular symptoms, colchicine could also be used in our patient, either as monotherapy or in combination with benzathine penicillin, which accelerates the effect of colchicine [13]. We associate the improvement in our patient with the use of NSAIDs in support of broad-spectrum antibiotic therapy. In the maintenance treatment phase, the first-line drug is azathioprine [1]. However, it reaches maximum blood levels after 8–12 weeks of use, thus it is used in combination with NSAIDs to bridge acute attacks of the disease. The second-line drug is interferon alfa (IFN-α) and cyclosporine. In a randomized, placebo--controlled trial, the use of IFN-α2a significantly reduced the duration of exacerbations and pain [7]. Cyclosporine is usually preferred for conditions associated with ocular involvement. Due to its neurotoxicity, it is not recommended for use in patients with nervous system involvement [14].

CONCLUSIONS

BD is a multisystem disease, the diagnosis of which is often made more difficult by the different timing of symptoms. A multidisciplinary approach plays a key role in diagnosing patients. The patient's stay in the internal medicine ward contributed to a quicker

diagnosis because of the holistic view of the disease picture, and the numerous specialized consultations contributed a range of relevant information to the diagnosis. The diagnosis lacked an endoscopic examination of the gastrointestinal tract, but the patient was transferred to the Department of Rheumatology for further follow-up and diagnosis, and this will most likely be performed in the outpatient setting. As outlined above, making the diagnosis required a series of medical consultations ranging from neurology, ENT, gynecology, infectious diseases, dermatology and orthopedics. Owing to the unclear clinical picture, and in accordance with the recommendations of physicians from other specialties, a differential diagnosis was made for rheumatologic, autoimmune, bacteriologic (including sepsis), viral and STD diseases. The involvement of the skin, mucous membranes and joints is often less severe because of the low to moderate risk of permanent organ dysfunction. The key role is to control the inflammatory process, which can be achieved, as in the case presented here, by using NSAIDs in the cover of broad-spectrum antibiotics. This represents an interesting observation, however, the exact confirmation of such therapy, due to the small number of patients, may be difficult to achieve. Ocular involvement, CNS involvement and vasculitis have a worse prognosis and usually lead to significant disability, including blindness and even death, thus also requiring more aggressive treatment [15]. Most clinicians tailor BD treatment to the severity of the disease by assessing the risk of permanent organ damage and QOL considerations. The most common treatments are GCS, which in our case were limited by the possible recurrence of HCV infection, as well as disease-modifying drugs such as azathioprine, cyclosporine and interferon alfa. Unfortunately, even despite optimal treatment, relapses are common [1]. That is why it is so important to make an appropriate diagnosis and promptly initiate treatment to reduce the ongoing inflammatory process, which requires a multidisciplinary approach.

Authors' contribution

Study design – K. Gołojuch, P. Major, J. Smyk, A. Kamińska, W. Kosiba
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OPIS PRZYPADKU
CASE REPORT

Treatment of hemorrhagic retinal detachment additionally complicated by vitreous hemorrhage in a patient with end-stage renal failure

Leczenie krwotocznego odwarstwienia siatkówki dodatkowo powikłanego krwotokiem do ciała szklistego u pacjenta ze schyłkową niewydolnością nerek

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ABSTRACT

INTRODUCTION: End-stage renal disease (ESRD) is thought to be the cause of a number of retinal conditions such as retinal vein thrombosis, retinal artery occlusion, age-related macular degeneration or serous retinal detachment. ESRD is more often observed in adults than in children. Exudative or hemorrhagic retinal detachment is the pathological separation of the neurosensory retina from the pigment epithelium through the accumulation of exudative fluid and/or blood between them. Subretinal hemorrhage (SRH) then occurs, resulting in hemorrhagic retinal detachment.
CASE REPORT: A 73-year-old woman presented with sudden visual impairment in the right eye. She has been on hemodialysis three times a week for four years due to ESRD. Visual acuity testing showed light perception in the right eye and 5/16 in the left eye. The intraocular pressure was 15 mmHg in the right eye and 18 mmHg in the left eye. An ultrasound of the right eye revealed hemorrhagic retinal detachment with hemorrhage into the vitreous chamber. The patient was qualified for pars plana vitrectomy. A pars plana vitrectomy procedure was performed with subretinal blood removal, retinal laser therapy and silicone oil endotamponade of the right eye. In the postoperative period, in the examination follow-up, visual acuity in the right eye was achieved at the level of hand movements in front of the eye, and intraocular pressure at 13 mmHg.
CONCLUSIONS: Pars plana vitrectomy with silicone oil administration proved to be an effective treatment for this patient. Improvement and stabilization of the local condition was achieved.

KEYWORDS

vitrectomy, retinal detachment, subretinal hemorrhage, vitreous hemorrhage, technical note

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STRESZCZENIE

WPROWADZENIE: Schyłkową niewydolność nerek (*end-stage renal disease* – ESRD) uważa się za przyczynę wielu schorzeń siatkówki, takich jak zakrzep żyły siatkówki, zator tętnicy siatkówki, zwyrodnienie plamki związane z wiekiem czy surowicze odwarstwienie siatkówki. ESRD częściej jest obserwowana u osób dorosłych niż u dzieci. Surowicze czy krwotoczne odwarstwienie siatkówki to patologiczne oddzielenie siatkówki neurosensorycznej od nabłonka barwnikowego poprzez gromadzący się między nimi płyn wysiękowy i/lub krew. Dochodzi wtedy do krwotoku podsiatkówkowego (*subretinal hemorrhage* – SRH), który powoduje krwotoczne odwarstwienie siatkówki.
OPIS PRZYPADKU: 73-letnia pacjentka zgłosiła się z nagłymi zaburzeniami widzenia w oku prawym. Od czterech lat dializowana trzy razy w tygodniu z powodu ESRD. Badanie ostrości wzroku wykazało poczucie światła w oku prawym i 5/16 w oku lewym. Ciśnienie wewnątrzgałkowe wynosiło 15 mmHg w oku prawym i 18 mmHg w oku lewym. W badaniu ultrasonograficznym oka prawego wykazano krwotoczne odwarstwienie siatkówki z krwotokiem do komory ciała szklistego. Pacjentka została zakwalifikowana do witrektomii z dostępu tylnego. Wykonano witrektomię tylną z usunięciem krwi podsiatkówkowej, laseroterapią siatkówki oraz endotamponadą olejem silikonowym oka prawego. W okresie pooperacyjnym w badaniu kontrolnym uzyskano ostrość wzroku w oku prawym na poziomie ruchów ręki przed okiem oraz ciśnienie wewnątrzgałkowe na poziomie 13 mmHg.
WNIOSKI: Witrektomia z dostępu tylnego z podaniem oleju silikonowego w przypadku krwotocznego odwarstwienia siatkówki jest skuteczną metodą leczenia, dającą szansę na poprawę stanu miejscowego i zachowanie użytecznej ostrości wzroku.

SŁOWA KLUCZOWE

witrektomia, odwarstwienie siatkówki, krwotok podsiatkówkowy, krwotok do ciała szklistego, opis techniki operacyjnej

INTRODUCTION

End-stage renal disease (ESRD), is thought to cause a number of retinal conditions such as retinal vein thrombosis, retinal artery occlusion, age-related macular degeneration or serous retinal detachment [1,2,3,4]. ESRD is more often seen in adults than in children [5]. Exudative or hemorrhagic retinal detachment is the pathological separation of the neurosensory retina from the pigment epithelium through the accumulation of exudative fluid and/or blood between them [6,7]. Such pathology may be related to chronic renal failure as previously described. Blood in this space comes from the choroidal and/or retinal circulation [8]. Subretinal hemorrhage (SRH) then occurs, resulting in hemorrhagic retinal detachment [8]. In very rare cases, SRH can occur, also leading to hemorrhagic retinal detachment. An additional complication that can accompany SRH is hemorrhage into the vitreous body (vitreous hemorrhage – VH). This occurs because SRH infiltrates and punctures the retina in VH [9]. This is a situation that puts the patient in direct threat of permanent vision loss.

CASE REPORT

A 73-year-old woman presented with sudden visual impairment in the right eye. The patient suffers from hypertension, lower limb atherosclerosis, dyslipidemia, hepatic steatosis, chronic obstructive pulmonary disease and diabetes. She has been on dialysis three times a week for 4 years due to ESRD, creatinine level 4.11 mg/dl. The patient underwent left breast cancer 23 years ago, treated with a radical unilateral mastectomy, radiation therapy and chemotherapy. She takes amlodipine 5 mg, atorvastatin 10 mg, pentoxifylline and acetylsalicylic acid 75 mg on a daily basis. A visual acuity test showed light perception in the right eye and 5/16 in the left eye. The intraocular pressure was 15 mmHg in the right eye and 18 mmHg in the left eye. An ultrasound examination of the eyeball in the A projection of the right eye was performed; the image could correspond to VH and SRH, but a proliferative process could not be excluded either (Figure 1).

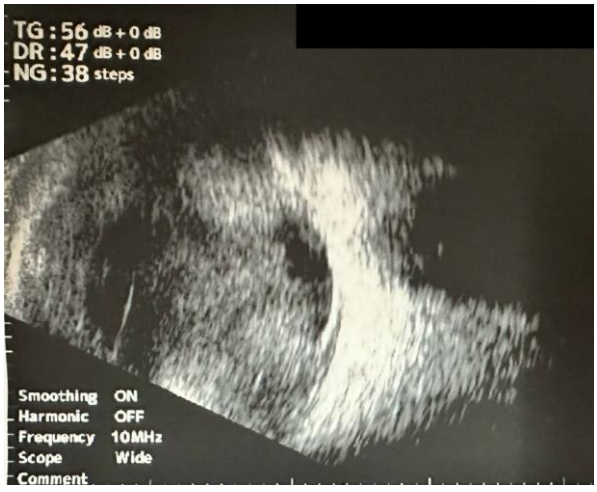

Fig. 1. Ultrasound showing an irregular outline of fundus of the eye and dense extra echoes in vitreous chamber.

On the basis of the patient's clinical picture, the diagnosis of an intraocular tumor that bleeds into the vitreous chamber was initiated. Consultation at the Ophthalmic Oncology Clinic was ordered. During the

consultation, ultrasound of the right eye (Figure 2) showed no malignant intraocular tumor. The lesion was most likely post-hemorrhagic in nature.

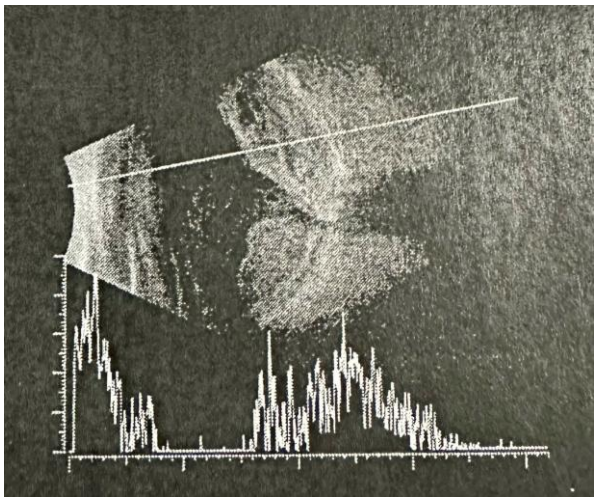

Fig. 2. Ultrasound examination, image corresponding to hemorrhagic retinal detachment.

The possibility of an intraocular tumor was excluded and hemorrhagic retinal detachment with hemorrhage into the vitreous chamber was diagnosed.

The patient was referred to the Adult Ophthalmology Department, where she was admitted on an elective basis after 21 days. On admission, her blood pressure was 141/92 mmHg and her heart rate was 113 beats per minute. Visual acuity testing showed light perception in the right eye and 5/16 in the left eye. The intraocular pressure was 16 mmHg in the right eye and 18 mmHg in the left eye. Routine laboratory tests were ordered; the blood test showed decreased levels of white blood count (3,85 × 10^3/μL) and platelets (3,38 × 10^3/μL) while there was an increased level of the mean corpuscular volume of 116.3 fL, and the mean corpuscular hemoglobin was 39.3 pg. The fasting blood glucose concentration was 129.8 mg/dL, creatinine was 4.11 mg/dL, the glomerular filtration rate was 11.21 ml/min. The coagulation panel and liver function panel were completely normal.

The patient was qualified for an emergency pars plana vitrectomy with (23G) of the right eye. The patient was anesthetized by periocular injection (2% lignocaine solution and 0.5% bupivacaine solution in a 1:1 ratio). After excision of the vitreous body, simultaneous injection of perfluorocarbon liquid into the vitreous chamber with drainage of the subretinal space by means of an additionally placed trocar and retinal incision. There was no need for a recombinant tissue plasminogen activator as the blood was noncoagulated (the medical history stated that the hemorrhage was only several weeks old) and was easily evacuated. After obtaining full-thickness retinal attachment across its entire surface, using aforementioned technique, laser therapy was performed on the peripheral retina. The perfluorocarbon liquid and the tamponade with 1000 cSt silicone oil were removed. Stage 1 of the surgical treatment was completed (Figure 3).

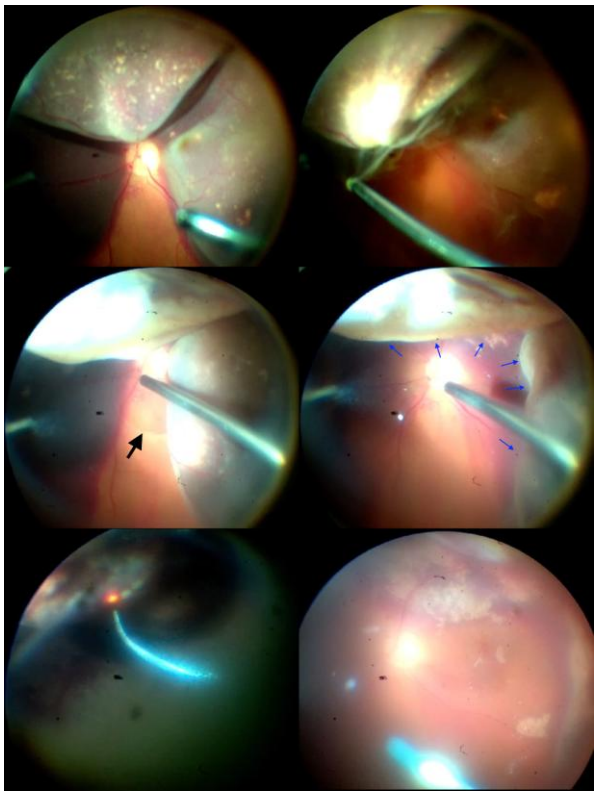

Fig. 3. Stages of pars plana vitrectomy (23G) of right eye; black arrow – administration of perfluorocarbon liquid, blue arrows – application of retina.

DISCUSSION

A complication that can correspond with SRH is VH. This occurs because SRH infiltrates and punctures the retina in VH [9]. Substances formed in the blood clotting process during SRH can cause mechanical damage to the outer retina layers and interfere with oxygen and nutrient transport. Fibrin, iron and hemosiderin present in the clot show direct toxic effects on the retina and choroidal capillaries. Indirect evidence of this phenomenon is the fact that experimentally induced SRH in rabbits causes necrosis of the retina, with erythrocytes moving into the vitreous body cavity through the necrotic area. VH occurs within a few weeks after SRH, and retinal ruptures do not occur in most cases. Hemorrhage into the vitreous body usually presents as an old immobilized hemorrhage, suggesting that erythrocytes are moving into the vitreous body cavity from the existing SRH. This toxicity begins 7 days after the hemorrhage, and the damage is irreversible after 3 weeks. Therefore, removal of the hemorrhage is critical to ensure the best

functional prognosis. This evidence underscores the importance of a quick diagnosis process and minimizing delay in surgical intervention in hemorrhagic retinal detachment [9]. In our case, the delay in surgical intervention was due to the fact that the clinical picture initially raised the suspicion of an intraocular tumor bleeding into the vitreous chamber. After ruling out a proliferative process in the eye, the decision was made to attempt surgical reattachment of the retina. Although the procedure was performed late (21 days after the patient reported to the hospital), inconsistent with data on retinal survival after hemorrhage, in this case the surgical outcome looks promising, even after such a long period of toxic effect on the retina. The patient's visual acuity in the operated eye improved from light perception to the recognition of hand movements in a follow-up examination one month after the intervention.

Tumor metastases are the most common intraocular tumors in adults, among which breast and lung adenocarcinoma are the most common in women and men alike [10,11]. These metastases can be the direct cause of exudative retinal detachment (ERD), but cases in which ERD occurred without the presence of secondary tumor foci have been described [12,13]. The pathogenesis of ERD is based on disturbances in the physiology of the cells that build the blood-retinal barrier due to an inadequate blood supply, resulting in chronic hypoxia. This can result from a variety of diseases, usually systemic, including chronic inflammation, infection, vascular malformations, degenerative conditions or cancer [12]. The disorder can result from the dysfunction of blood-retinal barrier cells owing to the mere presence of cancer cells in the blood, eventually resulting in disruption of their function and leakage of fluid into the subretinal space. The patient developed cancer of the left breast in 2001, which required treatment with a left radical mastectomy, radiation therapy and chemotherapy. Despite the passing of a long period of time since the disease and treatment, we cannot fully exclude the presence of a few cancer cells in the bloodstream. Therefore, their presence can be suspected as one of the potential causes of ERD in the described clinical case.

The mechanism described above underscores the deleterious effect of systemic diseases themselves, which can cause ERD. Of the patient's many conditions, ESRD (she has been on dialysis for 4 years with a creatinine level of 4.11 mg/dl) and high blood pressure appear to be the most worrisome. ESRD and high blood pressure result in vasoconstriction in the ocular arteries, leading to choroidal ischemia and hypertensive choroidopathy. There is also damage to the blood-retinal barrier cells, which leads to exudates in the space between the neurosensory retina and the retinal pigment epithelium, hence ERD [14]. According to Gass [15], ESRD plays a key role in the pathomechanism of ERD. Because the fibrin exudates were located below the margins of the detached pigment epithelium and the surrounding subretinal space, he hypothesized that large molecules such as fibrinogen could enter the subretinal space. This is associated with a focal increase in the permeability of the choriocapillaries in the uremic state and causes ESRD [15]. Troiano and Buccianti [16] suggested that there is a greater importance of dialysis in the pathomechanism of ERD, which causes changes in osmolarity and induces a shift of fluid between different compartments through membranes with different permeabilities. Therefore, fluid below the pigment epithelium or the subretinal space surrounding the detached pigment epithelium causes detachment in later stages and eventually ERD. A cohort study showed that the incidence of ERD in ESRD patients undergoing dialysis was 3.39 times higher than in control subjects [4]. These findings may be related to changes in choriocapillary permeability as a consequence of dialysis-induced changes in osmolarity and fluid shifts. It was also observed that patients undergoing peritoneal dialysis had a higher percentage of ERD than hemodialysis patients. Dialysis therapy is associated with the presence of chronic inflammation in the body, which is consistent with the pathomechanism of ERD. In the case of peritoneal dialysis, an additional factor causing inflammation is prolonged peritoneal glucose loading, leading to fluid accumulation due to cumulative peritoneal membrane damage and increased peritoneal membrane permeability [4]. The causes described above, by various mechanisms, damage both the blood-peritoneal barrier cells and the vessels themselves. As a result of such impaired choroidal and retinal circulation, the patient may have suffered vascular rupture as well as active subretinal and subchoroidal hemorrhage, which, combined with exudative fluid or blood, caused exudative or hemorrhagic retinal detachment.

CONCLUSIONS

Pars plana vitrectomy with silicone oil administration proved to be an effective treatment for this patient. Improvement and stabilization of the local condition was achieved.

Conflict of interest

All the authors declare that they have no conflicts of interest.

Authors' contribution

Study design – M. Guzikowski, S. Sirek, W. Rokicki
Manuscript preparation – M. Guzikowski, S. Sirek
Literature research – M. Guzikowski, S. Sirek
Final approval of the version to be published – W. Rokicki

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PRACA ORYGINALNA
ORIGINAL PAPER

Survival analysis of patients operated by NSS compared to patients operated conventionally for renal cell carcinoma

Analiza przeżycia pacjentów operowanych metodą NSS w porównaniu z pacjentami po nefrektomii radykalnej z powodu raka nerkowokomórkowego

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ABSTRACT

INTRODUCTION: Renal cell carcinoma (RCC) accounts for 2% of all cancers worldwide and causes 2% of cancer deaths. There are three types of RCC: clear cell (ccRCC), papillary (pRCC), and chromophobe (chRCC). The most common symptoms are hematuria (often periodic), pain in the lumbar region, weight loss, weakness, and periodic fever with night sweats. Often, in advanced stages, there is an abdominal tumor, enlargement of the cervical and supraclavicular lymph nodes, swelling of the lower limbs, and varicose veins.

MATERIAL AND METHODS: 249 patients with RCC were enrolled in the study, including 203 (81.5%) with ccRCC, 32 (12.9%) with pRCC, and 14 (5.6%) with chRCC. We focused on a comparison of the surgical treatment outcomes between radical nephrectomy (RN) and nephron-sparing surgery (NSS) in terms of qualitative and quantitative characteristics.

RESULTS: It was estimated that factors such as the maximum tumor size, age at the day of surgery and sarcomatic transformation had the greatest impact on survival. Also, important factors are the cancer type, cancer stage, WHO grading, embolism, vascular invasion, nerve invasion, fat capsule infiltration and fibrous capsule infiltration.

CONCLUSIONS: The results suggest that the above factors should be taken into account when choosing the appropriate treatment method as it allows the patient's life to be extended and the number of postoperative complications to be reduced.

KEYWORDS

renal cell carcinoma, nephron-sparing surgery, radical nephrectomy, survival analysis

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STRESZCZENIE

WPROWADZENIE: Rak nerkowokomórkowy (*renal cell carcinoma* – RCC) stanowi 2% wszystkich nowotworów na świecie i jest przyczyną 2% zgonów z powodu nowotworów. Wyróżnia się trzy typy RCC: jasnokomórkowy (*clear cell* – ccRCC), brodawkowaty (*papillary* – pRCC) i chromofobowy (*chromophobe* – chRCC). Najczęstszymi objawami są krwiomocz (często okresowy), ból w okolicy lędźwiowej, utrata masy ciała, osłabienie, okresowa gorączka z nocnymi potami. W zaawansowanych stadiach często występują: guz jamy brzusznej, powiększenie węzłów chłonnych szyjnych i nadobojczykowych, obrzęki kończyn dolnych oraz żylaki powrózkowe.
MATERIAŁ I METODY: Do badania włączono 249 pacjentów z RCC, w tym 203 (81,5%) z ccRCC, 32 (12,9%) z pRCC i 14 (5,6%) z chRCC. Skupiono się na porównaniu wyników leczenia chirurgicznego: nefrektomii chirurgicznej (*radical nephrectomy* – RN) i organooszczędnej resekcji guza nerki (*nephron-sparing surgery* – NSS) pod względem cech jakościowych i ilościowych.
WYNIKI: Oszacowano, że największy wpływ na przeżycie mają takie czynniki, jak maksymalna wielkość guza, wiek w dniu operacji oraz transformacja sarkomatyczna. Do istotnych czynników zalicza się również typ nowotworu, stopień zaawansowania nowotworu, ocenę stopnia złośliwości według WHO, zatory, inwazję naczyń, inwazję nerwów, naciek torebki tłuszczowej oraz naciek torebki włóknistej.
WNIOSKI: Wyniki sugerują, że przy wyborze odpowiedniej metody leczenia należy wziąć pod uwagę wspomniane czynniki, gdyż pozwala to na wydłużenie życia pacjenta i zmniejszenie liczby powikłań pooperacyjnych.

SŁOWA KLUCZOWE

rak nerkowokomórkowy, organooszczędna resekcja guza nerki, nefrektomia radykalna, analiza przeżycia

INTRODUCTION

Renal cell carcinoma (RCC) arises from the epithelial cells of the renal tubules. The most common forms are categorized as clear cell RCC (ccRCC), papillary RCC (pRCC), and chromophobe RCC (chRCC), which together account for around 85% of primary renal cancers. The remaining 15% are transitional cell carcinoma, Wilms tumor or nephroblastoma, collecting duct tumors, and renal sarcomas [1].

In Europe and North America, the lifetime risk of developing RCC ranges from 1.3% to 1.8%. According to the most recent data provided by the World Health Organization (WHO), over 140,000 RCC-related deaths occur annually, with RCC ranked 13th among the leading causes of cancer deaths worldwide [2].

Most RCCs are asymptomatic and are detected as an unexpected result of imaging performed for unrelated clinical indications [3].

The main cure for localized RCC is surgery. Open radical nephrectomy (RN), described by Robson, has long been the gold standard. Nevertheless, as a result of the increased use of abdominal imaging modalities, a continuous migration towards small, low-grade RCC lesions has become apparent over the past decades. Along with this stage of migration, nephron-sparing surgery (NSS) has developed and is gaining in popularity [4].

The goal of the NSS approach is to preserve as much parenchymal reserve capacity as possible while achieving complete surgical excision with adequate margins to protect the patient from excessive loss of renal parenchyma [5].

The aim of the study was to compare the clinical and pathological parameters, including the survival of patients with RCC treated by means of RN surgery and NSS. The overarching hypothesis is that NSS may lead to comparable oncological outcomes and improved postoperative recovery for appropriately selected patients.

MATERIAL AND METHODS

We performed a cross-sectional, descriptive study involving 249 cases of RCC (203 ccRCC, 32 pRCC, and 14 chRCC) between the ages of 34 and 85. The search was conducted from January 2015 to May 2021 at the Department of Pathology in Zabrze. Each patient was treated with the intention of curing them by means of partial or radical nephrectomy. The histopathology specimens used in all the cases were treated according to the current guidelines of the Polish Society of Pathologists and in accordance with International Society of Urological Pathology (ISUP) in addition to WHO recommendations for sample handling, sampling, and reporting [6,7].

Each sample was reviewed by two pathologists, allowing grading according to WHO/ISUP and WHO/UICC (Union for International Cancer Control) TNM (tumor, node, metastasis) pathologic staging categories [8].

The samples were evaluated for: tumor size, histologic type, WHO/ISUP staging, the presence of necrosis, sarcomatoid and rhabdoid differentiation, the infiltration of small lymphatic vessels, macroscopic infiltration of the renal vena cava neuroinvasion, infiltration of the renal capsule, the infiltration of perinephric fat, renal sinusoidal fat, as well as renal sinusoidal vascular infiltration. WHO/UICC TNM pathological staging was performed for primary tumors (pT) and lymph node metastasis (pN). Perinephric fat infiltration was estimated for a total of 249 tumors,

while renal sinus infiltration was assessed only for the cases terminated with radical nephrectomy, i.e. 142 cancers. For ccRCC, we evaluated the percentage of cells with clear cytoplasm, while pRCC was classified as type 1 or 2.

Qualitative data are presented as the number of cases with percentages, while quantitative data are presented as the median with the first and third quartiles. A graphical method using a Q–Q chart was employed to assess normality distribution. The analysis of qualitative variables was performed using Fisher's exact test for 2 × 2 tables and the Chi-squared test for larger tables. Cramér's V value is given for each analysis to determine the power of the test. For quantitative variables, the Mann-Whitney U test was utilized. Survival analyses were performed by means of the Kaplan-Meier method, with the log-rank test used to compare the two curves. The Cox model was employed to assess the multivariate impact of tumor histology, the type of surgery, and tumor size (possibly grading) on the relative hazard.

RESULTS

Characteristics of the included studies

The study evaluated 249 RCC samples, including 203 (81.5%) ccRCC, 32 (12.9%) pRCC, and 14 (5.6%) chRCC. The study group consisted of 156 men aged 62.6 ± 10.5 years and 93 women aged 65.6 ± 8.6 years ($P < 0.05$).

Major differences were observed for the age at the time of surgery, clear-cell cancerous tissue, maximum tumor size, sarcomatoid and rhabdoid transformation, as well as necrosis (Table I). Significant differences in the survival and recurrence rates between the RN and NSS patients underscore the importance of careful patient selection. A notable observation was the overrepresentation of chRCC in the NSS group. This discrepancy may be attributed to the generally favorable prognosis and less aggressive behavior of chRCC, making it a suitable candidate for nephron-sparing approaches.

Table I. Comparison of qualitative features of operations performed using nephron-sparing surgery (NSS) methods and radical nephrectomy (RN) methods

Variable	NSS n = 107			nonNSS n = 142			p
	median	q1	q3	median	q1	q3	
Age on day of surgery	63.00	34.00	85.00	65.50	40.00	85.00	0.021
Clear-cell pattern (%)	100.00	40.00	100.00	90.00	5.00	100.00	p < 0.001
Max tumor size (cm)	3.00	1.00	11.00	7.00	1.00	18.00	p < 0.001
Necrosis (%)	0.00	0.00	30.00	0.00	0.00	99.00	p < 0.001
Sarcomatic transformation	0.00	0.00	0.00	0.00	0.00	80.00	p < 0.001
Rhabdoid transformation	0.00	0.00	0.00	0.00	0.00	40.00	0.017
Survival	1740.00	20.00	3660.00	1549.00	21.00	3693.00	0.078

Table II. Comparison of quantitative features of operations performed using nephron-sparing surgery (NSS) methods and operations qualifying for NSS, but performed using radical nephrectomy (RN)

Variable	NSS possible n = 57				NSS n = 107		
	median	q1	q3	p	median	q1	q3
Age on day of surgery	65.00	34.00	85.00	0.455	63.000	34.000	85.000
Clear-cell pattern (%)	100.00	5.00	100.00	p < 0.001	100.000	40.000	100.000
Max tumor size (cm)	4.50	1.00	7.00	0.102	3.000	1.000	11.000
Necrosis (%)	0.00	0.00	99.00	p < 0.001	0.000	0.000	30.000
Sarcomatic transformation	0.00	0.00	30.00	p < 0.001	0.000	0.000	0.000
Rhabdoid transformation	0.00	0.00	1.00	p < 0.001	0.000	0.000	0.000
Survival	1776.00	20.00	3660.00	0.151	1740.000	20.000	3660.000

Table III. Clinicopathologic characteristics

Variable	NSS n (%)		nonNSS n (%)		p (V – Cramér)
Type of tumor					
ccRCC	75	(70.1)	128	(90.1)	p < 0.001
pRCC	21	(19.6)	11	(7.7)	
chRCC	11	(10.3)	3	(2.1)	
total	107	(100.0)	142	(100.0)	
The location of tumor					
left kidney	46	(43.0)	66	(46.5)	p = 0.338
right kidney	61	(57.0)	76	(53.5)	
T parameter					
pT1	80	(74.8)	58	(40.8)	p < 0.001 (V = 0.378)
pT2	7	(6.5)	19	(13.4)	
pT3	15	(14.0)	64	(45.1)	
pT4	0	(0.0)	1	(0.7)	
total	102	(95.3)	142	(100.0)	
WHO grading					
G1	52	(48.6)	33	(23.2)	p < 0.001 (V = 0.441)
G2	41	(38.3)	51	(35.9)	
G3	1	(0.9)	25	(17.6)	
G4	2	(1.9)	30	(21.1)	
total	96	(89.7)	139	(97.9)	
Lymphatic invasion	1	(0.9)	9	(6.3)	p = 0.029
Angioinvasion	2	(1.9)	42	(29.6)	p < 0.001
Neuroinvasion	0	(0.0)	4	(2.8)	p = 0.104
Necrosis	55	(51.4)	87	(61.3)	p = 0.077
Fibrous capsule infiltration	13	(12.1)	33	(23.2)	p = 0.018

NSS – nephron-sparing surgery; ccRCC – clear cell renal cell carcinoma; pRCC – papillary renal cell carcinoma; chRCC – chromophobe renal cell carcinoma; pT – primary tumor; WHO – World Health Organization.

Table IV. Comparison of average values for quantitative features of operations performed using nephron-sparing surgery (NSS) methods and radical nephrectomy (RN) methods

Variable	NSS			nonNSS		
	average	lower 95% CI	upper 95% CI	average	lower 95% CI	upper 95% CI
Age on day of surgery	61.888	59.919	63.857	65.113	63.541	66.684
Clear-cell tissue (%)	97.067	94.622	99.511	77.891	72.880	82.901
Max tumor size (cm)	3.503	3.148	3.857	7.068	6.488	7.647
Necrosis (%)	1.224	0.404	2.044	14.676	10.485	18.867
Sarcomatic transformation (%)	0.000	0.000	0.000	2.536	0.903	4.169
Rhabdoid transformation (%)	0.000	0.000	0.000	0.949	0.065	1.833

CI – confidence interval.

Table V. Comparison of relative hazard for quantitative characteristics of operations performed using nephron-sparing surgery (NSS) and radical nephrectomy (RN) methods

Variable	HR	Lower 95% CI	Upper 95% CI	p
Age on day of surgery	1.030	1.003	1.057	0.031
Clear cell fabric (%)	0.989	0.979	0.998	0.015
Max tumor size (cm)	1.150	1.067	1.240	0.000
Necrosis (%)	1.016	1.005	1.026	0.003
Sarcomatic transformation (%)	1.029	0.997	1.062	0.074
Rhabdoid transformation (%)	0.973	0.913	1.036	0.391

HR – hazard ratio; CI – confidence interval.

DISCUSSION

The discussion examines the rising incidence of RCC and highlights the challenges in surgical management. We explored the potential for selection bias and the influence of surgical expertise on patient outcomes. The overrepresentation of chromophobe RCC in the NSS group may suggest a deliberate selection bias favoring tumors with lower metastatic potential. Further multicenter studies are recommended to validate these findings.

Limitations and future directions

This study acknowledges several limitations, including the single-center design and the relatively small sample size. Future research should aim to include multicenter cohorts, longer follow-up periods, and molecular profiling to provide a more comprehensive understanding of RCC management strategies. Additionally, addressing the potential for selection bias and standardizing surgical protocols across institutions could further refine outcomes.

CONCLUSIONS

The results suggest that NSS should be considered the standard approach for tumors up to 7 cm, while RN remains preferred for larger tumors. A precise assessment of tumor differentiation and staging is crucial to optimize patient outcomes and minimize postoperative complications.

Authors' contribution

Study design – P. Kiczmer, J. Wątor
Data collection – M. Chrabańska, M. Bluszcz, M. Bar
Data interpretation – B. Drozdzowska, M. Bluszcz
Statistical analysis – P. Kiczmer, M. Katra
Manuscript preparation – M. Bar, J. Wątor
Literature research – M. Chrabańska, M. Katra

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PRACA ORYGINALNA
ORIGINAL PAPER

Assessment of medical and non-medical university students' knowledge about vitamin D

Ocena wiedzy studentów uczelni medycznej i niemedycznej na temat witaminy D

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ABSTRACT

INTRODUCTION: Vitamin D is very important for our body. This is confirmed by the World Health Organization (WHO), the Polish Society for Obesity Research (Polskie Towarzystwo Badań nad Otyłością – PTBO) and the Polish Diabetic Society (Polskie Towarzystwo Diabetologiczne – PTD). Nowadays, due to spending most of our time indoors and using sunscreen, we commonly experience deficiencies of this vitamin. In order to assess the knowledge of students from the Medical University of Silesia and the University of Economics in Katowice regarding vitamin D, a survey was conducted based on a proprietary questionnaire available in electronic form.
MATERIAL AND METHODS: The study was conducted with the help of the author's questionnaire containing 18 substantive questions. The study involved 272 students.
RESULTS: Students of the Medical University of Silesia have a greater knowledge of vitamin D compared to students of the University of Economics in Katowice. A significant number of respondents (49.8%) have an adequate understanding of supplementation, though some are unaware of the recommended standards (34.7%) or the effects of deficiencies (43.6%).
CONCLUSIONS: Students of the Medical University of Silesia in the vast majority have adequate knowledge related to vitamin D, while the knowledge of students of the non-medical university, namely the University of Economics in Katowice, is lower.

KEYWORDS

vitamin D, dietetics, supplementation, deficiency, knowledge, synthesis, standards, comparison

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Publisher: Medical University of Silesia, Katowice, Poland

STRESZCZENIE

WPROWADZENIE: Witamina D jest bardzo ważna dla naszego organizmu. Potwierdza to Światowa Organizacja Zdrowia (World Health Organization – WHO), Polskie Towarzystwo Badań nad Otyłością (PTBO) i Polskie Towarzystwo Diabetologiczne (PTD). Współcześnie, w wyniku spędzania czasu głównie w zamkniętych pomieszczeniach oraz stosowania kremów z filtrem, mamy do czynienia z powszechnymi niedoborami tej witaminy. W celu oceny stanu wiedzy na temat witaminy D wśród studentów Śląskiego Uniwersytetu Medycznego oraz Uniwersytetu Ekonomicznego w Katowicach przeprowadzono badanie ankietowe z użyciem autorskiego kwestionariusza dostępnego w formie online.
MATERIAŁ I METODY: Badanie przeprowadzono z użyciem autorskiego kwestionariusza, zawierającego 18 pytań merytorycznych. W badaniu wzięło udział 272 studentów.
WYNIKI: Wiedzę na temat witaminy D w większym stopniu posiadają studenci Śląskiego Uniwersytetu Medycznego niż studenci Uniwersytetu Ekonomicznego w Katowicach. Znaczna liczba ankietowanych (49,8%) ma wystarczający poziom wiedzy na temat suplementacji, jednak część badanych nie zna norm (34,7%) ani skutków niedoborów (43,6%).
WNIOSKI: Studenci Śląskiego Uniwersytetu Medycznego w zdecydowanej większości posiadają wystarczającą wiedzę na temat witaminy D, natomiast wiedza studentów uczelni niemedycznej, tj. Uniwersytetu Ekonomicznego w Katowicach, jest niższa.

SŁOWA KLUCZOWE

witamina D, dietetyka, suplementacja, niedobór, wiedza, synteza, normy, porównanie

INTRODUCTION

Vitamins are involved in almost all metabolic processes occurring in the body as coenzymes or biological active substances, acting already in small amounts; they are not a source of energy, although they are necessary for its production in the body, and have little importance as a building material. Vitamins are characterized by low durability, resulting in little resistance to high temperatures, storage, as well as culinary processing, i.e. light, oxygen, alkaline reaction of the environment, which can lead to a significant reduction in the nutritional value of prepared food. Most vitamins must also be supplied to the body from outside due to the fact that they cannot be synthesized by our body as only some of them, such as vitamin D_3, are partially synthesized in the body under the influence of UV radiation, produced by bacteria in the intestines of humans and animals, an example of which is vitamin K_2, or can be formed from other compounds (such as niacin from tryptophan) [1].

Fat-soluble vitamins, which include vitamins A, D, E and K, are stored in the body mainly in adipose tissue and the liver, which can result in their over--accumulation – hypervitaminosis, above the tolerable upper intake level (UL) for a given age group. Fish liver oil tablets containing 400 IU of vitamin D are commonly used, and the most commonly recommended daily dose is 400 to 1,000 IU [2].

Vitamin D_3 is one of the few vitamins that the body can produce endogenously, hence it does not meet the definition of a vitamin. Vitamin D_2 and D_3 do not raise blood levels of vitamin D in the same way. Vitamin D_3 is much better at raising calcifediol levels and maintaining normal blood calcium levels. Of importance is the fact that although the metabolic effects of vitamin D_2 and vitamin D_3 are similar, these compounds bind to different types of plasma proteins. As a result, vitamin D_3 lasts longer and is 2–10 times more effective than vitamin D_2 [3].

Symptoms of vitamin D poisoning in adults can be induced by excessive doses exceeding 20,000 IU, while in children it is a daily dose of more than 1,800 IU. Vitamin D poisoning is a very rare complication of supplementation or treatment with pharmaceutical preparations of cholecalciferol, and it actually only affects people with a genetic hypersensitivity to vitamin D [4].

The aim of this study is to draw attention to the important but overlooked vitamin D and to analyze the knowledge possessed by medical students, using the example of the Medical University of Silesia (Śląski Uniwersytet Medyczny w Katowicach – ŚUM) and students of a non-medical university – the University of Economics in Katowice (UE).

MATERIAL AND METHODS

A survey was conducted using a proprietary questionnaire containing 18 questions including 4 demographic questions and 14 factual questions. It was divided into students of the medical university (ŚUM) and students of the non-medical university (UE). The survey was conducted online by means of Google Forms between 11–25/09/2023. Respondents from both the universities were solicited utilizing the snowball method; in addition, a link requesting completion was also posted on social media, i.e. Messenger and Instagram. Additionally, via Facebook, a link to the survey questionnaire was posted on "Spotted" of every major city in the Silesian province (including Piekary Śląskie, Myszków, Tychy, Jaworzno, Mikołów, Rybnik) since most of the students come from neighboring cities.

The survey included one open-ended question regarding age, while the remaining questions were

closed-ended with single-choice answers. The majority of the respondents (40 people) from the non-medical university declared to be 21 years old (31%), similarly, among the students from the medical university, the majority (30 people) were also 21 years old (21%). The substantive questions concerned vitamin D – its sources, standards, absorption, impact on the human body, and supplementation.

The inclusion criteria were to study at the ŚUM or the UE. A total of 143 (52.6%) students from the ŚUM and 129 (47.4%) students from the UE participated in the study. The total number of people taking part in the survey was 272. The number of people taking part in the survey was estimated using a sampling calculator (Figure 1). The size of the population is the number of students from both universities according to the information provided by each university.

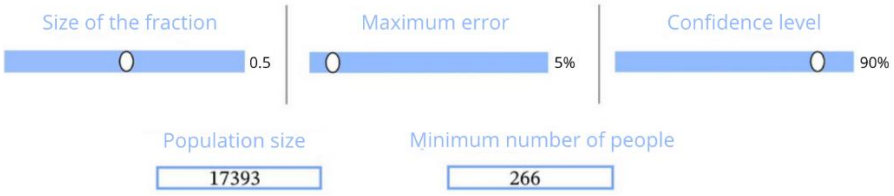

Fig. 1. Sampling calculator (author's own work).
Ryc. 1. Kalkulator doboru próby (opracowanie własne).

RESULTS

The conducted studies confirm the existence of a relationship between the individual data obtained from the responses and the students' knowledge, which is necessary to live with full awareness, about the role and importance of this important vitamin for our body. They allowed the author to verify the stock of knowledge declared by the respondents participating in the study on the standards, effects, absorption and supplementation of vitamin D. From the results obtained in the study, it can be seen that the level of knowledge about vitamin D in the medical community is higher compared to a comparable one in students from non-medical universities.

One of the questions asked about products rich in the vitamin in question. The correct answer (fish), was given by 37.8% of the medical college students and 27.1% of the non-medical college students (Figure 2).

Regarding the effect of vitamin D on the functioning of the human body, more than ¾ of the students associated with medical faculties gave the correct answer; in the case of the non-medical college students, 29.5% of the respondents marked the correct answer (Figure 3).

Vitamin D is synthesized with the help of the sun's rays; however, it is dependent on the environmental conditions prevailing at any given time. The correct answer to the presented question was given by 90.2% of the ŚUM students and 76.7% of the UE students (Figure 4).

In the following question, the correct answers were absorption through the skin and the oral route – this was the answer given by the majority of students from the two universities, 76.9% and 40.3%, respectively (Figure 5).

The majority of the ŚUM respondents, 67.1%, believe they know the health consequences of a deficiency of this vitamin. The remainder do not know the consequences of insufficient concentrations of this vitamin. Nonetheless, among the UE respondents, 32.6% gave the correct answer (Figure 6).

A large discrepancy in the results was observed in the question about supplementation. 65.7% of the ŚUM respondents know when to supplement this vitamin, while 34.3% do not have adequate knowledge on the subject. In contrast, the opposite is true for the UE students, where the results are as follows: 27.9% have knowledge of when to supplement vitamin D, and 72.1% have no such knowledge (Figure 7)

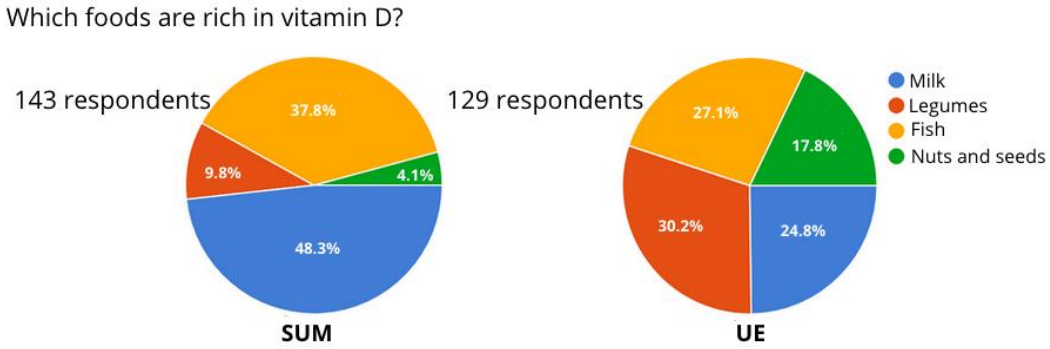

Fig. 2. Food sources of vitamin D.
Ryc. 2. Źródła witaminy D w pożywieniu.

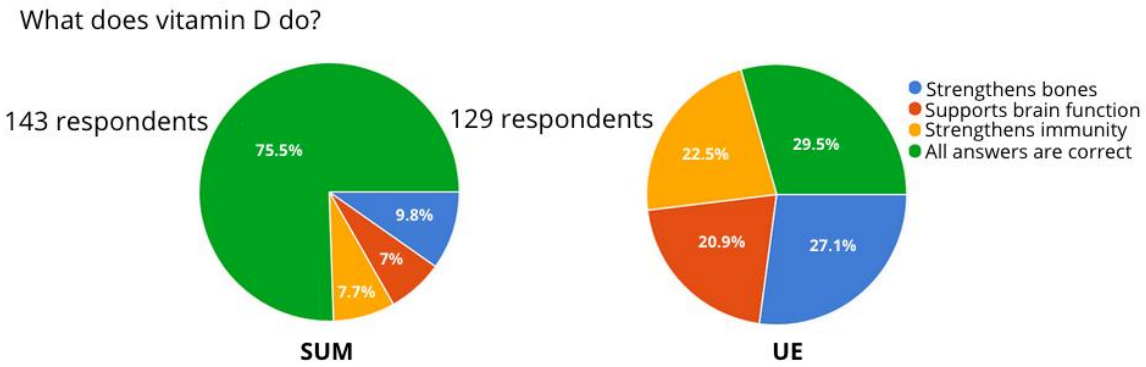

Fig. 3. Positive effects of vitamin D on the body.
Ryc. 3. Pozytywny wpływ witaminy D na organizm.

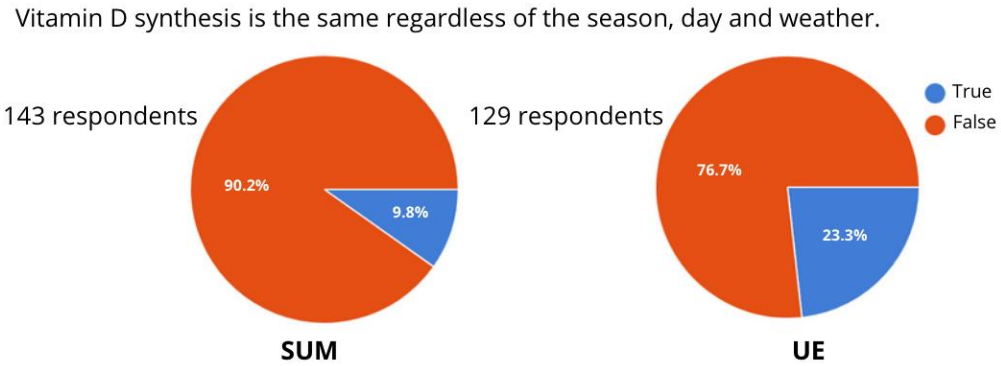

Fig. 4. Efficient dermal synthesis of vitamin D.
Ryc. 4. Efektywna synteza skórna witaminy D.

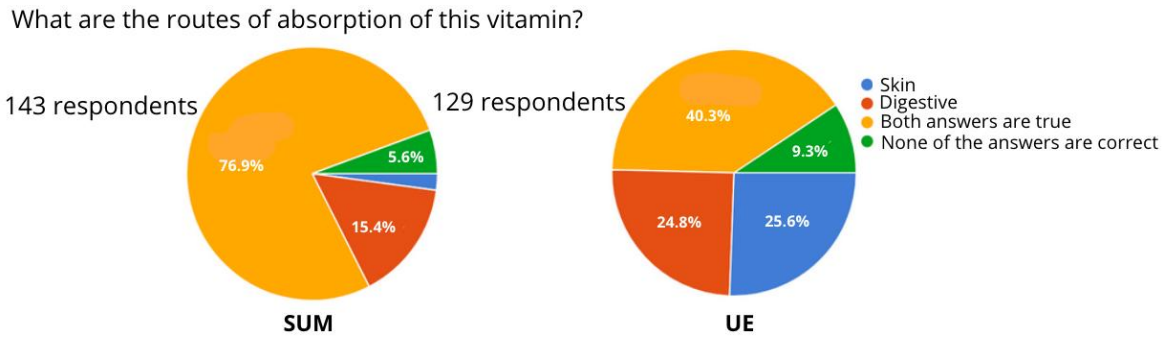

Fig. 5. Routes of vitamin D absorption as perceived by respondents.
Ryc. 5. Drogi wchłaniania witaminy D w opinii respondentów.

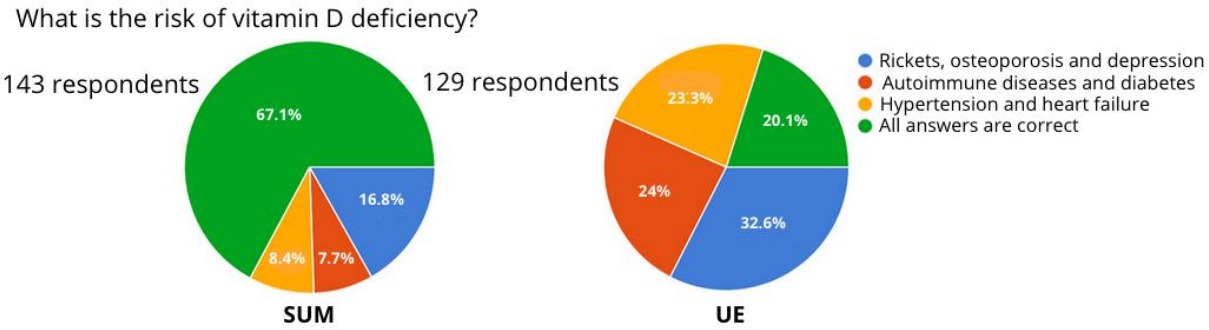

Fig. 6. Negative effects on the body due to vitamin D deficiency.
Ryc. 6. Negatywne skutki dla organizmu z powodu niedoboru witaminy D.

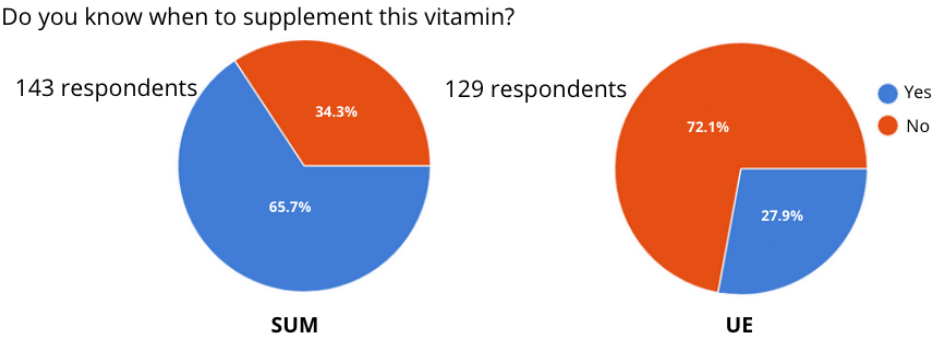

Fig. 7. Respondents' knowledge of need for supplementation.
Ryc. 7. Wiedza respondentów na temat konieczności suplementacji.

DISCUSSION

Nearly half of the respondents from the compared universities declared that they often encounter information about vitamin D. Despite this, more than 30% of all the respondents believe that the knowledge they have is insufficient. This means that some students have gaps in their knowledge. It is presumed that some students also spent a great deal of time studying the topic. The most common responses regarding the norms, deficiencies and excesses, were that the students knew the relevant norms, the effects of incorrect values, and when to supplement the vitamin. More than half of the students believe that inadequate values can pose risks to the body, and the majority (83.45%) are aware that the production of vitamin D is not the same at all times of the year, day and depends on the intensity of sunlight.

Comparing the results presented in the paper with those obtained by female students of the Department of Physical Rehabilitation at the Bronisław Czech University of Physical Education in Krakow [5], many similarities as well as differences were noted. More than half of the respondents (51.9%) declare knowledge of the physiological function of vitamin D_3, where in

the survey conducted on ŚUM and UE students, the respondents were found to have adequate knowledge on the subject. Both the study groups were mostly aware of the effects of hypovitaminosis and hypervitaminosis. In the comparative study, 58.3% of the respondents report ignorance about the need for cholecalciferol in different age groups, which is comparable to the results of the ŚUM students, but 20% lower than that of the UE students. The study also showed negligible knowledge among young adults about the role, sources and specificity of vitamin D_3.

The knowledge of the elderly population regarding the role of vitamin D for health maintenance and indications for supplementation [6] is not at a good level either. The cited study showed that the vast majority of respondents (73.7%) presented a low level of knowledge on the subject. The younger generation, on the other hand, is familiar with basic information related to this issue. More than half (51.3%) of those taking part in the survey did not use the necessary vitamin D supplementation at all. Similar results were obtained in a study conducted by the ŚUM [7], where 59% of the people knew about the main source of vitamin D, which is sunlight, and in the author's conducted study, such an answer was given by 76.9% of the ŚUM students and 40.4% of the UE ones. The main source of vitamin D, which is fish, was known to 58% of the respondents, where ¾ of the students associated with medical faculties gave the correct answer. The use of vitamin D supplements was declared by 45% of the survey participants – a result of almost half that of the ŚUM and EU students at 28% and 17.1%, respectively. The recommended daily supplementation dose of vitamin D, according to the Institute of Food and Nutrition (Instytut Żywności i Żywienia – IŻŻ), of 2018 amounting to 800–2000 IU for an adult, was correctly selected by 41% of the respondents – among the medical university students, the answers were at a similar level of 46.9%, while the non-medical university students have less knowledge (22.5%) in terms of the standards from 2020 also published by the IŻŻ [2].

Similar questions were also included in a study conducted by the University of Rzeszow [8], where when asked about the use of dietary supplements or medications containing vitamin D, 47.3% of the respondents answered in the affirmative – answers to this question differ as 28% of the ŚUM students and 17.1% of the UE students regularly take supplements containing vitamin D. When asked about their knowledge of the effects of vitamin D deficiency, 53.2% answered in the affirmative, which is close to the answers obtained by the ŚUM respondents (67.1%). Nevertheless, a significant difference can be seen with respect to those studying at the UE. Only 20.2% marked such an answer.

Other European countries are also conducting studies on vitamin D. An example is the United Kingdom (UK) [9], where only 43.5% of the survey participants said they take vitamin D supplementation. The most commonly reported reason for its use was insufficient sun exposure (57%). This is justified by the typical weather in the UK, health benefits (51%) and insufficient food intake containing adequate doses to meet the standard (46%). Most participants took supplements daily (77%), with the rest declaring a wide range of practices, including weekly (12%), less than weekly (5%), seasonally (1%) and other (5%). Dermal synthesis is dependent on the prevailing environmental conditions at any given time, i.e. season, time of day and weather. This question was answered correctly by 90.2% of the ŚUM students and 76.7% of the UE students.

Not only European countries, but also countries located in Asia are conducting a number of studies on vitamin D. This type of research is mainly conducted by Saudi Arabia, which has conducted a large number of studies in different age groups related to vitamin D. One of the most important studies was conducted by specialists from the Saudi Arabian Ministry of Health [10], a study in which few respondents were able to give a correct answer about the benefits of adequate vitamin D levels in the human body.

In a survey of Polish students, the majority (75.5%) of medical school students filling out the questionnaire gave the correct answer that the vitamin strengthens bones and the immune system, as well as supports proper brain function. A big difference is evident in the use of supplementation as all the respondents (100%) from Saudi Arabia declared that they did not take vitamin D supplements, which may be related to the country's geographic location, while in Poland 46.2% and 55.8% of medical and non-medical university students, respectively, do not use oral supplementation. In the pre-discussed articles from various scientific centers around the world and in the author's own research, it can be noted that knowledge regarding this vitamin is at an insufficient level in Europe, in contrast to Asian countries, i.e. Saudi Arabia, where the level of declared knowledge is higher. It should be noted, however, that all the studies were conducted on different research and age groups. The large differences in the results between the studies show how much of a lack of interest there is in this vitamin. In particular, the attitude of medical students is extremely important since they are the ones who have the most knowledge to pass on to patients, and the author's research shows that some students do not think they have adequate knowledge related to this vitamin. This indicates that not enough time has been spent on the subject, and therefore the knowledge gaps should be filled. It also seems necessary for state institutions to take measures

to change the eating habits of the population by introducing the subject of nutrition education in schools from an early age.

A proper diet can contribute in the future to reducing morbidity and mortality from many diseases of civilization, categorized as diet-related diseases, while the demonstrated passivity towards the possibility of prevention and treatment of hypovitaminosis among the studied population indicates the need to increase public awareness, with the aim of preventing systemic pathologies.

Studies conducted in Poland in recent years indicate that the level of public knowledge about vitamin D is low. Some people do not know basic information about the functions, sources, risks and supplementation of vitamin D. Few people are aware that vitamin D deficiency can have serious health consequences, i.e. osteoporosis, rickets, heart disease or cancer.

The study shows that there is a serious problem related to the lack of knowledge about hypovitaminosis D. The participants are unaware of the negative consequences of deficiencies in this vitamin, which can result from inadequate dietary habits. In addition, the study participants showed low awareness of the importance of sun exposure and vitamin D supplementation.

CONCLUSIONS

Based on the analysis of the obtained results and all the relevant aspects of the covered topic, the following conclusions were drawn:

1. Students of the ŚUM mostly have knowledge based on the latest research and scientific reports, compared to students of the UE.
2. The students of ŚUM mostly gave correct answers to questions related to vitamin D biosynthesis, dependent on environmental conditions and the Polish latitude.
3. Research has shown that non-medical university students' knowledge about vitamin D is insufficient. To effectively counteract this issue, various educational activities should be conducted, targeting all age groups, with a particular focus on the elderly.
4. It is necessary to both increase the number of informational campaigns and extend their reach. Education should take place in schools by including the topic of vitamins in the curriculum of primary and secondary schools, as well as in medical facilities such as clinics, hospitals, and pharmacies to ensure that patients have access to information about vitamin D and the possibilities of its testing and supplementation.

Authors' contribution

Study design – W. Ficoń, R. Polaniak, B. Całyniuk
Data collection – W. Ficoń
Data interpretation – W. Ficoń
Statistical analysis – W. Ficoń
Manuscript preparation – W. Ficoń, R. Polaniak
Literature research – W. Ficoń
Final approval of the version to be published – W. Ficoń, R. Polaniak, B. Całyniuk

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PRACA ORYGINALNA
ORIGINAL PAPER

Analysis of echocardiographic parameters suggestive of pulmonary hypertension in patients with heart failure with preserved ejection fraction and assessment of clinical features favoring development of the PH-phenotype

Analiza parametrów echokardiograficznych wskazujących na nadciśnienie płucne u pacjentów z niewydolnością serca z zachowaną frakcją wyrzutową oraz ocena cech klinicznych sprzyjających rozwojowi fenotypu PH

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ABSTRACT

INTRODUCTION: Heart failure with preserved ejection fraction (HFpEF) is characterized by left ventricle (LV) diastolic dysfunction. Impaired diastolic function induces pulmonary congestion and leads to postcapillary pulmonary hypertension (PH), which is an important contributor to clinical deterioration and increased mortality.

MATERIAL AND METHODS: A retrospective one-centre analysis of 63 consecutive patients hospitalized due to HFpEF was performed. The study group was divided according to the echocardiographic probability of PH using tricuspid regurgitation peak velocity (TRV) into two groups: TRV ≥ 2.8 m/s – with an increased probability of PH (n = 15 (23.8%); females: 3 (20%); mean age 72.7 ± 10.8) and TRV < 2.8 m/s – with a low probability of PH (n = 48 (76.2%); females: 25 (52.1%); mean age 72.3 ± 13.7). The clinical data, transthoracic echocardiography (TTE) parameters and laboratory tests were analyzed.

RESULTS: The group of patients with an increased probability of PH was characterized by more severe HF symptoms, more frequent fatigue ($p = 0.03$) and the occurrence of ankle swelling ($p < 0.01$). Analysis of the baseline data revealed a trend towards a greater incidence of atrial fibrillation (AF; $p = 0.08$) in this group. The patients who had TRV ≥ 2.8 m/s had a larger left atrial area ($p < 0.001$), a higher E/A ratio ($p < 0.001$) with borderline differences in the left ventricular mass index (LVMI; $p = 0.06$) and left ventricular ejection fraction (LVEF; $p = 0.07$).

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CONCLUSIONS: About 25% of patients with HFpEF, mostly males, present with moderate features of PH that are associated with more advanced LV and left atrium (LA) remodeling and dysfunction. However, they are not reflected in the classic comorbidities, with the exception of AF.

KEYWORDS

heart failure, heart failure with preserved ejection fraction, postcapillary pulmonary hypertension, chronic atrial fibrillation

STRESZCZENIE

WPROWADZENIE: Niewydolność serca z zachowaną frakcją wyrzutową (*heart failure with preserved ejection fraction* – HFpEF) charakteryzuje się dysfunkcją rozkurczową lewej komory (*left ventricle* – LV). Zaburzenia funkcji rozkurczowej powodują zator płucny i prowadzą do zakapilarnego nadciśnienia płucnego (*pulmonary hypertension* – PH), które jest istotnym czynnikiem pogorszenia stanu klinicznego i zwiększonej śmiertelności.
MATERIAŁ I METODY: Przeprowadzono retrospektywną analizę jednoośrodkową, obejmującą 63 pacjentów hospitalizowanych z powodu HFpEF. Grupę badaną podzielono w zależności od echokardiograficznego prawdopodobieństwa PH na podstawie szczytowej prędkości niedomykalności zastawki trójdzielnej (*tricuspid regurgitation velocity* – TRV) na dwie grupy: TRV ≥ 2,8 m/s – zwiększone prawdopodobieństwo PH (n = 15 (23,8%); kobiety: 3 (20%); średni wiek 72,7 ± 10,8) oraz TRV < 2,8 m/s – niskie prawdopodobieństwo PH (n = 48 (76,2%); kobiety: 25 (52,1%); średni wiek 72,3 ± 13,7). Przeanalizowano dane kliniczne, parametry echokardiograficzne (*transthoracic echocardiography* – TTE) oraz wyniki badań laboratoryjnych.
WYNIKI: Grupa pacjentów ze zwiększonym prawdopodobieństwem PH cechowała się bardziej nasilonymi objawami HF, częstszym odczuwaniem zmęczenia (p = 0,03) oraz występowaniem obrzęków wokół kostek (p < 0,01). Analiza danych wyjściowych wskazała na tendencję do częstszego migotania przedsionków (*atrial fibrillation* – AF; p = 0,08) w tej grupie. U pacjentów z TRV ≥ 2,8 m/s obserwowano większą powierzchnię lewego przedsionka (p < 0,001), wyższy wskaźnik E/A (p < 0,001), a także graniczne różnice we wskaźniku masy lewej komory (*left ventricular mass index* – LVMI; p = 0,06) oraz frakcji wyrzutowej lewej komory (*left ventricular ejection fraction* – LVEF; p = 0,07).
WNIOSKI: U około 25% pacjentów z HFpEF, w większości mężczyzn, występują umiarkowane objawy PH, które wiążą się z bardziej zaawansowaną przebudową i dysfunkcją LV oraz lewego przedsionka (*left atrium* – LA). Nie znajdują one jednak odzwierciedlenia w typowych chorobach współistniejących, z wyjątkiem AF.

SŁOWA KLUCZOWE

niewydolność serca, niewydolność serca z zachowaną frakcją wyrzutową, postkapilarne nadciśnienie płucne, przewlekłe migotanie przedsionków

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a complex condition characterized by left ventricular diastolic dysfunction with an left ventricular ejection fraction (LVEF) ≥ 50% [1]. Impaired LV diastolic function leads to inadequate ventricular filling. Prolonged elevation of pressure in the left of the heart and pulmonary veins as well as the presence of inflammation significantly impedes proper relaxation of vascular smooth muscles and leads to their stiffness [2,3]. Consequently, this progressive disturbance prompts pathological remodeling of the pulmonary arteries and leads to increased pulmonary vascular resistance. This cascade results in the development of pulmonary hypertension (PH), characterized by both pre- and sub-capillary features [3,4].
Furthermore, because of PH the right ventricle (RV) undergoes hypertrophy as an adaptive response to sustain normal ejection capability. Prolonged exposure to this increased workload can induce fibrotic alterations in the RV muscle, subsequently diminishing its contractile function, which in the long term may lead to RV failure. Together, these hemodynamic changes in HFpEF impede blood circulation, negatively impact cardiac function and eventually lead to clinical symptoms such as dyspnea, fatigue as well as an increased risk of cardiovascular complications [3,5].
Right heart catheterization (RHC) is the gold standard method for confirming the diagnosis of PH. However, by means of transthoracic echocardiography (TTE), we can assess in a non-invasive way the likelihood of PH and further determine if the patient needs RHC. There are numerous echocardiographic signs suggestive of PH. Considering the structural and functional remodeling of the myocardium, assessment of the peak tricuspid regurgitation volume (TRV) is recommended [6]. The presence of TRV ≥ 2.8 m/s indicates at least an intermediate probability of PH. Nonetheless, the presence or absence of PH cannot be reliably determined by TRV alone. TRV < 2.8 m/s without any additional echocardiographic signs suggests a low probability of PH. To alter the level of PH likelihood, the presence of signs from at least two echocardiographic categories regarding the ventricles, pulmonary artery, vena cava inferior (VCI) or right atrium (RA) is required [7]. A tricuspid regurgitation

(TR) peak velocity > 2.8 m/s is particularly relevant regarding the assessment of HFpEF patients because it also indicates increased pulmonary artery systolic pressure and is one of the major as well as the most commonly used indirect markers of LV diastolic dysfunction [8].

The majority of studies have investigated the connections between PH in patients with HF with reduced EF (HFrEF). Nevertheless, considering the possible alternative pathways contributing to the onset and development of PH in patients with HFpEF, further investigation and analysis of the clinical and echocardiographic features of PH among HFpEF patients is still limited, yet necessary.

The main objective of this study was to evaluate the prevalence of patients with at least an intermediate probability of PH in a group of patients with HFpEF, as well as assess the clinical and echocardiographic features in this group.

MATERIAL AND METHODS

Our analysis included 63 patients (aged 72 ± 13 years) on optimal medical therapy who were hospitalized in the 1st Department of Cardiology, Medical University of Silesia in Katowice European Reference Network for Rare and Low Prevalence Complex of the Heart (ERN GUARD Heart) between 02.2022–12.2022. A retrospective database was created from electronic medical records and included the assessment for HF symptoms and signs, typical clinical demographics, medications taken, in addition to the results of diagnostic laboratory tests and the available TTE parameters.

All the patients satisfied the predefined inclusion criteria of HFpEF – the presence of symptoms and signs of HF, LVEF ≥ 50% and objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides [9]. We excluded from the study patients with HFrEF, heart failure with mildly reduced ejection fraction (HFmrEF) or heart failure with improved ejection fraction (HFimpEF), acute coronary syndrome, a congenital heart defect, infective endocarditis, known pericardial constriction, infiltrative or hypertrophic cardiomyopathy, a previous heart operation, as well as patients scheduled for valve surgery.

Subsequently, the patients were divided following their TTE results into two groups based on their TRV value: a group with an increased probability of PH – with TRV ≥ 2.8 m/s (n = 15; 23.8%), and a group with a low probability of PH – with TRV < 2.8 m/s without any additional TTE signs (n = 48, 76.2%) (Figure 1).

Fig. 1. Flowchart representing course of the study. HFpEF – heart failure with preserved ejection fraction; PH – pulmonary hypertension.

Then we collected, analyzed and compared the available data regarding additional echocardiographic signs suggestive of PH as proposed by the European Society of Cardiology (ESC) Guidelines [10].

Assessment of the additional TTE parameters in the group of patients with an increased likelihood of PH show that 4 patients (26.7%) had 1 additional TTE sign suggestive of PH, 5 (33%) had 2 TTE signs, and 2 patients (13.3%) had 3 additional TTE signs.

The patients from the group with TRV < 2.8 m/s did not exhibit any additional sign from the ≥ 2 echocardiographic categories that could alter the level of probability of PH; therefore, all of them presented a low echocardiographic probability of PH.

Definitions

- HFpEF was defined as the presence of HF symptoms and signs, with evidence of structural and/or functional cardiac abnormalities and/or raised natriuretic peptides with an LVEF ≥ 50%.
- Increased probability of PH was defined as the presence of TRV ≥ 2.8 m/s.
- Low probability of PH was determined by the presence of TRV < 2.8 m/s without any additional echocardiographic signs.
- Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 documented or inferred for > 3 months.

- Chronic atrial fibrillation (AF) was defined as patients with persistent AF, which is AF persisting continuously for > 7 days, including episodes interrupted by cardioversion (pharmacological or electrical) after ≥ 7 days as well as permanent AF, which is AF that has been accepted by the patient and physician and no further attempts will be made to restore maintaining sinus rhythm [11].
- VCI dilatation was defined as a VCI diameter > 21 mm.
- Left ventricular end-diastolic pressure (LVEDP) was estimated non-invasively and calculated using an equation by Abd-El-Aziz [12], which employs the measurement of blood pressure and EF.

Statistics

To analyze the distribution for quantitative data, the Shapiro-Wilk test was used. Quantitative data with normal distribution were compared using Student's t-test and presented as the mean ± standard deviation (SD). On the other hand, quantitative data with a skewed distribution were compared by means of the Mann-Whitney U test and presented as medians. The statistical significance of the qualitative values was determined by Pearson's Chi-squared test. Statistical significance was considered for p-values < 0.05. The analysis was performed with STATISTICA 13.3 PL Software by StatSoft, Medical University of Silesia, Katowice, Poland.

RESULTS

The statistical analysis revealed no statistically significant differences between the groups in terms of age, height, weight, body mass index (BMI) or body surface area (BSA; Table I). However, the patients from the group with a low probability of PH had a tendency towards greater values of BMI, but it did not reach statistical significance (p = 0.06).

In terms of the clinical assessment, the patients from the group with the greater probability of PH exhibited a more pronounced severity of symptoms. Notably, this particular group displayed a statistically significantly greater prevalence of fatigue and ankle oedema compared to the group with the low likelihood of PH (Figure 2).

The baseline characteristics analysis revealed that the incidence of hypertension, diabetes mellitus, coronary artery disease, dyslipidemia, and chronic kidney disease exhibited no statistically significant differences between the studied groups. Nevertheless, it is noteworthy that the group with the increased probability of PH demonstrated a tendency towards a higher prevalence of AF (p = 0.08), without differences regarding its clinical types (Table II).

Considering pharmacological treatment, it was found that in the group with the increased likelihood of PH, loop diuretics (p = 0.001) and sodium glucose-linked transporter 2 (SGLT-2) inhibitors (p = 0.028) were prescribed more often in comparison to the group with the low probability of PH. Moreover, significant differences were found in the number of patients treated with novel oral anticoagulants (NOACs). Similarly, these medications were used more frequently in the group with the greater probability of PH (p = 0.017). None of the patients were taking drugs registered for the treatment of PH, such as phosphodiesterase-5--inhibitors, an endothelin receptor antagonist or prostanoids (Table III).

Table I. Baseline characteristics comparison between groups of patients with increased probability of pulmonary hypertension (PH) and low probability of PH

Demographic and anthropometric parameters	HFpEF (n = 63, F/M 40/23, mean age 72 ± 13)		p-value
	increased PH probability (n = 15/23.8%)	low probability of PH (n = 48/76.2%)	
Sex: females (n/%)	3/20	25/52	**0.029**
Age [y]	72.2 ± 10.8	72.3 ± 74.5	0.890
Height [cm]	166.8 ± 9.9	164.8 ± 164.0	0.340
Weight [kg]	75.0 ± 17.1	80.5 ± 80.0	0.169
BMI [kg/m^2]	26.7 ± 4.6	29.6 ± 28.7	**0.063**
BSA [m^2]	1.9 ± 0.3	1.9 ± 1.9	0.460

HFpEF – heart failure with preserved ejection fraction; F – female; M – male; BMI – body mass index; BSA – body surface area.

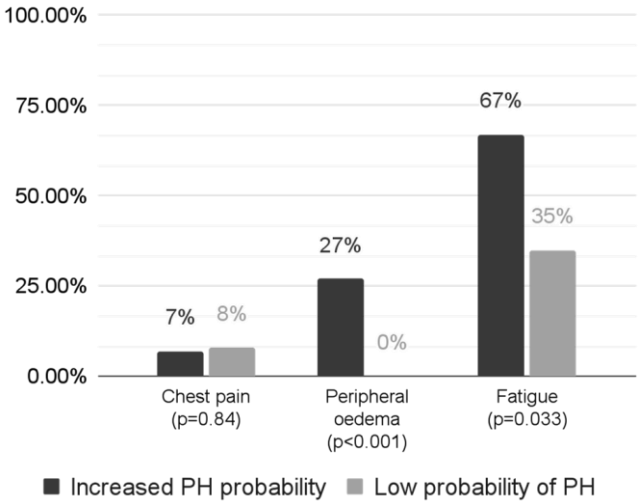

Fig. 2. Comparison of presented symptoms of heart failure in patients with increased pulmonary hypertension (PH) probability and low probability of PH.

Table II. Comparison of comorbidities and risk factors between groups of patients with increased pulmonary hypertension (PH) probability and low probability of PH

Clinical parameters	Increased PH probability (n = 15)	Low probability of PH (n = 48)	p-value
	n (%)	n (%)	
Hypertension	11 (73.3)	37 (77.1)	0.766
Diabetes mellitus	7 (46.7)	21 (43.8)	0.843
AF – any type	7 (46.7)	11 (22.9)	**0.076**
Paroxysmal AF	4 (26.7)	7 (14.6)	0.282
Chronic AF	3 (20)	4 (8.3)	0.209
Coronary artery disease	7 (46.7)	17 (35.4)	0.434
Dyslipidemia	7 (46.7)	32 (66.7)	0.164
Chronic kidney disease (eGFR < 60 mL/min/1.73 m^2)	7 (46.7)	16 (33.3)	0.349

AF – atrial fibrillation; eGFR – estimated glomerular filtration rate.

Table III. Comparison of selected medications taken between groups of patients with increased pulmonary hypertension (PH) probability and low probability of PH

Pharmacological treatment	Increased probability of PH (n = 15)	Low probability of PH (n = 48)	p-value
	n (%)	n (%)	
ACEI	9 (60)	26 (54.2)	0.691
ARB	0	5 (10.4)	0.193
Beta-blockers	7 (46.7)	23 (47.9)	0.933
Ca-blockers	3 (20)	14 (29.2)	0.485
MRA	8 (53.3)	12 (25)	0.141
ARNI	0	4 (8.3)	0.248
Loop diuretics	12 (80)	16 (33.3)	**0.001**
Thiazides	0	3 (6.3)	0.321
SGLT-2 inhibitors	4 (26.7)	3 (6.3)	**0.028**
Statins	11 (73.3)	37 (77.1)	0.766
Antiplatelet drugs	6 (40)	28 (58.3)	0.214
NOACs	7 (46.7)	8 (16.7)	**0.017**

ACEI – angiotensin-converting-enzyme inhibitors; ARB – angiotensin receptor blockers; Ca-blockers – calcium channel blockers; MRA – mineralocorticoid receptor antagonist; ARNI – angiotensin receptor-neprilysin inhibitor; SGLT-2 inhibitors – sodium glucose-linked transporter 2 inhibitors; NOACs – novel oral anticoagulants.

The mean values of the selected diagnostic laboratory tests were generally within the established reference ranges, except for N-terminal pro-B-type natriuretic peptide (NT-proBNP), which exceeded the threshold in both study groups. In the patients with an increased probability of PH, the NT-proBNP levels were 1435.9 ± 1404.2 pg/ml, compared to 1143.8 ± 1144 pg/ml in those with a low probability of PH ($p = 0.139$). The laboratory results were comparable in both groups.

Statistically significant differences were observed among the echocardiographic parameters, notably in the measurements of the right atrial (RA; $p < 0.001$) and left atrial (LA; $p < 0.001$) areas, as well as the left ventricular end-diastolic diameter (LVEDD; $p = 0.013$) and left ventricular end-systolic diameter (LVESD; $p = 0.01$).

There were also significant differences between the groups regarding TTE abnormalities consistent with the presence of HFpEF, such as the left ventricular mass index (LVMI; $p = 0.057$), the relative wall thickness (RWT; $p = 0.063$), E-wave ($p < 0.001$) and E/A ratio ($p < 0.001$) – it demonstrated greater values in the group with the increased probability of PH in comparison to the group with the low likelihood of PH.

Owing to the baseline structure and objectives of our study, there was a significant statistical difference regarding the measurements of TRV ($p < 0.001$). Furthermore, in the group with the increased probability of PH, the VCI was dilated more frequently than in the group with the low PH probability ($p = 0.01$). To estimate the right ventricular systolic pressure (RVSP) a simplified Bernoulli equation was used – it utilizes the TRV value and estimates right atrial pressure based on VCI measurements. Therefore, RVSP similarly demonstrated greater values in the group with the increased likelihood of PH ($p < 0.001$; Table IV).

The assessment of significant valvular defects in both the research groups revealed comparable results. Nonetheless, statistically significant differences were observed between these groups in terms of the presence of severe TR. It was more frequent in the group with the increased probability of PH in comparison to the group with the low likelihood of PH ($p < 0.001$).

Table IV. Comparison of echocardiographic parameters between patients with increased pulmonary hypertension (PH) probability and low probability of PH

Echocardiographic parameters	Increased PH probability (n = 15)	Low probability of PH (n = 48)	p-value
1	2	3	4
IVS thickness [mm]	13.8 ± 3.2	14.8 ± 15	0.085
PWT [mm]	11.3 ± 1.6	11.6 ± 11	0.928
LVEF [%]	55.1 ± 7	57.4 ± 55	**0.071**
LVESD [mm]	31.1 ± 6	26.5 ± 26	**0.010**
LVEDD [mm]	50 ± 5.1	45.8 ± 46	**0.013**
LVEDP [mmHg]	22.0 ± 4.1	23.7 ± 21.7	0.825
LVMI [g/m²]	138.4 ± 37.7	119.2 ± 115.3	**0.057**
LA area [cm2]	29.5 ± 5.7	22.4 ± 21.3	**< 0.001**
RA area [cm2]	26.8 ± 9.7	16.7 ± 15	**< 0.001**
RVOT in PLAX [mm]	32.5 ± 4.9	30 ± 30	0.083
RWT [g/m²]	0.5 ± 0.1	0.5 ± 0.5	**0.063**
Mitral valve			
Presence of severe MR	1 (6.7%)	0	0.071
E-wave [m/s]	1.2 ± 0.5	0.8 ± 0.8	**< 0.001**
IVS thickness [mm]	13.8 ± 3.2	14.8 ± 15	0.085
PWT [mm]	11.3 ± 1.6	11.6 ± 11	0.928
A-wave [m/s]	0.8 ± 0.4	1.0 ± 0.9	0.500
E/A ratio	2.0 ± 1.4	0.9 ± 0.8	**< 0.001**
Aortic valve			
Presence of severe AS	3 (20%)	19 (39.6%)	0.165
Ao Vmax [m/s]	3.0 ± 1.6	3.9 ± 4.1	**0.044**
PG mean [mmHg]	39.3 ± 21.1	40.4 ± 42.0	0.611
AVA [cm²]	0.8 ± 0.3	2.5 ± 0.8	0.524

cd. tab. IV

1	2	3	4
Tricuspid valve			
Presence of severe TR	8 (53.3%)	2 (4.2%)	**< 0.001**
TRV [m/s]	3.4 ± 0.4	0.5 ± 0.2	**< 0.001**
RVSP [mmHg]	53.5 ± 13.5	31.7 ± 31.5	**< 0.001**
Pulmonary valve			
PA Vmax [m/s]	0.8 ± 0.3	0.9 ± 26.5	0.412
AcT [ms]	106.3 ± 31.3	108.9 ± 110	0.439
VCI dilatation	4 (26.7%)	2 (4.2%)	**0.010**

IVS – interventricular septum; PWT – posterior wall thickness; LVEF – left ventricular ejection fraction; LVESD – left ventricular end-systolic diameter; LVEDD – left ventricular end-diastolic diameter; LVEDP – left ventricular end-diastolic pressure; LVMI – left ventricular mass index; LA – left atrium; RA – right atrium; RVOT – right ventricular outflow tract; PLAX – parasternal long axis; RWT – relative wall thickness; MR – mitral regurgitation; AS – aortic stenosis; Ao Vmax – maximum aortic velocity; PG mean – peak-to-mean pressure gradient; AVA – aortic valve area; TR – tricuspid regurgitation; TRV – tricuspid regurgitation peak velocity; RVSP – right ventricular systolic pressure; PA Vmax – pulmonary artery maximum velocity; AcT – acceleration time; VCI – vena cava inferior.

DISCUSSION

Our study showed that among patients with HFpEF, nearly 24% present with at least an intermediate probability of PH. Studies have reported a wide range of prevalence rates, which often depend on various factors including the study population, diagnostic criteria or the specific methods used to identify PH. In the trial PARAGON-HF [13], which tested the efficacy of sacubitril-valsartan on patients with HFpEF, the prevalence of PH based on echocardiographic criteria reached 31%. Similarly, in the TOPCAT study [14] among patients with HFpEF and a measurable TR jet, the peak velocity was elevated over 2.9 m/s in 36% of patients. However, the estimated prevalence can be even greater and reach up to 80% of patients with HFpEF when employing echocardiographic estimates of pulmonary artery systolic pressure (PASP) ≥ 35 mmHg to define PH [15]. Nevertheless, it is noteworthy that Leung et al. [16] conducted a study among patients with HFpEF who underwent RHC – the prevalence of PH, defined as a mean pulmonary artery pressure > 25 mmHg, reached 52.5%.

The prevalence of comorbidities in our research was comparable in both groups. The results are similar to other studies [15]. However, we found a tendency towards a greater BMI in the group of patients with HFpEF and a low probability of PH in comparison to the group with the increased likelihood of PH ($p = 0.063$). In a study by Lam et al. [15], the mean BMI was also greater in the HFpEF group without PH than in the group with PH, nonetheless, it did not reach statistical significance. Nevertheless, studies indicate the presence of an obesity-related HFpEF phenotype – obese patients with HFpEF exhibited greater values of pulmonary capillary wedge pressure (PCWP) than in the non-obese group with HFpEF [17].

In our study the individuals with the increased likelihood of PH were more commonly diagnosed with AF, irrespective of its type, compared to the group with the low probability of PH although it did not attain statistical significance ($p = 0.076$). In HFpEF, because of the diastolic dysfunction of the LV and an increased LV filling pressure, the LA undergoes stiffening, dilation and remodeling, increasing its susceptibility to fostering the development of AF [18]. Therefore, it was not surprising that while analyzing the TTE parameters in the patients with the greater probability of PH, we observed a larger LA area ($p < 0.001$), as well as RA area ($p < 0.001$) compared to the group with the low likelihood of PH. These alterations in patients with HFpEF often result in an exacerbation of symptoms, the development of pulmonary vascular dysfunction, a more pronounced RV dysfunction, a reduced exercise tolerance and finally adverse outcomes [19,20]. Hence, the conclusion is that the development of AF may be an indicator of a more advanced stage of HFpEF in the group with the increased probability of PH.

Furthermore, a meta-analysis of 10 studies regarding different phenotypes of HFpEF showed that, among others, the presence of AF and a high BMI were related to phenotypes with adverse outcomes [21].

In our study, the patients with the greater probability of PH more frequently exhibited HF symptoms – especially fatigue ($p = 0.033$), ankle swelling ($p < 0.001$) and dyspnea ($p = 0.091$), compared to the group with the low probability of PH. Scientific evidence suggests that in patients with HFpEF, despite slight differences at rest and a normal LVEF, systolic and diastolic function dramatically deteriorates during exercise, which is manifested by a decreased exercise capacity [22]. What is more, in the meta-analysis mentioned previously, a worse symptom severity was one of the key factors in identifying HFpEF phenotypes associated with adverse outcomes [21].

In accordance with the inclusion criteria, all the participants had an LVEF ≥ 50%; however, upon comparing the mean values at the threshold of statistical significance, we observed that the value of

LVEF in the group of patients with the greater probability of PH was slightly lower than in the group with the low likelihood (p = 0.071). In HFpEF, despite having a normal EF, patients display impairments beyond diastolic dysfunction and evidence suggests abnormal LV systolic performance, which subtly impacts cardiac output and LV filling pressures [22].

Despite the lack of statistical significance, the group with the greater probability of PH had higher values of LVMI (p = 0.057), RWT (p = 0.063). The mean values of these parameters surpass the threshold values in both the examined groups, which also points to the presence of concentric LV hypertrophy related to HFpEF. Nonetheless, in the group of patients with HFpEF and the greater likelihood of PH, the mean values of LVEDD (p = 0.013) and LVESD (p = 0.01) were statistically significantly greater compared to the patients in the group without PH. This might suggest a more severe state of dysfunction and remodeling of the heart among patients with HFpEF and an increased probability of PH.

In our study, the patients with the increased probability of PH statistically more frequently exhibited severe TR (p < 0.001). It might be associated with the development of the atrial functional type of this regurgitation, which in our study was reflected by an enlarged RA and the greater prevalence of AF in this group. However, in HFpEF the presence of a diastolic dysfunction of LV, improper relaxation and remodeling of the left of the heart with further pulmonary vascular disease consequently leads to pressure overload of the RV, affects its geometry and function, thereby contributing to the development of TR [3,5].

In comparison to the group with a low probability of PH, the patients in the group with an increased likelihood of PH used loop diuretics (p = 0.001) and SGLT-2 inhibitors (p = 0.028) statistically more frequently. This inclination is probably connected to the heightened symptomatology and signs of pulmonary congestion within this subset. Additionally, a more prevalent use of NOACs (p = 0.017) is likely linked to more frequent occurrences of AF in this group, as mentioned previously.

Limitations

There are numerous echocardiographic signs suggestive of PH. Considering the functional and structural remodeling of the myocardium, we applied the simplification associated with the definition of HFpEF; hence, the idea of evaluating patients with an elevated TRV that present with features of HF. The current study was conducted using a retrospective analysis with all the inherent limitations of a single center. Because of the retrospective nature of the study, we did not have all the available parameters regarding TTE. Therefore, we were unable to compare every given value and create detailed cut-off points because of the limited amount of data. Furthermore, some of the TTE signs may be dependent on the patient's state of hydration.

To determine the presence of PH, it is necessary to perform RHC – it would be intriguing to examine these findings within the context of our study to see if they align with echocardiographic data or yield different outcomes.

CONCLUSIONS

About 25% of HFpEF patients exhibit intermediate echocardiographic features of PH that are associated with more severe remodeling and dysfunction of the LV and LA. Features of PH are associated with AF and are not reflected in the classic comorbidities.

Authors' contribution

Study design – J. Dołęga, K. Ciekot, K. Mizia-Stec
Data collection – J. Dołęga, K. Ciekot, A. Owczarska, G. Majta, M. Macnar, K. Marcinkiewicz
Data interpretation – J. Dołęga, K. Ciekot, A. Owczarska, G. Majta, M. Macnar, K. Marcinkiewicz
Statistical analysis – K. Ciekot, J. Dołęga
Manuscript preparation – J. Dołęga, K. Ciekot, A. Owczarska, G. Majta, M. Macnar, K. Marcinkiewicz
Literature research – J. Dołęga, K. Ciekot
Final approval of the version to be published – K. Mizia-Stec

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OPIS PRZYPADKU
CASE REPORT

Hidden umbilical anomalies: case reports of newborns with a persistent urachus and a persistent vitellointestinal duct

Ukryte anomalie pępkowe: opis przypadków noworodków z przetrwałym moczownikiem i przetrwałym przewodem żółtkowo-jelitowym

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ABSTRACT

INTRODUCTION: Anomalies in the umbilical region of newborns encompass a range of congenital malformations that require careful diagnosis. These conditions may lead to delayed healing of the umbilical stump, discharge from the navel, and pose challenges for pediatricians. Among these, vitellointestinal duct (VID) anomalies are the most common, occurring in approximately 2–3% of the population. The VID, an embryonic structure connecting the yolk sac to the primitive midgut, normally regresses during development. Failure of this process can result in various anomalies, the most common being Meckel's diverticulum. Similarly, urachal anomalies arise when embryonic urachus persists, potentially presenting as abnormalities at the umbilicus.

CASE REPORTS: A 6-day-old male newborn with a draining fistula at the umbilicus was transferred to our institution with a suspected diagnosis of persistent urachus. After admission, the visible fistula was catheterized under ultrasound guidance, revealing a connection to the intestinal loops. This finding indicated a diagnosis of a persistent VID, which was subsequently excised. Another patient was a 15-day-old female newborn with a bladder defect detected during a prenatal ultrasound examination. An everted patent urachus was diagnosed after birth, which was subsequently treated by means of surgical excision.

CONCLUSIONS: Abnormalities in the umbilicus may raise the suspicion of persistent fetal structures. A thorough physical examination, supplemented by ultrasound and catheterization, can effectively make the correct diagnosis. Surgical treatment is recommended, involving resection of the persistent urachus or resection of the persistent VID with the bowel fragment.

KEYWORDS

umbilical fistula, omphalomesenteric duct remnant, patent vitellointestinal duct, congenital malformations, patent urachus

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STRESZCZENIE

WPROWADZENIE: Nieprawidłowości w okolicy pępka u noworodków obejmują szereg wrodzonych wad rozwojowych, które wymagają dokładnej diagnostyki. Stany te mogą prowadzić do opóźnionego oddzielenia kikuta pępowiny, wycieku z pępka, a także stanowić wyzwanie diagnostyczne dla pediatrów. Spośród nich anomalie przewodu żółtkowo-jelitowego (*vitellointestinal duct* – VID) należą do najczęstszych – występują u około 2–3% populacji. Przewód żółtkowo-jelitowy, struktura embrionalna łącząca pęcherzyk żółtkowy z pierwotnym jelitem środkowym, zwykle ulega regresji w trakcie rozwoju. Brak tego procesu może prowadzić do różnych nieprawidłowości, z których najczęstszą jest uchyłek Meckela. Podobnie anomalie moczownika powstają w wyniku przetrwania tej struktury zarodkowej, co może skutkować zmianami w obrębie pępka.

OPIS PRZYPADKÓW: 6-dniowy noworodek płci męskiej z przetoką drenującą w pępku został przetransportowany do naszego ośrodka z podejrzeniem przetrwałego moczownika. Przy przyjęciu widoczną przetokę cewnikowano pod kontrolą ultrasonografii, ujawniając połączenie z pętlami jelitowymi, co pozwoliło na rozpoznanie przetrwałego VID, który został chirurgicznie usunięty. U drugiego pacjenta, 15-dniowego noworodka płci żeńskiej z podejrzeniem wady pęcherza moczowego w badaniach prenatalnych, zdiagnozowano przetrwały moczownik, który poddano resekcji.

WNIOSKI: Nieprawidłowości pępkowe mogą budzić podejrzenie przetrwałych struktur płodowych. Dokładne badanie fizykalne, wspomagane ultrasonografią i cewnikowaniem, umożliwia przeprowadzenie precyzyjnej diagnostyki. Zalecane jest leczenie chirurgiczne, obejmujące resekcję przetrwałego moczownika lub resekcję przetrwałego VID z fragmentem jelita.

SŁOWA KLUCZOWE

przetoka pępkowa, pozostałość przewodu żółtkowo-jelitowego, drożny przewód żółtkowo-jelitowy, wady wrodzone, przetrwały moczownik

INTRODUCTION

The umbilicus, though a small structure, holds significant medical importance not only as a symbolic marker of birth, but also as a site where several fetal structures are present during development. These structures typically tend to involute, however, they may persist in some cases. The navel forms during the fourth week of fetal life with the occurrence of the embryonic plate. Initially, it appears as a primitive umbilical ring that consists of a connecting stalk, umbilical vessels, the vitelline duct, allantois, and loops of the intestine. Subsequently, it develops into the definitive cord, including one vein and two arteries suspended in Wharton's jelly. After birth, these structures obliterate and develop into ligaments [1]. Congenital malformations in the umbilical region are most commonly vitellointestinal duct (VID) anomalies affecting ca. 2–3% of the population, followed by urachal remnants (ca. 1%) [2,3]. While the prevalence of VID varies between 1 in 5000–8000, the prevalence of patent urachus is extremely rare, occurring in only 1–2 cases per 100 000 [4].

VID is defined as the embryonic connection between the yolk sac and the primitive midgut of the developing fetus. The anomaly occurs when these structures fail to resorb, the most frequent one being Meckel's diverticulum [5]. VID or its adjacent tissue can also contain ectopic mucosa, which may be found in pancreatic, gastric, duodenal or colonic tissue. Therefore, a thorough excision of the surrounding heterotopic tissue should be performed, along with histopathology examination [6]. The prolapse of the small bowel through the umbilical opening is considered to be a rare presentation of persistent VID [7].

Urachal anomalies occur when there is a persistence of embryonic urachal remnant without involution into the median umbilical ligament [2]. A study conducted in Canada reports a prevalence rate of approximately 1% in the general population. The preferred approach for managing patent urachus is surgical removal, even for asymptomatic remnants, due to the risk of future infection and potential malignancy [2,3].

Both VID and urachal anomalies should be considered when diagnosing congenital lesions in the umbilical region. Our report presents two neonatal cases that illustrate these malformations and emphasizes the crucial role of thorough physical examination, together with ultrasound imaging in distinguishing between them. Considering their distinct embryological origins and anatomical features, accurate diagnosis is essential.

CASE REPORTS

Case 1

A 6-day-old male neonate born by caesarean section at 38 weeks of an uncomplicated pregnancy was referred to our institution due to suspected persistent urachus. His general condition upon admission was good. Apart from secreting fistula at the umbilical cord stump (Figure 1), the newborn exhibited no significant abnormalities on physical examination and laboratory testing. Abdominal ultrasound revealed a urine-filled bladder that did not empty following catheter insertion into the fistula. Furthermore, the intestinal contents were visualized in the catheter. These findings suggested a diagnosis of VID. The child underwent

VID excision with wedge resection of the small bowel via an open laparotomy (Figure 2). The patient was discharged home on postoperative day 8 following an uncomplicated recovery. The histology examination of the resected VID confirmed the presence of small bowel mucosa with signs of inflammation. No complications were observed during the 6-month follow-up.

Fig.1. Patent vitellointestinal duct.

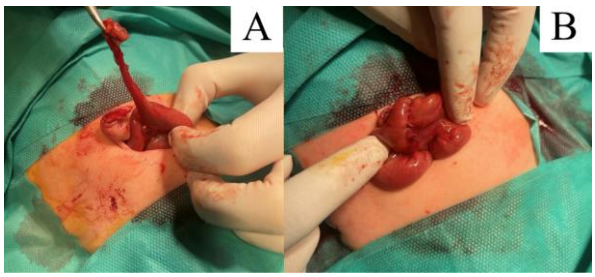

Fig. 2. Vitellointestinal duct before excision (A). Small bowel after wedge resection (B).

Case 2

A 15-day-old female neonate was referred to our institution with a prolapsed bladder through a patent urachus. The diagnosis was initially suggested on prenatal ultrasound and later confirmed during physical examination by inserting a catheter through the urethra, which was subsequently visualized within the fistula (Figure 3). The child underwent excision of the patent urachus with wedge resection of the adjacent bladder fragment (Figure 4). A catheter was kept in the bladder for 6 days. The child was discharged home on postoperative day 14 following an uncomplicated recovery. Histological examination of the excised specimen revealed urachal epithelium, which confirmed the initial diagnosis. No further complications were observed during the 7-month follow-up.

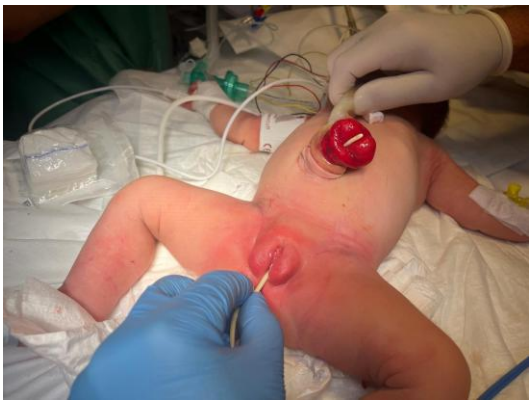

Fig. 3. Catheter inserted through urethra and visualised in patent urachus.

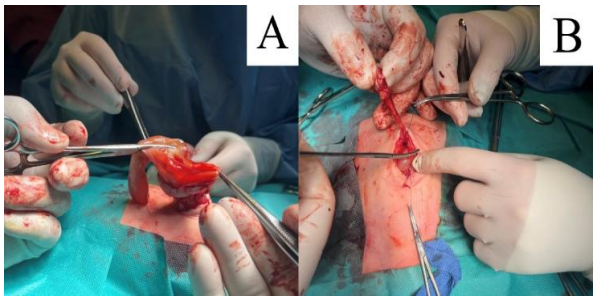

Fig. 4. Patent urachus before excision (A). Excision of patent urachus with wedge resection of adjacent bladder fragment (B).

DISCUSSION

Persistent embryonic structures in newborns may initially present with similar clinical manifestations, but the associated complications can vary significantly. Approximately 15% of VID anomalies are related to a patent VID, while other manifestations include Meckel's diverticulum, cysts, sinuses, and fibrous cords [7]. VID remnants can lead to complications such as an acute abdomen, painless rectal bleeding, intestinal obstruction, or umbilical anomalies, with these issues typically occurring in infancy [8]. Similarly, a persistent urachus may result in complications, including abscess formation in the surrounding area, further underscoring the need for timely surgical intervention [9,10]. Although rare, malignant transformation of urachal mucosa has been reported. Urachal carcinoma is a rare and aggressive tumor, with a poor prognosis once diagnosed [11].

Rare persistent embryonic structures in the umbilical region often pose a diagnostic challenge due to their overlapping clinical presentations. Without clear signs such as umbilical discharge or a fistula, these anomalies can be easily misdiagnosed or overlooked. For instance, cases have been reported where a suspected persistent VID was later diagnosed as an inflamed

appendix adjacent to the abdominal wall [12], or an umbilical cyst observed on prenatal ultrasound was ultimately identified as a persistent urachus postnatally [13]. Similarly, in our case, what initially resembled an urachal remnant was later confirmed as a VID anomaly following postnatal evaluation with physical examination and ultrasound.

Prenatal diagnosis of urachal anomalies remains uncommon as these conditions are primarily considered when umbilical drainage occurs during the neonatal period [14]. However, advancements in ultrasound technology and increasing expertise among ultrasonographers have improved the potential for prenatal detection. For example, a case report describing two cases of bladder prolapse through a patent urachus included one case diagnosed prenatally, enabling surgical intervention at just 9 hours of life [15]. In another report, Japanese authors presented a situation where the symptoms initially suggested a VID anomaly, but abdominal CT identified an anomalous congenital band instead [16]. This band, connecting the mesentery to the umbilicus, lacked the mucosal layer characteristic of VID histology.

Accurate diagnosis of congenital malformations relies heavily on imaging techniques. Our case highlights the utility of ultrasound in evaluating the umbilical region for suspected VID or urachal anomalies. Ultrasound is particularly beneficial for ruling out other conditions, such as polyps, umbilical remnants, or granulomas, and for preoperative planning or assessing connections to the bowel or urinary bladder [17]. While VID and urachal remnants are more likely in neonates and infants, conditions like umbilical granuloma, umbilical polyp, omphalolith, neoplasms, or benign soft tissue masses should be considered in older children [7,17,18].

When planning surgical intervention, the choice of operative approach depends on the type of anomaly. For VID or Meckel's diverticulum, wedge resection or segmental resection is preferred. If the base of the diverticulum is narrow, a wedge resection is typically performed; if the base is wide, segmental resection with anastomosis is required [19]. Histological findings often reveal ectopic gastric, duodenal, colonic, or pancreatic tissue within the VID or adjacent intestinal tissue, which may cause bleeding or ulceration. Consequently, excising a small portion of the intestinal wall near the duct opening is recommended to prevent complications. In a study analyzing symptomatic VID remnants in children, wedge resection was the predominant surgical approach, particularly in cases presenting with abdominal pain (63%) [20].

For persistent urachus, surgical excision involves removing the structure along with a section of the adjacent bladder tissue to mitigate the risk of malignancy. Given the potential for malignant transformation, excision of the surrounding tissue is considered to be a preventive measure [20].

This discussion underscores the importance of accurate prenatal and postnatal diagnosis, appropriate imaging modalities, and timely surgical intervention to address persistent embryonic structures in the umbilical region effectively.

CONCLUSIONS

Abnormalities in the umbilicus: a fistula, signs of inflammation, or fluid leakage may raise the suspicion of persistent fetal structures. A thorough physical examination, supplemented by ultrasound and catheterization, can effectively make the correct diagnosis. Surgical treatment is recommended, involving resection of the persistent urachus with the adjacent bladder fragment to prevent potential malignant transformation of the bladder or resection of the persistent VID with the bowel fragment to prevent bowel pathology associated with the presence of ectopic tissue.

Authors' contribution

Study design – G. Kudela, A. Wiernik
Manuscript preparation – A. Kątnik, K. Szala, G. Kudela, A. Wiernik
Literature research – A. Kątnik, K. Szala, G. Kudela, A. Wiernik
Final approval of the version to be published – G. Kudela, A. Wiernik

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PRACA ORYGINALNA
ORIGINAL PAPER

Poziom akceptacji choroby i jej związek z jakością życia pacjentów z padaczką

Level of acceptance of illness and its association with quality of life of patients with epilepsy

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STRESZCZENIE

WPROWADZENIE: Padaczka to przewlekła choroba neurologiczna o dynamicznym przebiegu. Narzuca ograniczenia codziennego życia, które mogą negatywnie wpływać na akceptację choroby, a tym samym na jakość życia osób nią dotkniętych. Niemożność pogodzenia się z trudną sytuacją wywołuje dyskomfort psychiczny i obniżenie poczucia własnej wartości. Akceptacja choroby wpływa pozytywnie na proces leczenia oraz podnosi ocenę jakości życia. Celem pracy była ocena poziomu akceptacji choroby i jej związku z jakością życia pacjentów z padaczką.

MATERIAŁ I METODY: W pracy zastosowano metodę sondażu diagnostycznego z wykorzystaniem autorskiego formularza ankiety oraz standaryzowanych kwestionariuszy: *Skali akceptacji choroby* (Acceptance of Illness Scale – AIS) i kwestionariusza oceny jakości życia SF-36 (36-Item Short Form Health Survey). Uzyskane dane opracowano z użyciem arkusza kalkulacyjnego MS Excel oraz oprogramowania statystycznego JASP. Zebrane informacje zobrazowano za pomocą tabel i ryciny.

WYNIKI: Większość badanych miała trudności z przystosowaniem się do ograniczeń narzuconych przez chorobę. Pacjenci, którzy zaakceptowali chorobę, wykazywali wyższy poziom jakości życia niż pacjenci, którzy jej nie akceptowali. Wraz ze wzrostem częstości występowania napadów zmniejszała się akceptacja choroby i pogarszała jakość życia ankietowanych. Akceptacja choroby i jakość życia ankietowanych nie zmieniały się istotnie wraz z wydłużającym się czasem trwania choroby.

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WNIOSKI: Akceptacja choroby jest jednym z najważniejszych elementów przystosowania pacjenta do życia z przewlekłą lub nieuleczalną chorobą. Na jej poziom w badanej grupie wpływały wykształcenie i częstotliwość napadów, natomiast nie miały na nią wpływu płeć ani posiadanie rodziny. Akceptacja choroby wykazywała silny związek z jakością życia.

SŁOWA KLUCZOWE

padaczka, akceptacja choroby, jakość życia

ABSTRACT

INTRODUCTION: Epilepsy is a chronic neurological illness with a dynamic course. Seizures are temporary, violent discharges of neurons manifested in a sudden onset of consciousness, movement or behavioral disorders. This illness is caused by many factors. It can manifest itself at any age from the neonatal period to old age. The illness imposes restrictions on everyday life. The aim of the study was to assess the level of acceptance of the illness and its relationship with the quality of life of patients with epilepsy.
MATERIAL AND METHODS: In this work, the diagnostic survey method was employed with the use of questionnaires: Acceptance of Illness Scale (AIS) and 36-Item Short Form Health Survey (SF-36). The material was sorted by means of MS Excel spreadsheet and JASP statistical software. The collected information was visualized using tables and figure.
RESULTS: Most of the subjects had trouble adapting to the restrictions imposed by the illness. The patients who accepted the illness showed a higher quality of life than the patients who did not accept it. With the rise in the incidence of seizures, acceptance of the illness decreased and the quality of life of the respondents deteriorated. Neither acceptance of the illness nor quality of life of the respondents changed significantly with the increase in the duration of the illness.
CONCLUSIONS: Acceptance of the illness is one of the most important elements of the patient adapting to life with a chronic or incurable illness. Its level in the examined group was influenced by education and the frequency of seizures; it was not affected by gender, or having a family. Illness acceptance showed a strong correlation with quality of life.

KEYWORDS

epilepsy, acceptance of the illness, quality of life

WPROWADZENIE

Padaczka (epilepsja) jest przewlekłą chorobą neurologiczną o dynamicznym przebiegu. Charakteryzuje się zespołem objawów wegetatywnych, psychicznych i somatycznych, zachodzących w mózgu w wyniku nieprawidłowej czynności bioelektrycznej komórek nerwowych [1,2,3,4]. Obecnie padaczkę określa się jako stan przewlekły o zróżnicowanej etiologii, z nawracającymi napadami przebiegającymi z zaburzeniami czucia, zachowania, świadomości, ruchu czy postrzegania, które mogą być złożone lub pojedyncze. Definicja ta umożliwia wcześniejsze rozpoznanie choroby, a tym samym włączenie leczenia bez oczekiwania na następny napad [4].
Światowa Organizacja Zdrowia (World Health Organization – WHO) podaje, że ponad 50 milionów ludzi na świecie cierpi na padaczkę. Średnio co roku rozpoznaje się ją u 2,4 miliona pacjentów. Zaobserwowano większe roczne występowanie padaczki w krajach o niskich i średnich dochodach (700/100 tys.) w porównaniu z krajami rozwiniętymi (50/100 tys.). W Polsce na padaczkę cierpi 1% populacji, czyli około 300–400 tys. osób. Średni wskaźnik zachorowalności wynosi 60–70 osób na 100 tys. [4,5,6,7,8,9].
Pomimo wzrostu świadomości zdrowotnej nadal istnieje problem stygmatyzacji osób z padaczką. Postawa ta wynika z niezrozumienia choroby, jej objawów oraz przebiegu. Większość uważa, że jest to choroba psychiczna, a chory traktowany jest z uprzedzeniem.
Padaczka nasila lęk i myśli depresyjne [9]. U chorych obserwuje się także zaburzenia koncentracji, postrzegania, myślenia czy pamięci [10,11]. Im częstsze napady i intensywniejszy przebieg choroby, tym większe ryzyko upośledzenia funkcji poznawczych. Negatywny wpływ ma również politerapia [12]. Pacjenci skarżą się na senność, uczucie zmęczenia oraz zaburzenia pamięci, co negatywnie wpływa na uczenie się, pracę, aktywność fizyczną, a także na relacje rodzinne i społeczne [13,14]. Ponadto ograniczenia zdrowotne i stała kontrola lekarska obniżają poczucie własnej wartości [15].
Akceptacja choroby jest jednym z najważniejszych elementów przystosowania pacjenta do życia z nieuleczalną chorobą przewlekłą. Poziom akceptacji uzależniony jest od wieku, płci, wykształcenia, rodzaju choroby, osobowości, nasilenia objawów klinicznych, a także rodzaju podjętego leczenia [16]. Akceptacja choroby wpływa na proces leczenia, podnosi poziom zaufania do personelu medycznego oraz ocenę jakości życia. Chory potrafi dostosować się do danej sytuacji, radzi sobie w sferze fizycznej, psychicznej, społecznej i duchowej. Obserwuje się też mniejsze natężenie negatywnych emocji [17].
Jakość życia według WHO to indywidualna, subiektywna ocena sytuacji przez jednostkę, jej pozycji życiowej w kontekście oceny zdrowia fizycznego, stanu emocjonalnego i samodzielności życiowej [18].

Pojęcie jakości życia jest elementem oceny funkcjonowania człowieka w ówczesnym świecie. Na jakość życia składają się takie elementy jak: zadowolenie z życia, zdrowie, warunki socjalno-bytowe, środowisko kulturowe, wzajemne relacje, edukacja, wypoczynek, zatrudnienie, bezpieczeństwo osobiste i rodzinne, zależność i niezależność od substancji medycznych oraz pomocy medycznej, poglądy osobiste czy przekonania religijne. Najważniejszym celem w świetle nauk medycznych jest poprawa jakości życia pacjentów cierpiących na nieuleczalne, przewlekłe choroby. Poprawa komfortu życia chorych wpływa na lepsze funkcjonowanie w społeczeństwie [19,20].

Celem badań była ocena poziomu akceptacji choroby i jej związek z jakością życia pacjentów z padaczką.

MATERIAŁ I METODY

Badaniem objęto 118 osób, w tym 91 kobiet (77,1%) i 27 mężczyzn (22,9%). Ponad połowa respondentów (65 osób; 55,1%) mieszkała na wsi, kolejne 53 osoby (44,9%) w mieście. Prawie połowa respondentów (52 osoby; 44,1%) była w związku małżeńskim, 20 spośród badanych (16,9%) to osoby rozwiedzione, 3 (2,5%) owdowiałe, ponad jedna trzecia (43 osoby; 36,4%) deklarowała stan wolny. Najliczniejszą grupę (54 osoby; 45,8%) stanowiły osoby czynne zawodowo, jedna piąta respondentów (25 osób; 21,2%) przebywała na rencie chorobowej, 20 osób (16,9%) było bezrobotnych, 19 (16,1%) to studenci. Połowę respondentów (60 osób; 50,8%) stanowiły osoby z wykształceniem wyższym. Liczną grupę stanowili także ankietowani z wykształceniem średnim (28 osób; 23,7%) oraz zawodowym (25 osób; 21,2%). Najmniej respondentów miało wykształcenie podstawowe (5 osób; 4,2%).

Kwestionariusze ankiet zostały sprawdzone przez Komisję Bioetyczną Uczelni Państwowej im. Jana Grodka w Sanoku. Zgodnie z wymogami Uczelni przeprowadzono również procedurę badania. Udział w badaniu był dobrowolny, anonimowy i poufny. Wszyscy pacjenci wyrazili na niego zgodę i mogli przerwać swój udział w dowolnym momencie lub odmówić odpowiedzi na jakiekolwiek pytanie bez podania przyczyny.

Narzędziami badawczymi wykorzystanymi w opracowaniu były trzy kwestionariusze:

- kwestionariusz ankiety autorskiej, który zawierał 25 pytań o charakterze socjodemograficznym (tzw. metryczkę, pytania 1–6) oraz 19 pytań dotyczących choroby, metod leczenia i jego skutków;
- Skala Akceptacji Choroby (Acceptance of Illness Scale – AIS) [21], przeznaczona do badania osób dorosłych, aktualnie chorych; badany określa aktualny stan swojego zdrowia w skali od 1 („zdecydowanie zgadzam się") do 5 („zdecydowanie nie zgadzam się"); zdecydowana zgoda oznacza złe przystosowanie do choroby, natomiast zdecydowana niezgoda wyraża akceptację choroby; niska liczba punktów uzyskana w ankiecie świadczy o braku akceptacji choroby, co jest oznaką dyskomfortu psychicznego i złego przystosowania do choroby; wysoka liczba punktów oznacza akceptację choroby, zatem brak negatywnych emocji towarzyszących chorobie i brak negatywnego wpływu na zdrowie psychiczne [14,21,22];
- kwestionariusz oceny jakości życia SF-36 (36-Item Short Form Health Survey) [21], przeznaczony do subiektywnej oceny stanu zdrowia; składa się z 11 pytań zawierających 36 stwierdzeń, które pozwalają określić 8 elementów, tj. funkcjonowanie fizyczne, ograniczenia z powodu zdrowia fizycznego, odczuwanie bólu, ogólne poczucie zdrowia, witalność, funkcjonowanie socjalne, funkcjonowanie emocjonalne i zdrowie psychiczne; suma punktów określa wskaźnik jakości życia i umożliwia ogólną ocenę stanu zdrowia; według polskiej wersji kwestionariusza najwyższa wartość punktowa oznacza najniższy stopień w ocenie jakości życia, natomiast najniższa – najwyższy poziom jakości życia; odpowiedzi ankietowanych można również przeliczyć na skalę procentową według wskaźnika podawanego przez autorów kwestionariusza oryginalnego; im wyższy wynik uzyskany po takim przeliczeniu, tym wyższy poziom jakości życia.

Kryteriami włączenia do badań były wiek powyżej 18 lat oraz zdiagnozowana padaczka trwająca dłużej niż rok, natomiast kryteriami wyłączenia – wiek poniżej 18 lat i choroby psychiczne.

Wyniki opracowano z użyciem arkusza kalkulacyjnego MS Excel oraz oprogramowania statystycznego JASP. Rodzaje testów statystycznych dobierano w zależności od wymagań i typów analizowanych zmiennych. W przypadku korelacji podawano ich wartość (*r* Pearsona, *rho* Spearmana) oraz poziom istotności (*p*). Dla każdego z testów jako graniczny poziom istotności przyjęto $p \leq \alpha = 0{,}05$. Wysoką istotnością statystyczną charakteryzują się zależności na poziomie $p \leq \alpha = 0{,}01$, a bardzo wysoką istotnością na poziomie $p \leq \alpha = 0{,}001$.

Badanie prowadzono od grudnia 2022 r. do lutego 2023 r. Zostało zrealizowane za pomocą techniki CAWI (*computer-assisted web interview*), polegającej na przeprowadzeniu ankiety za pomocą elektronicznego formularza, gdzie zapisywano uzyskane odpowiedzi.

WYNIKI

Ponad jedną trzecią respondentów (38 osób; 32,2%) stanowiły osoby mające stany padaczkowe 11–20 lat, 27 badanych (22,9%) chorowało na padaczkę 3–5 lat,

20 osób (16,9%) miało napady padaczkowe od ponad 20 lat, 17 osób (14,4%) chorowało 6–10 lat, 16 osób (13,6%) miało stany padaczkowe od roku do 2 lat.

Ponad połowa respondentów (64 osoby; 54,2%) wskazała, że napady padaczkowe występują u nich bez utraty przytomności, natomiast 54 badanych (45,8%) wskazało na napady padaczkowe z utratą przytomności.

Ponad jedna trzecia ankietowanych (40 osób; 33,9%) wskazała, że napadów padaczkowych doznaje częściej niż raz w miesiącu. Więcej niż jeden stan padaczkowy w ciągu pół roku miało 35 ankietowanych (29,7%), 28 osób (23,7%) zaznaczyła co najmniej jeden napad padaczkowy w ciągu roku, 12 respondentów (10,2%) przyznało, że przechodzi więcej niż jeden napad w tygodniu, 3 osoby (2,5%) stwierdziły, że obecnie nie mają stanów padaczkowych.

Prawie wszyscy ankietowani (96,7%) wskazali na inne choroby towarzyszące padaczce. Najczęstszą dolegliwością, wskazaną przez 61 respondentów (51,7%), była migrena. Około jedna czwarta ankietowanych (33 osoby; 28%) zaznaczyła choroby tarczycy oraz depresję (29 osób; 24,6%). Na przebyty uraz głowy wskazała jedna piąta badanych (24 osoby; 20,3%). Kolejne choroby zgłoszone przez respondentów to cukrzyca (19 osób; 16,1%), uzależnienie od alkoholu (15 osób; 12,7%), nadciśnienie (11 osób; 9,3%) oraz otyłość (6 osób; 5,1%).

Najliczniejsza grupa, bo połowa respondentów (60 osób; 50%), deklarowała, że raczej tak – może przewidzieć napad padaczkowy, podczas gdy jedna piąta badanych (25 osób; 21%) zdecydowanie potrafi go przewidzieć. Niewiele mniejsza grupa (21 osób; 18%) deklaruje, że raczej nie potrafi przewidzieć zbliżającego się napadu padaczkowego, a 12 ankietowanych (10%) zdecydowanie nie potrafi go przewidzieć.

Najczęstszym objawem zbliżającego się napadu padaczkowego według ankietowanych były bóle głowy (70 osób; 59,3%). Ponad połowa respondentów (65 osób; 55,1%) wskazała również na mrowienie kończyn i tyle samo na drętwienie. Dla prawie połowy badanych (56 osób; 47,5%) wskaźnikiem poprzedzającym zbliżający się napad padaczkowy były zawroty głowy. Ponad jedna trzecia ankietowanych (41 osób; 34,7%) wskazała stany lękowe, a prawie jedna piąta (22 osoby; 18,6%) przyspieszone bicie serca. Część badanych jako wskaźniki zbliżającego się napadu padaczkowego podawała również nudności (15 osób; 12,7%) oraz halucynacje (11 osób; 9,3%).

Pojedyncze osoby (po 0,8%) wskazały również inne objawy, tj. błyski przed oczami, silny ból brzucha, duże zmęczenie, problemy z mową, odczuwanie dziwnych zapachów czy metaliczny posmak w ustach. Jedna osoba stwierdziła, że nie ma objawów poprzedzających napad.

Spośród respondentów trzy czwarte (88 osób; 75%) deklarowały, że regularnie przyjmują leki przeciwpadaczkowe, 15 osób (13%) stwierdziło, że przyjmuje leki raczej regularnie. Do raczej nieregularnego przyjmowania leków przeciwpadaczkowych przyznało się 7 osób (6%), a do zupełnie nieregularnego – 8 (7%).

Ponad połowa respondentów (61 osób; 51,7%) była zdania, że stres wywołuje napady padaczkowe. Blisko jedna czwarta (28 osób; 23,7%) stwierdziła, że raczej jest to prawda. Prawie jedna piąta (22 osoby; 18,6%) uznała, że stres raczej nie jest przyczyną napadów padaczkowych, a 7 osób (5,9%) stwierdziło, że zdecydowanie nie jest.

Według najliczniejszej grupy respondentów (51 osób; 43,2%) osoby z padaczką raczej są wystarczająco zrozumiane i akceptowane przez społeczeństwo. Prawie jedna trzecia (38 osób; 32,2%) stwierdziła natomiast, że raczej nie są rozumiani i akceptowani, 12 ankietowanych (10,2%) wskazało, że są rozumiani i akceptowani przez społeczeństwo, natomiast 17 (14,4%) zdecydowane stwierdziło, że nie.

Spośród ankietowanych dwie trzecie (80 osób; 67,8%) wskazały, że są leczone za pomocą farmakoterapii skojarzonej, natomiast 38 osób (32,2%) za pomocą monoterapii.

Na podstawie wyników formularzy AIS oraz SF-36 można stwierdzić, że poziom jakości życia pacjentów dodatnio koreluje z poziomem akceptacji choroby. U osób akceptujących chorobę poziom jakości życia jest wyższy niż u osób, które nie akceptują choroby i wynikających z niej ograniczeń (tab. I).

Tabela I. Zależności pomiędzy poziomem akceptacji choroby a jakością życia (korelacja Pearsona)

Zmienne		Shapiro-Wilk	$p_{(s-w)}$	r	$p_{(r)}$
SF-36 Suma	AIS Suma	0,992	0,76	0,632	< 0,001

p – poziom prawdopodobieństwa; r – współczynnik korelacji; SF-36 – 36-Item Short Form Health Survey; AIS – Acceptance of Illness Scale.

Wskaźniki akceptacji choroby (AIS) mają największą wartość dla twierdzeń: „Mój stan zdrowia sprawia, że nie czuję się pełnowartościowym człowiekiem" oraz „Choroba sprawia, że jestem ciężarem dla swojej rodziny i przyjaciół" (M = 3,31 i 3,30). Średnie wartości wskaźnika AIS mają najmniejsze wartości dla twierdzeń: „Mam kłopoty z przystosowaniem się do ograniczeń narzuconych przez chorobę" (M = 3,08), „Problemy ze zdrowiem sprawiają, że jestem bardziej zależny od innych, niż tego chcę" (M = 3,03) oraz „Nigdy nie będę samowystarczalny w takim stopniu, w jakim chciałbym być" (M = 2,92; tab. II).

Tabela II. Średnie wartości wskaźnika oceny akceptacji choroby (AIS)

AIS	N	M	SD	Min.	Max.
6. Mój stan zdrowia sprawia, że nie czuję się pełnowartościowym człowiekiem	118	3,31	1,45	1	5
5. Choroba sprawia, że jestem ciężarem dla swojej rodziny i przyjaciół	118	3,30	1,42	1	5
3. Choroba sprawia, że czasem czuję się niepotrzebny	118	3,19	1,46	1	5
2. Z powodu swojego stanu zdrowia nie jestem w stanie robić tego, co najbardziej lubię	118	3,18	1,42	1	5
8. Myślę, że ludzie przebywający ze mną są często zakłopotani z powodu mojej choroby	118	3,11	1,38	1	5
1. Mam kłopoty z przystosowaniem się do ograniczeń narzuconych przez chorobę	118	3,08	1,42	1	5
4. Problemy ze zdrowiem sprawiają, że jestem bardziej zależny od innych, niż tego chcę	118	3,03	1,43	1	5
7. Nigdy nie będę samowystarczalny w takim stopniu, w jakim chciałbym być	118	2,92	1,44	1	5

AIS – Acceptance of Illness Scale; N – liczebność; M – mediana; SD – odchylenie standardowe; Min. – najniższa zanotowana wartość obserwacji; Max. – najwyższa zanotowana wartość obserwacji.

Na pytanie kwestionariusza SF-36: „Czy w ciągu ostatniego miesiąca Twoje problemy zdrowotne lub emocjonalne miały wpływ na zwyczajne czynności, kontakty z rodziną, przyjaciółmi, sąsiadami lub innymi grupami" porównywalne odsetki respondentów odpowiadały: „nawet bardzo" (28%) i „nie, wcale" (27,1%). Zbliżona była też częstość odpowiedzi „czasami" (21,2%) i „rzadko" (19,5%), natomiast niewielu ankietowanych stwierdziło, że problemy te miały „bardzo duży" wpływ na kontakty towarzyskie z najbliższymi, rodziną (4,2%).

Średnie arytmetyczne poziomu jakości życia dla poszczególnych grup ankietowanych były zbliżone: największą wartość miał poziom jakości życia kobiet samotnych (M = 57,939), a nieco niższą – kobiet zamężnych (M = 57,156) i mężczyzn (M = 55,650; tab. III). Różnice nie były istotne statystycznie, żadna grupa nie wykazywała wyższej jakości życia niż pozostałe (tab. IV).

Tabela III. Poziom jakości życia a stan cywilny kobiet oraz płeć

Grupa	N	M	SD
Mężatki	46	57,156	12,250
Kobiety samotne	45	57,939	12,581
Mężczyźni	27	55,650	14,486

N – liczebność; M – mediana; SD – odchylenie standardowe.

Tabela IV. Ocena różnic średniej w zależności od stanu cywilnego kobiet oraz od płci (ANOVA)

Obserwacje	Suma kwadratów	df	Średnia kwadratów	F	p
Grupa	88,59	2	44,29	0,266	0,767
Reszty	19172,67	115	166,72		

df – liczba stopni swobody; F – analiza wariancji; p – poziom prawdopodobieństwa.

Największą wartość średnią poziomu jakości życia odnotowano w grupie kobiet z wykształceniem średnim lub wyższym (M = 60,369), nieco niższą w grupie mężczyzn (M = 55,65), a najniższą w grupie kobiet z wykształceniem niższym niż średnie (M = 44,299; tab. V). Ze względu na duże różnice w liczebności badanych grup (N = 16–75) do analizy różnic użyto nieparametrycznego odpowiednika ANOVY – testu Kruskala-Wallisa. Wartość statystyki dla poziomu jakości życia wyniosła 21,458 i jest to wynik bardzo wysoko istotny ($p < 0,001$; tab. VI).

Tabela V. Poziom jakości życia a płeć i wykształcenie kobiet

Grupa	N	M	SD
Kobiety z wykształceniem niższym niż średnie	16	44,299	7,941
Kobiety z wykształceniem średnim lub wyższym	75	60,369	11,259
Mężczyźni	27	55,65	14,486

N – liczebność; M – mediana; SD – odchylenie standardowe.

Tabela VI. Ocena różnic średniej w zależności od płci oraz wykształcenia kobiet (test Kruskala-Wallisa)

Czynnik	Statystyka	df	p
Zmienna grupująca	21,458	2	< 0,001

df – liczba stopni swobody; p – poziom prawdopodobieństwa.

Różnica wartości średnich pomiędzy grupą kobiet z wykształceniem średnim lub wyższym a grupą z wykształceniem niższym niż średnie była bardzo wysoko istotna statystycznie ($p < 0,001$), natomiast różnica średnich pomiędzy kobietami z wykształceniem niższym niż średnie i mężczyznami była wysoko istotna statystycznie ($p = 0,007$). Mężczyźni nie różnili się istotnie pod względem średniej od kobiet z wykształceniem średnim i wyższym ($p = 0,176$; tab. VII).

Korelacja Spearmana wykazała, że częstotliwość napadów koreluje odwrotnie z poziomem akceptacji choroby ($p = 0,005$) oraz ze wskaźnikiem jakości życia ($p < 0,001$). Oznacza to, że im częstsze napady padaczkowe u ankietowanych, tym niższa odczuwana jakość życia i akceptacja choroby (tab. VIII). Ujemna wartość korelacji wskazuje na odwrotną zależność czasu trwania choroby od jej akceptacji (*rho* = -0,043) i jakości życia (*rho* = -0,142), jednak wyniki nie były istotne statystycznie (tab. IX).

Tabela VII. Porównania wielokrotne różnic pomiędzy grupami (test Tukeya)

Grupy		Różnica średnich	SE	t	$p_{(Tukey)}$
Kobiety z wykształceniem średnim lub wyższym	Kobiety z wykształceniem niższym niż średnie	16,069	3,226	4,981	< 0,001*
	Mężczyźni	4,718	2,629	1,795	0,176
Kobiety z wykształceniem niższym niż średnie	Mężczyźni	-11,351	3,696	-3,071	0,007**

* p < 0,001; ** p < 0,01.

SE – błąd standardowy; t – wartość statystyki testowej; p – poziom prawdopodobieństwa.

Tabela VIII. Częstotliwość napadów padaczkowych a akceptacja choroby i jakość życia (korelacja Spearmana)

	Zmienne	rho	p
Częstotliwość napadów padaczkowych	AIS Suma	-0,257	0,005*
	SF-36 Suma	-0,425	< 0,001**

* p < 0,01; ** p < 0,001.

rho – współczynnik korelacji; p – poziom prawdopodobieństwa; AIS – Acceptance of Illness Scale; SF-36 – 36-Item Short Form Health Survey.

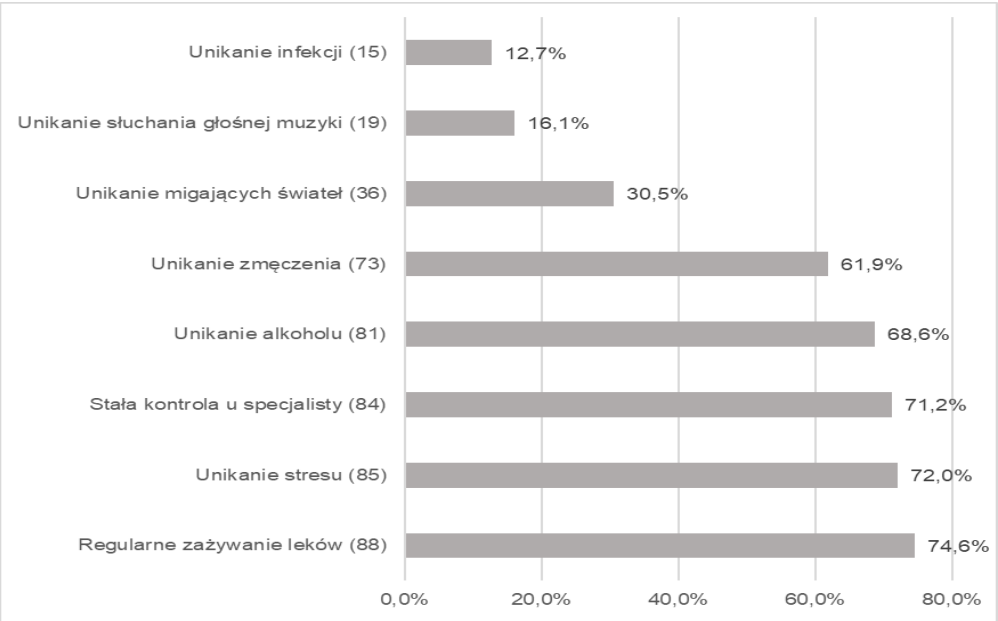
Tabela IX. Czas trwania choroby a akceptacja choroby i jakość życia (korelacja Spearmana)

	Zmienne	Shapiro-Wilk	$p_{(s-w)}$	r	$p_{(r)}$
Czas trwania choroby w latach	AIS Suma	0,914	< 0,001	-0,043	0,641
	SF-36 Suma	0,906	< 0,001	-0,142	0,127

p – poziom prawdopodobieństwa; r – współczynnik korelacji; AIS – Acceptance of Illness Scale; SF-36 – 36-Item Short Form Health Survey.

Zdecydowana większość ankietowanych (97 osób; 82,2%) jako jeden z najważniejszych aspektów życia wskazała zdrowie. Ponad połowa respondentów (72 osoby; 61,0%) wskazała niezależność finansową, a 68 osób (57,6%) rodzinę. Prawie jedna trzecia badanych (37 osób; 31,4%) wskazała aktywność zawodową, a prawie jedna czwarta (29 osób; 24,6%) rozwój osobisty.

Prawie trzy czwarte respondentów (88 osób; 74,6%) wskazało, że regularne zażywanie leków to wystarczający środek zapobiegający chorobie. Niewiele mniejsza grupa wskazała unikanie stresu (85 osób; 72,0%), stałą kontrolę u specjalisty (84 osoby; 71,2%) oraz unikanie alkoholu (81 osób; 68,6%) jako wystarczające środki, by zapobiegać chorobie (ryc. 1).



Ryc. 1. Środki zapobiegawcze zmniejszające ryzyko napadów padaczkowych.

DYSKUSJA

W przeprowadzonych badaniach połowa respondentów zadeklarowała, że prawdopodobnie może przewidzieć napad padaczkowy, a jedna piąta potrafi przewidzieć zbliżający się stan padaczkowy. Najczęstszym objawem zbliżającego się napadu padaczkowego według ankietowanych były bóle głowy, mrowienie i drętwienie kończyn oraz zawroty głowy.

Spośród respondentów trzy czwarte (75%) deklarowało, że regularnie przyjmuje leki przeciwpadaczkowe, 13% stwierdziło, że przyjmuje leki raczej regularnie. Do raczej nieregularnego przyjmowania leków przeciwpadaczkowych przyznało się 6% ankietowanych, a do zupełnie nieregularnego – 7%. Spośród ankietowanych dwie trzecie (67,8%) wskazały, że leczy się za pomocą farmakoterapii skojarzonej, natomiast pozostałe 32,2% za pomocą monoterapii. Najliczniejszą grupę ankietowanych (45,8%) stanowiły osoby, które ze względu na padaczkę poddawały się leczeniu szpitalnemu raz w roku. Blisko jedna trzecia badanych (31,4%) leczyła się w szpitalu raz na pół roku, natomiast raz w miesiącu ze względu na chorobę przebywało w szpitalu 10,2% respondentów.

W badaniach Pulsipher i wsp. [23] połowa pacjentów zgłaszała somatyczne (choroby naczyń mózgowych, układu oddechowego, zaburzenia endokrynologiczne) oraz psychiczne (lęk i zaburzenia nastroju) choroby współistniejące. Autorzy zauważyli, że wraz ze wzrostem liczby chorób towarzyszących spadała całkowita jakość życia i satysfakcja życiowa chorych. Podkreślali również konieczność rozpoznawania chorób współistniejących u pacjentów z padaczką.

Wykazano, iż pacjenci cierpiący na padaczkę skarżą się na zaburzenia pamięci i problemy z uczeniem się, a także z koncentracją uwagi [24]. W przeprowadzonym przez International Bureau for Epilepsy badaniu ponad połowa dorosłych pacjentów zgłaszała zaburzenia funkcji poznawczych, które utrudniały pracę, edukację i aktywność w czasie wolnym [25]. Zaburzenia te miały też wpływ na życie rodzinne i kontakty społeczne. W badaniach Jacoby i wsp. [26] ankietowani wyróżnili takie działania niepożądane, jak senność, uczucie zmęczenia i zaburzenia pamięci. Podobne wyniki, uwzględniające codzienne funkcjonowanie i umiejętności poznawcze, uzyskali Baker i wsp. [24] w badaniu z udziałem rodziców i ich dzieci. W badaniach własnych ponad połowa respondentów przyznała, że przyjmowanie leków przeciwpadaczkowych powoduje skutki uboczne, głównie senność, wahania nastroju, zaburzenia równowagi i poczucie zmęczenia. Według najliczniejszej grupy respondentów (43,2%) osoby z padaczką są raczej wystarczająco zrozumiane i akceptowane przez społeczeństwo. Prawie jedna trzecia (32,2%) stwierdziła natomiast, że raczej nie są rozumiani i akceptowani. Kolejne 10,2% ankietowanych wskazało, że są rozumiani i akceptowani przez społeczeństwo, natomiast 14,4% badanych zdecydowane stwierdziło, że nie.

Badania nad postawami społecznymi wobec padaczki były prowadzone w różnych krajach. Jensen i Dam [27] analizowali postawy wobec zatrudniania osób cierpiących na padaczkę. Opinie były na ogół przychylne, chociaż niecałe 10% respondentów wyrażało sprzeciw wobec równych zasad zatrudniania osób z padaczką. Podobna liczba respondentów była przeciwna kontaktom swoich dzieci z osobami chorymi. W badaniach Staniszewskiej i wsp. [28], dotyczących aktywności zawodowej chorych na padaczkę, niemal 65% ankietowanych zadeklarowało, że zatrudniłoby osobę z padaczką, a jedna czwarta nie miała zdania na ten temat. Ponadto 80% respondentów współpracowałoby z osobą cierpiącą na to schorzenie. Z badań wynikało również, że choroba utrudnia zarówno podjęcie, jak i utrzymanie pracy. Również badania Rosińczuk-Tonderys i wsp. [29] potwierdzają, że z powodu padaczki chorzy mają poważne problemy z pracą.

Poszczególne analizy wykazały, że poziom akceptacji choroby wpływa na jakość życia pacjentów z padaczką. Większość badanych miała kłopoty z przystosowaniem się do ograniczeń narzuconych przez chorobę, czuła się zależna od innych i miała poczucie, że nigdy nie będzie samowystarczalna w takim stopniu, jak ludzie zdrowi. Ankietowani rzadko natomiast rezygnowali z życia społecznego. Pacjenci, którzy zaakceptowali chorobę, wykazywali wyższy poziom jakości życia niż ci, którzy nie akceptowali choroby i wynikających z niej ograniczeń.

U kobiet posiadających rodzinę odnotowywano podobny poziom jakości życia jak u mężczyzn oraz kobiet samotnych. Ponadto u kobiet z wykształceniem średnim lub wyższym obserwowano wyższy poziom jakości życia niż u kobiet z wykształceniem podstawowym, ale podobny jak u mężczyzn. Wraz ze wzrostem częstości występowania napadów zmniejszała się akceptacja choroby i pogarszała jakość życia ankietowanych.

Badania Kupcewicz i Abramowicz [30] wykazały, że na jakość życia pacjentów ma wpływ czas trwania choroby; pacjenci zmagający się z chorobami przez dłuższy czas są znacznie mniej zadowoleni z życia. Podobną zależność zauważyli Sawicka i wsp. [31], którzy przedstawili czas trwania choroby jako jeden z głównych elementów determinujących pogarszanie się ogólnego funkcjonowania człowieka w chorobie przewlekłej. Król i wsp. [32] wskazali, że czas trwania choroby jest nieodłącznym elementem wpływającym na stan psychiczny ludzi przewlekle chorych. Tedrus i wsp. [33] odnotowali, że zmiany w częstości napadów nie były związane ze znaczącą poprawą jakości życia, natomiast na jej pogorszenie wpływało zwiększenie liczby przyjmowanych leków. Podobne wnioski dotyczące braku istotnych korelacji między liczbą

epizodów a ogólną oceną jakości życia wyciągnęli Honari i wsp. [34]. System opieki zdrowotnej powinien przekazywać informacje i edukować pacjentów z padaczką oraz społeczeństwo na temat czynników, które mogą wpływać na jakość życia chorych. Wyższa jakość życia wiąże się z mniej wyraźnymi objawami depresyjnymi [35].

Badania własne wykazały, że akceptacja choroby i jakość życia ankietowanych nie zmieniały się istotnie wraz z wydłużającym się czasem trwania choroby. Najważniejszymi elementami życia w opinii chorych na padaczkę były zdrowie, niezależność finansowa i rodzina. Regularne zażywanie leków oraz unikanie czynników wyzwalających napady padaczkowe to według większości ankietowanych wystarczające środki, by zapobiegać chorobie. Istnieją doniesienia, że wpływ padaczki na nastrój i zdrowie psychiczne może być niedoceniany [36].

Głównym ograniczeniem badania był brak porównania z grupą kontrolną. Potrzebne są dalsze badania, które obejmą większą liczbę pacjentów oraz wskażą rodzaj przyjmowanych przez nich leków przeciwpadaczkowych.

WNIOSKI

1. U pacjentów, którzy zaakceptowali chorobę, obserwowano wyższy poziom jakości życia niż u pacjentów, którzy nie akceptowali choroby i wynikających z niej ograniczeń.
2. Większość badanych miała kłopoty z przystosowaniem się do ograniczeń narzuconych przez chorobę, czuła się zależna od innych i miała poczucie, że nigdy nie będzie samowystarczalna w takim stopniu, jak ludzie zdrowi. Ankietowani rzadko natomiast rezygnowali z życia społecznego.
3. U kobiet posiadających rodzinę obserwowano podobny poziom jakości życia jak u mężczyzn oraz kobiet samotnych.
4. U kobiet z wykształceniem średnim lub wyższym obserwowano wyższy poziom jakości życia niż u kobiet z wykształceniem podstawowym, ale podobny jak u mężczyzn.
5. Wraz ze wzrostem częstości występowania napadów zmniejszała się akceptacja choroby i pogarszała jakość życia ankietowanych.
6. Akceptacja choroby i jakość życia ankietowanych nie zmieniały się w znaczący sposób wraz z wydłużającym się czasem trwania choroby.
7. Najważniejszymi elementami życia w opinii chorych na padaczkę były zdrowie, niezależność finansowa i rodzina.
8. Regularne zażywanie leków oraz unikanie czynników wyzwalających napady padaczkowe to według większości ankietowanych wystarczające środki, by zapobiegać chorobie.
9. Personel medyczny powinien informować chorych o środkach zapobiegawczych zmniejszających ryzyko napadów padaczkowych.

Authors' contribution

Study design – M. Rychlicki, W. Roczniak
Data collection – M. Rychlicki, M. Babuśka-Roczniak, P. Szumniak
Data interpretation – B. Brodziak-Dopierała, M. Wojtanowska-Kaczka
Statistical analysis – B. Brodziak-Dopierała, P. Szumniak
Manuscript preparation – M. Rychlicki, W. Roczniak, M. Wojtanowska-Kaczka
Literature research – P. Szumniak, M. Babuśka-Roczniak, M. Wojtanowska-Kaczka, A. Świcińska

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OPIS PRZYPADKU
CASE REPORT

Kawasaki disease in children: diagnosis, treatment, and therapeutic guidelines in light of a clinical case

Choroba Kawasakiego u dzieci: diagnoza, leczenie i wytyczne terapeutyczne w świetle przypadku klinicznego

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ABSTRACT

Kawasaki disease (KD) is an acute inflammation of small- and medium-sized arteries of unknown etiology. It most commonly affects children under the age of 5, with a peak incidence at 2 years of age. Because of its nonspecific symptoms, the diagnostic process is prolonged and challenging. The primary symptoms include a high fever persisting for more than 5 days, lymphadenopathy, and skin changes. Other symptoms may include mucosal redness and cracking, "strawberry tongue", conjunctivitis, swelling of the hands and feet with sheet-like peeling of the skin, and desquamation in the perineal area. This article presents the case of a 2-year-old boy admitted to the pediatric department of a hospital due to a high fever lasting several days, elevated inflammatory markers, and diarrhea. During hospitalization, new symptoms were observed, allowing the diagnosis of incomplete Kawasaki syndrome. The patient was treated according to European standards with a favorable therapeutic outcome and was monitored in a cardiology clinic. The boy was discharged in good condition without complications. This case highlights KD as both a diagnostic and therapeutic challenge, especially in its incomplete and atypical forms.

KEYWORDS

Kawasaki disease, immunoglobulin therapy, arteritis, echocardiography, cardiovascular complications, prolonged fever, atypical Kawasaki disease, cardiology follow-up

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STRESZCZENIE

Choroba Kawasakiego (*Kawasaki disease* – KD) to ostre zapalenie małych i średnich tętnic o nieustalonej etiologii. Najczęściej występuje u dzieci do 5 roku życia, ze szczytem zachorowań w 2 roku życia. Z uwagi na nieswoiste objawy diagnostyka jest długotrwała i utrudniona. Do głównych objawów należą wysoka gorączka utrzymująca się dłużej niż 5 dni, limfadenopatia oraz zmiany skórne. Mogą współwystępować przekrwienie oraz pękanie błon śluzowych, tzw. malinowy język, zapalenie spojówek, obrzęk rąk i stóp z płatowo złuszczającym się naskórkiem dłoni oraz okolicy krocza. W pracy opisano przypadek 2-letniego chłopca przyjętego na oddział pediatryczny szpitala z powodu wysokiej gorączki utrzymującej się od kilku dni, podwyższonych parametrów zapalnych oraz biegunki. W trakcie hospitalizacji zaobserwowano nowe objawy, które pozwoliły postawić rozpoznanie niepełnoobjawowego zespołu Kawasakiego. Pacjenta leczono zgodnie z europejskimi standardami z dobrym efektem terapeutycznym oraz kontrolowano w poradni kardiologicznej. Chłopiec wypisany w stanie dobrym bez powikłań. Przypadek przedstawia KD jako wyzwanie diagnostyczne i terapeutyczne, szczególnie w postaci niepełnoobjawowej i atypowej.

SŁOWA KLUCZOWE

choroba Kawasakiego, leczenie immunoglobulinami, zapalenie tętnic, echokardiografia, powikłania sercowo-naczyniowe, gorączka wielodniowa, atypowa choroba Kawasakiego, kontrola kardiologiczna

INTRODUCTION

Kawasaki disease (KD) is an acute systemic inflammation of small- and medium-sized arteries, with a particular predisposition for affecting the coronary arteries, potentially leading to structural damage and the development of aneurysms over time [1]. The etiology of the disease remains unclear, but it is suggested that genetic factors and past upper respiratory infections may play a role [2]. A new hypothesis proposes that oligoclonal IgA plasma cells play a key role in the induction of vasculitis [3]. Over several weeks, the ongoing inflammation leads to vascular remodeling, wall thickening, and the formation of coronary artery aneurysms, which can later result in vessel rupture, myocardial infarction, or arrhythmias caused by ischemia [4].

The disease is characterized by a sudden onset with fever lasting at least 5 days, which responds poorly to antipyretics and antibiotic therapy. The course of the disease includes an acute phase, a sub-acute phase, and a recovery period [4].

According to the criteria of the American Heart Association (AHA), the classical form of KD is diagnosed based on a fever lasting at least 5 days and the presence of at least four of the following symptoms: bilateral non-exudative conjunctivitis, redness and cracking of the lips, redness of the tongue ("strawberry tongue"), and/or redness of the oral and pharyngeal mucosa, cervical lymphadenopathy (≥ 1.5 cm in diameter), typically unilateral, polymorphic rash, redness and swelling of the hands and feet during the acute phase and/or periungual peeling of the skin during the subacute phase [4].

Diagnosis involves clinical evaluation, laboratory tests, electrocardiography (ECG), echocardiography (ECHO), chest X-rays (CXR), abdominal ultrasound (USG), and ophthalmologic consultation [4,5].

The characteristic findings include elevated inflammatory markers – C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) – during the acute phase of the disease and increased white blood cell (WBC) and platelet counts during the subacute phase. ECHO may reveal perivascular increased echogenicity, changes in the coronary arteries, signs of inflammation, or fluid indicating pericarditis.

Incomplete KD can be diagnosed in patients who do not meet the classic criteria by lacking four of the five characteristic symptoms. Clinicians should also consider less specific symptoms such as redness and swelling at the Bacillus Calmette-Guérin (BCG) vaccination site (in children under 12 years old), generalized cervical lymphadenopathy, and abnormal laboratory findings including anemia, elevated alanine aminotransferase activity, platelet count ≥ 450,000/μl after the 7th day of illness, WBC ≥ 15,000/μl, leukocyturia ≥ 10 WBCs/hpf, and serum albumin ≤ 3.0 g/dl in children aged 4 years and older [6].

Further diagnostic steps include detecting changes via ECHO and ruling out other possible causes of these abnormalities. In cases with an unclear clinical presentation and the need for thorough differential diagnosis, treatment is often delayed, increasing the risk of a more severe disease course owing to the development of significant arterial damage compared to the classic form of KD. This variant is more common in younger infants and older children [4].

Treatment is tailored to the patient's condition. During the acute phase, it includes intravenous immunoglobulins and acetylsalicylic acid (ASA). Once the body temperature normalizes and inflammatory markers decrease, therapy continues with a reduced dose of ASA (3–5 mg/kg body weight/day in a single dose) until follow-up ECHO, approximately two months after symptom resolution and the normalization of inflammatory markers. Regular cardiological follow-up is crucial for managing KD [7].

CASE REPORT

A 2-year-old boy was admitted to the Pediatric Ward due to a high fever persisting for six days, accompanied by diarrhea, abdominal pain, moderate dehydration, and vomiting. The day before hospitalization, the child developed eyelid swelling, red and cracked lips, in addition to a fine papular, non-itchy rash covering the trunk, and to a lesser extent, the limbs. On the second day of hospitalization, the patient exhibited swelling and redness of the hands and feet, along with conjunctival hyperemia and itching.

The laboratory tests revealed high markers of inflammation: CRP at 109.9 mg/L, procalcitonin (PCT) at 10.65 ng/L and elevated D-dimer levels at 1561.68 ng/mL. To determine the cause of the abnormal laboratory results, urine, blood, and stool cultures were collected. Due to the unclear clinical picture and suspicion of a systemic inflammatory response, third-generation cephalosporin was initiated. During the diagnostic process, infections with influenza viruses, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV) were ruled out, and the blood, urine, and stool cultures were negative. No antibodies against SARS-CoV-2 in IgG/IgM classes were detected. The following day, swelling in the feet was observed, and the fever persisted despite the start of treatment. Immunoglobulins and nonsteroidal anti--inflammatory drugs, including ASA and paracetamol, were added to the therapy.

After treatment, the fever resolved, along with changes in the conjunctiva, lips, and feet. In the subsequent days of hospitalization, the inflammatory markers significantly decreased (CRP 2.40 mg/L, PCT 0.19 ng/L, D-dimer 1319.72 ng/mL). The liver function tests revealed persistently high alanine aminotransferase (ALT) levels, but aspartate aminotransferase (AST) levels normalized. The blood, urine, and stool cultures remained negative, and the virologic stool tests were normal.

ECHO did not reveal any abnormalities in the main coronary artery segments; the heart anatomy, function, and ejection fraction were normal. The ECG showed no deviations from the norm. The child was discharged in good condition with recommendations for continued treatment and follow-up.

At the follow-up examination after discharge, no abnormalities were found during the physical examination. The blood counts during the hospital stay were normal, and a follow-up ECHO showed no clots in the heart or changes in the coronary vessels; both the structure and function were normal. A follow-up visit six months later, including ECHO, showed no abnormalities either.

DISCUSSION

KD most commonly occurs in children between the ages of 1 and 5, with a significantly higher incidence among children of Asian descent compared to those from Europe [8]. There is a slight predominance of cases among boys (the male-to-female ratio is 1.5:1) [8,9]. Boys are also more prone to complications and the risk of death [10]. KD is rarely diagnosed in children under 4 months of age, which may suggest a protective effect of maternal antibodies [10]. It has also been observed that the disease is more prevalent during the winter and spring months, with a markedly higher frequency among children from the Far East compared to those from Europe [4,10]. In the European population, the incidence is approximately 5–10 cases per 100,000 individuals [11].

The classic form of KD is characterized by a fever lasting at least 5 days and the presence of at least 4 out of 5 clinical features: changes in the extremities (erythema or swelling), a non-vesicular rash (mainly on the torso during the acute phase), bilateral conjunctivitis (non-purulent), changes in the lips and oral cavity (mucosal hyperemia, “strawberry tongue”, cracked shiny lips), and enlargement of the cervical lymph nodes (at least one node > 1.5 cm) [1,4,5].

An atypical form of KD may not meet all the diagnostic criteria, complicating the diagnosis and potentially delaying treatment [4,6]. In children with atypical KD, the fever phase often lasts longer than in the classic form and more commonly affects infants under 6 months old or children over 5 years old. These cases may also respond less effectively to treatment [12]. The AHA has developed a diagnostic algorithm for incomplete KD [4].

For children with a prolonged fever and elevated inflammatory markers (CRP and/or ESR), additional parameters should be assessed, such as anemia, platelet count > 450,000/mm³, serum albumin concentration < 3 g/dL, elevated ALT levels, total WBC > 15,000/mm³, and urine WBC > 10/hpf [4].

Imaging techniques, such as ECG and ECHO, play a crucial role in managing patients. These methods help rule out severe complications, such as aneurysms, and assess changes in the coronary vessels of the heart [5]. ECHO should be performed at the time of KD diagnosis and repeated later at two weeks and six to eight weeks after the onset of the disease if no complications are present [4].

Due to the unknown etiology of the disease, particular attention should be paid to the patient’s medical history, especially regarding prior respiratory infections and the patient’s age. Differential diagnosis should include various diseases such as measles, scarlet fever, infectious mononucleosis, rheumatic fever, or Stevens-Johnson syndrome, owing to the similar

symptoms (fever, rash, exanthema, and oral changes) [1].

The use of immunoglobulins and high doses of ASA as an anti-inflammatory agent is a key element of treatment since it prevents the development of severe complications [7]. In the presented patient, this treatment led to the resolution of fever and changes in the conjunctiva, lips, and feet. Post-hospitalization follow-up is an important aspect of preventing recurrences and monitoring for side effects of the therapy [1].

CONCLUSIONS

KD poses a diagnostic and therapeutic challenge, particularly in its incomplete and atypical forms, as well as because of its unclear etiology. ASA and immunoglobulins are the mainstays of treatment because they prevent complications such as myocardial ischemia and coronary artery aneurysms. Comprehensive differential diagnosis and close monitoring of the patient's condition using laboratory and imaging studies, such as ECHO, are crucial for proper treatment, as highlighted in the described case. Adherence to current guidelines through close observation and a comprehensive therapeutic approach allows improvement in the patient's health, confirming their effectiveness. Advancing therapeutic and diagnostic strategies for KD through research into its etiology and pathogenesis remains a priority.

Authors' contribution

Study design – E. Rychlicka, A. Kocjan, M. Heba, B. Żaczek
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PRACA POGLĄDOWA
REVIEW

The impact of anesthetics on the transcriptome

Wpływ anestetyków na transkryptom

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ABSTRACT

Anesthetic agents are routinely used as a crucial component of many procedures, but little is known about the long-term effects of their use. Anesthetics vary in their efficacy and the frequency of adverse effects depending on their mechanism of action. The aim of the study is to review the latest literature on the impact of anesthetics on the transcriptome and the human body. A wide range of variations arising from the use of anesthetics has been presented, along with their effects that may extend beyond the perioperative period. Certain functions of anesthetics in the cancer process have been outlined, such as increasing and decreasing gene expression as well as weakening components of the immune system. The promising role of local anesthetics in reducing cancer recurrence has been highlighted. The issue of exposure among large groups of professionals working in operating rooms and clinical departments has also been described. Studies have confirmed that anesthetics are not neutral for the human body; they affect the immune system, may exert pro-tumorigenic effects, influence cell proliferation and differentiation, additionally play a role in tumor growth and the development of metastases. New research on the effects of anesthetic drugs is necessary. The results of these studies may provide new therapeutic targets in cancer cells, and well-chosen therapy could increase the safety of clinical prognosis, reduce the potential occurrence of behavioral and neurocognitive disorders, and decrease the spread of metastases.

KEYWORDS

anesthetics, inflammatory cytokines, gene expression, induction of apoptosis factors, oncogenesis

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STRESZCZENIE

Środki znieczulające są rutynowo stosowane jako kluczowy element wielu zabiegów, niewiele jednak wiadomo o długotrwałych skutkach ich stosowania. W zależności od mechanizmu działania anestetyki różnią się pod względem skuteczności i częstości występowania działań niepożądanych. Celem badania jest przegląd najnowszej literatury na temat wpływu środków znieczulających na transkryptom i organizm człowieka. Przedstawiono szeroki zakres zmian powstających w wyniku stosowania anestetyków, a także ich działanie mogące wykraczać poza okres okołooperacyjny. Przybliżono pewne funkcje anestetyków w procesie nowotworowym, takie jak zwiększenie i zmniejszenie ekspresji genów czy osłabienie elementów układu odpornościowego. Podkreślono obiecującą rolę środków miejscowo znieczulających w ograniczaniu nawrotów nowotworu. Opisano również problem narażenia dużych grup specjalistów pracujących na salach operacyjnych i oddziałach klinicznych. Badania potwierdziły, że anestetyki nie są obojętne dla ludzkiego organizmu; wpływają na układ immunologiczny, mogą wywierać działanie rakotwórcze, wpływać na proliferację, różnicowanie komórek, a także odgrywać rolę we wzroście guza i rozwoju przerzutów nowotworowych. Konieczne są nowe badania nad wpływem leków znieczulających. Wyniki tych badań mogą zapewnić nowy cel terapeutyczny, a odpowiednio dobrana terapia może zwiększyć szansę dobrego rokowania klinicznego, zmniejszyć prawdopodobieństwo wystąpienia zaburzeń behawioralnych i neurokognitywnych oraz ograniczyć rozprzestrzenianie się przerzutów.

SŁOWA KLUCZOWE

anestetyki, cytokiny zapalne, ekspresja genów, czynniki indukcji apoptozy, onkogeneza

Introduction

The Lancet reports that each year over 300 million people worldwide receive general anesthesia under various conditions. General anesthesia is routinely used as an essential component of surgical procedures [1]. Increasingly, it is recognized that a significant portion of the beneficial effects of anesthetics has a molecular basis. However, less than 2% of the mammalian genome encodes proteins, which means that more than 90% consists of non-coding RNA responsible for controlling development, differentiation, metabolism, and cell growth. It is widely believed that the regulation of gene expression is required in all kinds of biological processes, including proliferation, differentiation, and the progression of disease in cells [2].

The first microarray study of inhalational anesthetics revealed that the expression of 1.5% of 10,000 genes in various organs was altered. Anesthetic agents are also capable of inducing long-lasting and transgenerational epigenetic effects.

The aim of this study is to present the existing research describing the impact of anesthetics on the transcriptome. The safety of general anesthesia has been assessed and confirmed by numerous clinical studies. However, little is known about its comprehensive effects on the body, including its influence on gene expression. In this paper, we aim to present data regarding this issue [3].

We also refer to studies regarding the influence of sevoflurane on the induction of apoptosis in both normal and cancer cells [4]. Increasing evidence suggests that perioperative factors, including the choice of anesthetic agent, influence cancer recurrence after surgery, although little is still known about the impact of anesthetics on the cancer cells themselves. It is known that certain anesthetic agents affect the signaling mechanisms of hypoxia in healthy cells by activating hypoxia-inducible factors (HIFs). HIFs are also strongly associated with tumorigenesis, and their high levels are linked to a poor prognosis, which we also address in our work [5].

The aim of this study is also to elucidate how individual anesthetics affect the transcriptome and what consequences this has for the whole organism. By means of this comparison, physicians and clinicians can consider the choice of dosage or another anesthetic agent tailored to the procedure. The role of anesthetics appears to have a long-term impact on the functioning of individual systems, and the changes that occur after their use may be irreversible, which should encourage a holistic approach to the patient before the use of any of them. Figure 1 shows the non-operative effects of anesthetics.

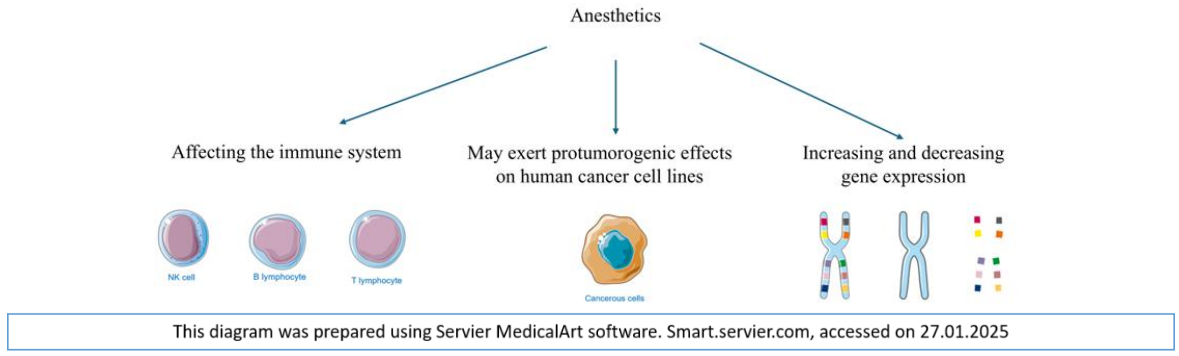

Fig. 1. Non-operative effects of anesthetics.

The literature analysis included a systematic review of scientific and medical literature from the PubMed and Google Scholar databases. After entering three keywords, i.e. "Anesthetics", "Impact", and "Transcript", 583 records were obtained in two databases. After discarding duplicate records, the analysis of 200 works were subjected to substantive analysis, of which 90 were used.

Halogenated anesthetics

Inhaled anesthetics (nitrous oxide, halothane, isoflurane, desflurane, sevoflurane) are administered as the primary therapy for preoperative sedation and to assist in maintaining anesthesia with intravenous (IV) anesthetics (such as midazolam, propofol) during the perioperative period. Inhaled anesthetics are commonly used in clinical practice due to their chemical properties, which allow rapid introduction of the agent into arterial blood through pulmonary circulation compared to the more circuitous route of venous circulation [6].

Scientific research demonstrates a close relationship between halogenated anesthetics and the immune system. Halogenated anesthetics lead to its suppression by affecting the activity of natural killer (NK) and T lymphocytes [7].

Nitrous oxide

Nitrous oxide (N_2O) is a colorless, non-flammable, practically odorless gas. It exhibits anesthetic, analgesic, and sedative effects. In clinical practice, it is not used as a standalone anesthetic for general anesthesia due to its insufficient anesthetic effect. However, it can be combined with other agents to complement or enhance anesthesia. Among the adverse effects of nitrous oxide, a moderate decrease in left ventricular contractility can be observed. Because of its low blood/gas partition coefficient, it is rapidly and completely eliminated through the respiratory tract, and its only metabolic effect is the inactivation of vitamin B_{12}, which affects foliate metabolism, leading to the disruption of DNA synthesis [8].

The diversity of nitrous oxide's targets suggests a complex pharmacological action of this drug. Indeed, treatment with N_2O in a study on mice affected the transcription not only of several genes related to the mitogen-activated protein kinases (MAPK) pathway but also of hundreds of other genes, including synaptic vesicle transport factors (*Apba1*, *Cplx1*, *Stxbp2*, *Syt13*, *Snap25*, *Unc13a*, *Picalm*, *Dnm3*), G protein-binding receptors (*Adgrl1*, *Chrm4*, *Gpr3*, *Htr1a*, *Htr2a*, *Htr6*, *Lpar1*, *Mc4r* and *Ptger4*), ion channels (*Gabra2* and *Gabra3*), postsynaptic scaffolding proteins (*Nlgn2*, *Nlgn3*, *Shank3*) and immediate early genes (*Arc*, *Egr1*, *Egr2*, *Fos*, *Egr4*, *Fosb*, *Junb*, *Klf4*, *Maff* and *Nr4a1*), which may be regulated by neuronal activity and subsequent MAPK activation [9].

In recent years, there has been a significant increase in the recreational use of N_2O, leading to growing concerns regarding its acute and chronic toxicity. There is a wide range of chronic symptoms, including myelopathy, neuropathy, psychiatric symptoms, cognitive impairments, and cardiovascular effects. N_2O interacts with neurotransmitter systems, producing anesthetic, analgesic, anxiolytic, and potentially antidepressant effects, with a potential for dependence [10].

Isoflurane

Isoflurane is an inhaled anesthetic used in the induction of anesthesia following the administration of a short--acting intravenous anesthetic and to maintain general anesthesia.

It has been demonstrated that isoflurane affects the immune system by reducing the activity of NK cells, induces the apoptosis of T and B cells, and decreases the Th1/Th2 ratio [11].

The commonly used anesthetic may also exert pro--tumorigenic effects on human cancer cell lines. It stimulates a cellular signaling pathway involving HIF, which is implicated in tumorigenesis and enhances cellular activities associated with a malignant phenotype. This occurs in a time- and dose-dependent manner, independent of oxygen, through the PI3K/Akt/mTOR pathway, resulting in de novo

synthesis of HIF, nuclear translocation, and the transcription of target genes. It thus promotes the growth of kidney cancer cells and has a noteworthy impact on the malignancy potential of cells [12].

Halothane

Halothane is a clear, heavy, and colorless liquid with a sweet and non-irritating odor. Its structure resembles an alkane. In 1956, halothane was introduced into clinical practice, but it caused fulminant hepatic necrosis, leading to the development of new inhalational agents [13].

The ability of inhalational anesthetics to induce DNA damage has been demonstrated, with halothane being identified as the most harmful in this group of drugs. These findings are consistent with earlier reports indicating that halothane metabolites persist longer in the body (15–20%) compared to sevoflurane (2–5%) and isoflurane (0.2–2%) [14].

DNA damage has also been observed in human peripheral blood lymphocytes in vitro using the alkaline comet assay. DNA strand breaks were dose--dependent on the administered dose of halothane. Halothane proved to be the strongest genotoxic agent, causing about a 5-fold increase in damage at the highest concentrations (100 mM) compared to the lowest (0.1 mM). The genotoxic properties of halothane are attributed to better penetration into cells and epithelial permeation. Additionally, it intensifies neutrophil apoptosis in cells [15].

Sevoflurane

Sevoflurane is an inhaled anesthetic. It is a volatile liquid with a mild odor. It is used for the induction and maintenance of general anesthesia in hospital and ambulatory settings in adults and children [16]. Postoperative cognitive dysfunctions (POCD) are conditions that develop after surgery under anesthesia and lead to deterioration in cognitive function [17]. Nevertheless, the mechanism of POCD still remains unknown. A study aiming to investigate the mechanism underlying the development of POCD during sevoflurane anesthesia in mice showed that it induces inflammation in primary hippocampal neurons by regulating the *Hoxa5/Gm5106/miR-27b-3p* positive feedback loop. Sevoflurane induces inflammation in the nervous system by increasing the expression of long non-coding RNA *Gm5106*, which is transcriptionally activated by *Hoxa5* and directly targeted by *miR-27b-3p*. *Hoxa5*, *Gm5106*, and *miR-27b-3p* form a positive feedback loop in sevoflurane-stimulated inflammation. Nonetheless, in this study, there is still a lack of evidence for the presence of *HOXA5-ABCB1* in human samples. At the current stage of research on *miR-27b-3p*, it is speculated that *Hoxa5* and *Gm5106* serve as biomarkers for sevoflurane-induced POCD [18].

The impact of sevoflurane anesthesia on signaling and metabolic pathways in susceptible cancer cells resulted in increased activity of *CYP2E1*, *caspase-3*, *p53*, and early de novo ceramide synthesis. The rate of apoptosis was higher in cancer cells originating from the gastrointestinal epithelium (16.9% after 24 hours). *HEp-2* laryngeal cancer cells lacking *CYP2E1* exhibited a lower apoptotic rate (7.4% after 24 hours) and a delayed increase in de novo ceramides. It can be suspected that sevoflurane may promote colon cancer cell growth, but this still requires further clinical investigation [4].

Sevoflurane is also widely used in hepatectomy, and there is a study available regarding its impact on the metastasis of hepatocellular carcinoma (HCC). It has been demonstrated that sevoflurane inhibits the migration and invasion of HCC cells in a dose--dependent manner and also suppresses HCC metastasis through *miR-665* [19].

Desflurane

It is the most modern inhalational anesthetic introduced into clinical practice and is characterized by low solubility in blood and rapid emergence from anesthesia. However, desflurane exhibits the highest minimum alveolar concentration (MAC, 6–7%) among halogenated anesthetics, which means that it is not as potent as other modern inhalational anesthetics, necessitating the use of higher concentrations of this agent [20].

As a consequence of desflurane use, there is a systemic increase in inflammatory cytokines IL-6 and IL-8. The increase in IL-6 in response to surgical stress is associated with neutrophilia, the release of adrenocorticotropic hormone, increased production of C-reactive protein, and its sustained elevation is correlated with a poor prognosis in critically ill patients. IL-8 activity is linked with IL-6 post-injury, attracting neutrophils and macrophages to the site of inflammation. During the inflammatory process, the release of reactive oxygen species (ROS) increases, which can damage DNA and other macromolecules. Studies describe a significant increase in DNA damage in the comet assay in patients anesthetized with desflurane and an increased formation of sister chromatid exchanges during desflurane anesthesia up to 7 days post-operation [21].

A subsequent study conducted by the GENOTOX Laboratory on patients undergoing minor procedures with or without N_2O-desflurane revealed a significant increase in the systemic levels of IL-6 and hs-CRP one day after surgery in both groups, as well as prolactin levels intraoperatively compared to the baseline and postoperative values for both groups. From this, it can

be inferred that N_2O does not impair the inflammatory profile or neuroendocrine response compared to patients anesthetized solely with desflurane. Further studies are warranted to compare DNA damage and inflammatory response in surgical patients who undergo desflurane or other inhalational or intravenous anesthetics to observe if one anesthetic is better or worse than the other concerning genotoxicity and inflammation [22].

Intravenous anesthetics

Ketamine, propofol, and thiopental

These are examples of drugs commonly used in intravenous anesthesia. Intravenous anesthetics have anti-inflammatory properties, which are beneficial for patients in most septic cases. Intravenous anesthetics act in multiple ways on the immune system. Ketamine and sodium thiopental decrease the number of helper T cells and natural killer cell activity while increasing the number of suppressor T cells [23]. Sodium thiopental and ketamine inhibit the release of IL-1, IL-6, tumor necrosis factor α (TNF-α), and IL-8. A low dose of ketamine, acting as an antagonist of N-methyl-D-aspartate (NMDA) receptors, shortens the half-life of IL-6 [24,25]. Additionally, these drugs increase the level of IL-10 [26].
Intravenous anesthetics are used to initiate and maintain anesthesia; in the case of total intravenous anesthesia (TIVA), the entire anesthesia process is managed intravenously [27]. In contrast to propofol, ketamine and thiopental inhibit the activity of NK cells. Ketamine induces apoptosis in lymphocytes via the mitochondrial pathway and inhibits the functional maturation of dendritic cells, while thiopental protects T lymphocytes from apoptosis by inducing heat shock proteins [28]. In this scenario, ketamine reduces the synthesis of pro-inflammatory cytokines such as IL-6 and TNF-α. On the other hand, thiopental inhibits neutrophil activity and suppresses the activation of nuclear factor kappa B (NF-κB), leading to the activation of T lymphocytes, secretion of IL-2, IL-6, and IL-8, as well as the overexpression of interferon gamma (IFN-γ) [29]. Ketamine can inhibit the expression of the *CYP* gene by suppressing calcium signaling, reducing ATP levels, generating an excessive amount of reactive oxygen species, and consequently disrupting cytoskeletal dynamics [30].

Ketamine

Ketamine is an antagonist of the NMDA receptor, used since the 1960s as an anesthetic agent, especially in hemodynamically unstable patients. Ketamine has proven to be a desirable drug due to its short half-life and lack of clinically significant respiratory depression. In subanesthetic doses, it exhibits potent analgesic properties without depressant effects on the respiratory and cardiovascular systems [31].
Ketamine inhibits the production of anti-inflammatory cytokines and may also suppress the activity of natural killer cells. It can induce apoptosis in lymphocytes and inhibit the functional maturation of dendritic cells [32]. Ketamine also exhibits anti-inflammatory effects, which may be associated with inhibiting the production of TNF by macrophages in the presence of bacteria [33]. Studies also describe that ketamine and sodium thiopental have a detrimental effect on mast cells in patients at a high risk of infection [34].

Sodium thiopental

Sodium thiopental is a rapidly acting intravenous anesthetic agent that acts on gamma-aminobutyric acid sub-type A receptors (GABA-A receptors), confirming their presence in immune system cells. Comparing the effects of propofol and sodium thiopental on the Th1/Th2 balance, by measuring the levels of IFN-γ, IL-4, and IL-2, it was shown that sodium thiopental reduced the concentration of IFN-γ and IL-4 without affecting the concentration of IL-2 [35].
In the case of intravenous administration in children and adolescents, there is significant variability in the required dosage. This necessitated a higher range of doses for children not previously medicated. Thiopental was withdrawn from the United States market in 2011, mainly due to its illegal use in the United States as a drug for lethal injections [36].

Propofol

A strongly and rapidly acting intravenous anesthetic inducing a dose-dependent loss of consciousness. The drug provides rapid induction, good control of the sedation level, and quick recovery of consciousness upon the discontinuation of infusion. Propofol has antioxidant and anti-inflammatory properties by inhibiting the production of prostaglandins and inflammatory cytokines as well as inhibiting cyclooxygenase activity [37].
Data on whether propofol anesthesia increases or decreases IL-6 levels are inconclusive. In vitro, propofol inhibits IL-6 production by means of stimulated lipoproteins and reduces the levels of cytokines IL-1, TNF-α, and IL-6. Literature also describes research results indicating that propofol increases IL-10 levels. Higher levels of anti--inflammatory cytokines in patients receiving propofol are the reason behind its anti-inflammatory properties. The administration of a high dose of propofol increases the IFN-γ/IL-4 ratio, while a low dose of propofol does not change the cytokine levels [38].
Propofol has a different mechanism of action than sodium thiopental; it relies on its anti-inflammatory

action, inhibition of COX-2, reduction of PGE-2, and decrease in pro-inflammatory cytokines [39].
The impact on *ADRB2* gene expression during propofol sedation for abdominal surgery has been investigated. An increase in *ADRB2* gene expression, responsible for stimulating the sympathetic nervous system and the cardiovascular system, has been described. Its application in regulating the clinical prognosis and treatment resistance is also demonstrated [40].
Additionally, a groundbreaking discovery regarding propofol was made in a study conducted by Zhao and Mo [41], where a significant decrease in subsets of T lymphocytes and NK cells during general anesthesia was described.
General anesthesia induced by propofol triggers phase shifts of circadian rhythms controlled by the suprachiasmatic nucleus (SCN) only at specific times of day (late rest period and early activity period). General anesthesia induced by propofol is associated with later reductions in the *Per2* mRNA levels throughout the brain. Short-term anesthesia induced by propofol leads to transient reductions in *Per1* and *Per2* expression in the SCN. These acute effects known from behavioral arousal and dark impulses play a role in the resetting properties of non-photic signals. Interestingly, even though treatment with exogenous melatonin can modify the SCN clock, as does propofol anesthesia, the initial molecular targets are not *Per* genes, but *Rev-erbα* and *Rorβ*. These data suggest that propofol anesthesia combines the activation of common SCN transduction pathways with classical non-photic signals and dark impulses, but not with pharmacological doses of melatonin [42].

Opioids

Morphine

Morphine belongs to the group of potent analgesic drugs known as opioids, also called narcotic analgesics. It is an alkaloid derived from opium and a derivative of phenanthrene. Morphine inhibits the activity of NK cells, promotes lymphocyte apoptosis, reduces T cell differentiation, and stimulates angiogenesis [43].
Morphine activates glial cells, leading to the release of cytokines, including IL-1β, IL-6, and TNF-α, which counteract the analgesic effects of morphine. The release of cytokines is not associated with the frequency and timing of morphine administration. Considering the short-term cytokine response to morphine (about 5 minutes), it can be assumed that morphine rather stimulates the release of stored cytokines than synthesizes them [35].
The study by Shavit et al. [44] suggests that IL-1 may reduce the analgesic effects induced by morphine. The authors also noted that IL-1 plays an important role in morphine tolerance. On the other hand, researchers discovered that IL-1β affects the expression of opioid receptors in glial cells, and IL-1β may regulate opioid receptors (μ, δ, and K) in astrocytes [45].
Studies have also shown that clinically relevant doses of morphine led to an increase in tumor volume and tumor vascularization. Endogenous μ-opioid receptor (MOR) ligands, endomorphin-1 and endomorphin-2, enhance angiogenesis in addition to the proliferation, migration, and adhesion of endothelial cells in vitro, effects that were reversed by the MOR antagonist, naltrexone [46].
The next study related to the developing tolerance to morphine after long-term use revealed an increased expression of *CircNf1* as well as decreased levels of *miR-330-3p* and *miR-665* in rats treated with morphine. The investigation revealed an increased expression and downregulation of *CircNf1*, *miR-330-3p* and *miR-665* in rats chronically treated with morphine, suggesting that increased *circNf1* and *CXCL12* expression mediates the development of morphine analgesic tolerance [47].
Scientists found that prolonged exposure to morphine and the development of tolerance are associated with the overexpression of *MRAK159688*, which enhances the expression and function of REST, thereby inhibiting the expression of the MOR and subsequently inducing morphine tolerance [48].

Fentanyl, sufentanil, alfentanil, remifentanil

Opioid analgesics are administered during surgery to alleviate pain (inhibit nociceptive signaling). In intraoperative anesthesia, piperidine derivatives are commonly prescribed. In Poland, the most frequently used medication from this group is fentanyl, although for several years now, remifentanil and sufentanil have also been available [49].
Fentanyl and sufentanil reduce the activity of NK cells and increase the number of regulatory T lymphocytes. Alfentanil, along with remifentanil, decreases NK cell activity, while remifentanil additionally inhibits lymphocyte proliferation [33].

Fentanyl

The immune response changes during the perioperative period. Fentanyl exhibits cytotoxicity towards NK cells. Researchers reported that fentanyl inhibits NK cell activity in mice [50]. Beilin et al. [51] found that 24 hours postoperatively, NK cell activity decreased at both low and high doses of fentanyl. During the first 24 hours after surgery, a rapid increase in NK activity was observed, after which there was a significant decrease in NK activity that returned to the baseline values after 8 days. Pain medications exhibit specific effects, with fentanyl reducing NK cell activity both postoperatively and in the absence of surgery.

Fentanyl in the conducted study demonstrated the ability to induce autistic-like behaviors by reducing the expression of *Grin2b*. Further research is necessary to determine the potential clinical significance for autism risk [52].

Local anesthetics

Lidocaine, ropivacaine, bupivacaine

Currently, local anesthetics are widely used in various fields of medicine with diverse application possibilities. The frequent use of local anesthetics cannot be without an impact on the increased likelihood of adverse effects of these agents, including hypersensitivity reactions [53].

Lidocaine, ropivacaine, and bupivacaine inhibit cell proliferation and differentiation, are cytotoxic to mesenchymal stem cells in vitro, and play a key role in tumor growth as well as metastasis development in cancer cells [54].

Locally administered lidocaine inhibits the receptor of the epidermal growth factor, which is a target molecule for many anticancer drugs. A study assessing the direct impact of local anesthetics showed that lidocaine and bupivacaine induce apoptosis in cancer cells both in vivo and in vitro, suggesting potential benefits in oncological surgery [55].

A study has shown that local lidocaine increases the activity of NK cells against cancer in vitro by releasing lytic granules [56].

Each of the drugs leads to an increase or decrease in the expression of genes. We present the previous discoveries of these genes in Table I.

Table I. Increase or decrease in expression of previously discovered genes after administration of specific anesthetic

Drug name	Increase in expression	Decrease in expression	Author	Year of study
Isoflurane	*HIF*	–	Benzonana et al. [5]	2013
Halothane	*HMGCS2*	*KRT31*	Wang et al. [74]	2023
Sevoflurane	*PARP-1*	*miR-27b-3p*	Zhu and Ma [18]	2021
	Gm5106			
	Hoxa5			
Desflurane	IL-6	–	Arruda et al. [22]	2019
	IL-8			
Thiopental	–	*NF-κB*	Chen et al. [30]	2018
Propofol	–	*Per-1* *Per-2*	Ben-Hamouda et al. [42]	2018
	ADRB2	–	Lin et al. [40]	2023
Morphine	*CircNf1*	*miR-330-3p*	Bai et al. [47]	2023
	MRAK159688	*miR-665*	Deng et al. [48]	2022
Fentanyl	–	*Grin2b*	Sheng et al. [52]	2022

HIF – hypoxia-inducible factor; IL-6 – interleukin 6; IL-8 – interleukin 8.

The involvement of laboratory animals in research on the role of anesthetics

Sevoflurane is the most commonly used inhalational anesthetic in general anesthesia. A whole-genome transcription analysis was conducted on the brains of mice exposed to sevoflurane. The results of the analysis suggest that sevoflurane induced both angiogenesis and the appearance of undifferentiated nerve cells in all the sampled brain regions. These changes in gene expression were not observed in the brains of sleeping mice and appeared to be specific to brains exposed to sevoflurane. The level of transcription factor *Klf4* was increased in all the brain samples, and the results of pathway and motif analysis suggest that *Klf4* is a key regulator of angiogenesis in addition to the appearance of undifferentiated nerve cell transcription [57]. The effect of sevoflurane on nerve cell transcription in mice is illustrated in Figure 2.

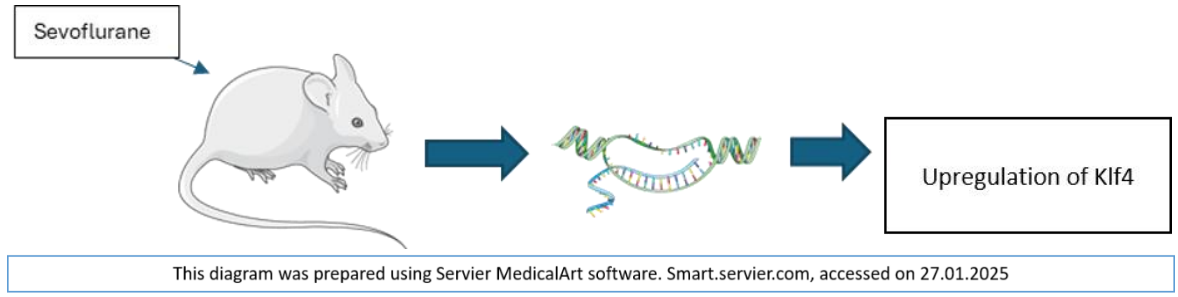

Fig. 2. Effect of sevoflurane on nerve cell transcription in mice.

Additionally, reduced DNA methylation in the promoter region of *Arc* and *JunB* – genes involved in synaptic plasticity and neuronal development – along with increased expression of their mRNA in rats exposed to six hours of sevoflurane exposure, is inherited transgenerationally in male offspring. These modifications to components crucial to synaptic plasticity could partially contribute to morphological and cognitive deficits known to occur with neonatal sevoflurane exposure. Further studies are required to directly link the observed epigenetic modifications and dysregulation of immediate early genes to anesthesia--induced neurotoxicity, synaptic morphological and a myriad of behavioral deficits [58].

The relationship between anesthetics and neurons

An important topic in many scientific studies is the impact of anesthesia in pediatric anesthesia. In humans, synaptogenesis begins in the third trimester of pregnancy, and rapid brain growth continues from 2 to 3 years after birth. Importantly, as part of normal brain development, up to 50% to 70% of neurons and progenitor cells undergo physiological cell death and cell elimination through an inherent programmed cell death process called apoptosis, which centers around the caspase enzyme family [59,60,61]. The diverse group of clinically used agents for general anesthesia includes intravenous anesthetics such as benzodiazepines, barbiturates, ketamine, propofol, and etomidate, as well as inhalational anesthetics such as halothane, isoflurane, sevoflurane, desflurane, nitrous oxide, and xenon. Although these compounds are chemically very different, their mechanism of action inhibiting neuronal activity is very similar, involving various degrees of changes in synaptic transmission involving γ-aminobutyric acid (GABA) and/or NMDA receptors [62]. Since neuronal activity mediated by GABA and NMDA is essential for mammalian brain development, exposure to general anesthetics may potentially disrupt normal brain maturation [63]. Studies describing structural brain abnormalities in children after anesthesia have not been found.

General anesthetics commonly administered during anesthesia necessarily modulate neuronal activity and may have effects beyond the perioperative period. The negative effects of anesthetics are more apparent in populations with reduced stress coping abilities, such as older individuals, in whom persistent neuronal dysfunction may manifest as memory or cognitive function deficits or the exacerbation of chronic neurodegenerative diseases. POCD develops in ~10–40% of patients, with risk factors including (among others) older age, the occurrence of perioperative complications, and pre-existing cerebrovascular disease. Determining the role of anesthetics is challenging owing to the chronic, typically slow, and progressive course of the disease process [64].

Anesthetics and the oncogenic process

Cancer is the second leading cause of death in developed countries, with the majority of deaths caused by metastasis. Surgery is the gold standard in treating most cancers. Nevertheless, tumor surgery can lead to the release of cancer cells into the systemic circulation. Surgical stress and several perioperative factors are suggested to accelerate tumor growth, thereby raising the risk of metastatic recurrence. The anesthetic technique may influence the neuroendocrine and immune response of the patient during surgery [29].

While surgical stress and pain can activate neuroendocrine cascades that inhibit NK cells perioperatively, anesthetics and analgesics (which alleviate pain and the stress response) may also independently suppress immune functions. This is because anesthetics weaken nearly all components of the immune system: cellular and humoral, in both humans and animals, both in vivo and in vitro [65].

The impact of propofol, thiopental, ketamine, and halothane was investigated: all the drugs reduced the number of circulating NK cells, and all except propofol reduced the cytotoxicity of NK cells [66]. Although opioids are effective pain relievers, there is increasing evidence that they may have negative consequences for individuals undergoing oncologic surgeries. Administering morphine to mice in clinically relevant doses leads to increased angiogenesis and breast tumor growth [67].

However, the interaction of opioids with the immune system is complex: perioperative morphine

administered to rats undergoing a laparotomy attenuated the surgical stress-induced tumor-retaining effect, particularly when administered before surgery [68].

Morphine promoted cell death and apoptosis in the adenocarcinoma cell line. Moreover, endogenous and exogenous opioids have distinct immunomodulatory properties, partially explained by their affinity for different subtypes of opioid receptors [69].

Data on N_2O was also provided, as demonstrated in an in vivo model, N_2O inhibits chemotaxis, which is potentially the strongest stimulator of metastatic development in the liver and lungs after surgery [70]. Patients receiving perioperatively β-adrenolytics have a lower frequency of metastatic recurrences after surgery. Additionally, a continuous infusion of propofol may inhibit the development of lung metastases [71].

Researchers observed that one-year survival was nearly 10% higher in oncologic surgeries where propofol was used as the anesthetic agent [72]. Another study assessing the direct impact of local anesthetics showed that lidocaine and bupivacaine induce apoptosis in cancer cells both in vivo and in vitro, suggesting potential benefits in oncologic surgery. These drugs may possess a new ability to reduce metastatic spread in cancer. Differential gene expression was demonstrated after ex vivo exposure of the *SH-SY5Y* brain cancer cell line and the *MCF-7* breast cancer cell line to enflurane, isoflurane, desflurane, halothane, sevoflurane, and nitrous oxide. Sevoflurane inhibits the viability, invasion, migration, and apoptosis of colorectal cancer cells in a dose-dependent manner by regulating the *circ-HMGCS1/miRNA-34a-5p/SGPP1* axis through the inactivation of *Ras/Raf/MEK/ERK* signaling and regulation of the *ERK/MMP-9* pathway through the upregulation of *miRNA-203* and regulation of the *miRNA-34a/ADAM10* axis. The study also showed a differential and specific impact on circulating exosomal miRNA during the surgical resection of colon cancer. Other anesthetics, such as nonsteroidal anti-inflammatory drugs, propofol, and ketamine, may also modulate epigenetics. Celecoxib inhibits the proliferation, migration, and invasion of osteosarcoma cells through *miRNA-34a*. Lidocaine in clinical concentrations (1 mM) induced DNA demethylation for 120 hours in *BT-20* and *MCF-7* breast cancer cells in vitro. Lidocaine also reduces the proliferation of *PaTu8988t* pancreatic cancer cells after 48 hours in vitro [73].

μ-opioid receptor agonists (MORAs) are indispensable for analgesia in bladder cancer (BC) patients, both during surgery and for chronic pain treatment.

Mouse models of hematogenous metastasis and in situ BC demonstrated that tumor metastasis was significantly increased after MORA treatment. A significant increase in the number of mesenchymal and/or epithelial circulating tumor cells (CTCs) was detected after MORA treatment in both the mouse models and clinical trial patients. Mechanistically, MORAs facilitated the formation of CTCs by activating the MOR/PI3K/AKT/Slug signaling pathway, thereby promoting the epithelial--mesenchymal transition (EMT) of BC cells, as the knockdown of MOR, Slug or blockade of PI3K inhibited the EMT process and CTC formation [74]. Influence of MORA on metastasis is illustrated in Figure 3.

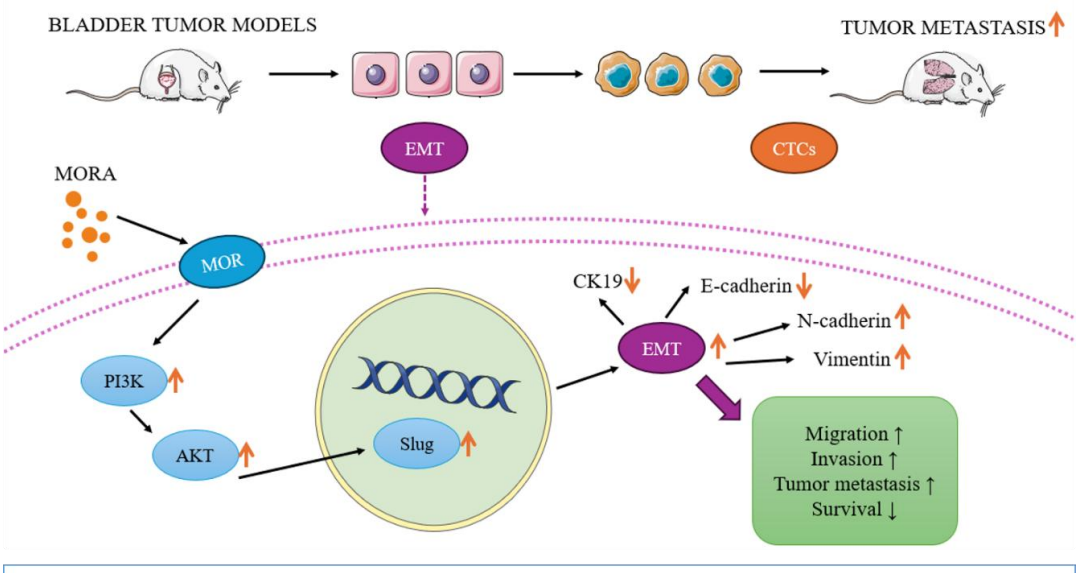

Fig. 3. Influence of μ-opioid receptor agonist (MORA) on metastasis. EMT – epithelial-mesenchymal transition; CTCs – circulating tumor cells; MOR – μ-opioid receptor; PI3K – phosphoinositide 3-kinases; AKT – protein kinase B.

Cancer recurrence

The main available studies evaluated regional and general anesthesia, showing that local or epidural anesthesia does not affect outcomes related to the progression of breast cancer (2132 patients), lung cancer (400 patients), or breast and abdominal cavity cancer (1802 patients). These studies seem to definitively suggest that local anesthesia-analgesia does not reduce the frequency of recurrences after potentially curative cancer surgery [73].
Nonetheless, these studies were not designed to detect differences between the cancer subtypes or the cancer stage. In one study, only 13.5% and 12.5% of patients in the general anesthesia and epidural groups, respectively, had advanced cancer [T3-4], while another study included multiple types of tumors (gastrointestinal, hepatobiliary pancreatic, and urogenital systems, as well as other tumors) [75,76,77].

Breast cancer

In the largest controlled randomized trial (The Breast Cancer Recurrence Trial – BCR), spinal anesthesia was compared with general anesthesia for breast cancer surgery. It included 2132 patients and showed no differences in tumor recurrence and survival between the anesthetic techniques. Unlike the research hypothesis based on residual disease, this trial included only low-stage disease, which has two implications. Firstly, surgery achieves a high cure rate (> 90%) after five years in low-grade disease, as demonstrated in the Mindact study. Secondly, surgery is less invasive in these cases, leading to a reduced stress response, less pain and opioid use, and a lower risk of recurrence [75].
A meta-analysis of six randomized controlled trials compared the impact of propofol-based anesthesia and inhalational anesthesia on postoperative immune function in breast cancer patients, with selected indicators of immune function limited to the cellular level. The results showed no difference in the effect on T lymphocytes between propofol anesthesia and inhalational anesthesia at the end of surgery and 1 day after surgery, but on the postoperative day, the patients anesthetized with propofol had higher CD4+ cell activity and CD4+/CD8+ ratio than those with inhalational anesthesia. Propofol may enhance antitumor immunity by increasing the activity of CD8+ T lymphocytes [78], which may retain lymphocyte activity. The results of the impact of propofol and inhalational anesthetics on subsets of T lymphocytes suggest that propofol may have potentially beneficial effects on the long-term prognosis after breast cancer surgery [79].

Pancreatic cancer

A challenge that may overshadow the effect of anesthesia and reduce enthusiasm for further research is surgical curability, which is now high, especially for low-grade malignancies [80]. On the other hand, the main cause of death from postoperative cancer is metastasis, which occurs in one-third of operated patients [81]. Only a small number of pancreatic cancer patients are eligible for surgery, and among them, 7% will survive for 5 years, indicating a high rate of recurrence and a lack of effective treatment methods [82]. It is well known that epigenetic mechanisms drive the development of pancreatic cancer. For these reasons, studies on epigenetics and pancreatic cancer with different anesthetics may be a promising area of research [83].

Occupational exposure to anesthetics

It is estimated that each year, over 312.9 million surgical procedures are performed worldwide, and the majority of them are conducted under general anesthesia, which can be administered via inhalational or intravenous agents [84]. Therefore, millions of professionals working in operating rooms (OR) and post-anesthesia care units (PACU) are exposed to trace amounts of inhalational anesthetics during their work. Hence, evaluating the potential toxic effects of anesthetics in humans is of paramount importance. Previous studies have shown that occupational exposure to waste anesthetic gases (WAGs) is not associated with oxidative stress or an inflammatory state assessed in serum/plasma, DNA damage assessed in lymphocytes and leukocytes, or molecular modulation assessed in peripheral blood cells in university anesthesiologists [85]. The latest available studies have documented few adverse effects associated with WAGs when permissible exposure values in the workplace are implemented. Specific measures include effective ventilation and purification systems, the regular monitoring of gas concentrations in the air to ensure they remain below the recommended limits, ensuring the proper maintenance of anesthesia equipment, avoiding desflurane and N_2O whenever possible, in addition to minimizing fresh gas flow rates (e.g. using low-flow anesthesia).
An alternative to inhalational anesthesia may be TIVA. Although TIVA is not associated with a risk of occupational exposure or air pollution inherently linked to volatile anesthetic gases, the clinical considerations should be taken into account when choosing an agent. To minimize the potential negative environmental impacts, appropriate procedures for disposing of intravenously administered anesthetic agents should be followed [86].

The role of anesthetics in toxicology

Anesthesia-related death is one of the most complex events to investigate in forensic pathology due to its rarity. Particularly emphasized are the challenges in

determining the cause of death in such circumstances [87].

Each year in the United States, anesthesia/anesthetics are reported to be the primary cause of approximately 34 deaths and contributory factors in an additional 281 deaths, with the risk of death being higher in older individuals and males [88].

A screening method for detecting fentanyl and its analogs in biological samples has been developed and validated. Fentanyl and its analogs are present in biological material at very low concentrations, not exceeding a few nanograms per milliliter or gram. The liquid chromatography-mass spectrometry (LC/MS) technique was employed. The method is characterized by limits of quantification (LOQ) and limits of detection (LOD) ranging from 0.6 to 2 ng/ml and from 0.2 to 0.6 ng/ml, respectively, for the four compounds mentioned above. This method was applied to detect fentanyl in three forensic cases. Blood, bile, and lung blood were collected during the autopsies of individuals who died shortly after surgical procedures where fentanyl was used as the adjunctive general anesthesia [89].

Conclusions

Anesthetics are commonly used drugs with confirmed safety. However, they are not neutral to the human body, affecting the immune system (including reducing NK cell activity, inducing the apoptosis of T and B cells), and may exert pro-tumorigenic effects on human cancer cell lines. Suspicion of the toxic effects of nitrous oxide requires further research, especially considering the increasing popularity of recreational N_2O use among the population.

Local anesthetics may influence cell proliferation and differentiation, are cytotoxic to mesenchymal stem cells in vitro, and may play a key role in tumor growth and metastasis development in cancer cells. The precise action of these agents also requires further research.

Recent interest in the potential impact of anesthesia and analgesic treatment regimens on the transcriptome, as well as their influence on cancer recurrence and metastasis, in addition to their effects on the immune system, suggests that in healthy patients, these effects are not significant. Moreover, in the context of short--term surgeries, the observed changes in the immune system are primarily attributable to the surgical procedure itself. In patients with immune deficiencies, the use of anesthetics may lead to disease progression with long-term drug administration. These agents used in the perioperative period can modulate the innate and acquired immune system, inflammatory response, and angiogenesis, which may affect tumor recurrence and the long-term prognosis. Nevertheless, this issue requires further research to draw additional conclusions.

Promising results also come from studies on reducing the spread of cancer cells and limiting the formation of metastatic lesions, suggesting the potential benefits of using anesthetics and analgesics in oncology, which requires further research.

New studies on the effects of anesthetics on cancer genetics are necessary. The results of these studies may provide an answer as to whether data from animal models and in vitro studies will be applicable in clinical practice, and these studies may provide a new therapeutic target in cancer cells.

MORAs promote BC metastasis by facilitating the formation of CTC. The EMT-CTC axis could be targeted for preventive measures during MORA treatment to inhibit the associated tumor metastasis or recurrence in BC patients.

Therefore, further research on the long-term effects of anesthetic and opioid use is necessary to better understand the potential risks and benefits of their use. There is also a need to develop new anesthesiologic strategies that are safer and more effective.

Authors' contribution

Study design – A. Pilarz, J. Brzoza, M. Tomsia
Data collection – A. Pilarz, J. Brzoza
Manuscript preparation – A. Pilarz, J. Brzoza, M. Tomsia
Literature research – A. Pilarz
Final approval of the version to be published – A. Pilarz, J. Brzoza, M. Tomsia

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PRACA POGLĄDOWA
REVIEW

Complications after blepharoplasty: a review of the literature

Powikłania po blefaroplastyce: przegląd piśmiennictwa

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ABSTRACT

INTRODUCTION: Blepharoplasty is a surgical procedure to correct or reconstruct the upper or lower eyelids. The main purpose of performing these surgeries is to correct the signs of aging that occur in the periorbital region and to improve the appearance of unsightly eyelids. Eyelid surgery is also used in the correction of ophthalmic conditions. The purpose of this review is to describe the most common complications after blepharoplasty of the upper or lower eyelids, to analyze the cause of the complications, and to propose methods of prevention and correction.

REVIEW: It is important to understand how and why complications occur after eyelid surgery. Most postoperative complications fall into one of four categories: (1) inaccurate preoperative evaluation, (2) improper surgical technique, (3) poor intraoperative assessment, and (4) idiopathic complications. Complications associated with this type of surgery include bleeding, infection, corneal injury, double vision, eyelid regurgitation (lagophthalmos), eyelid drooping (ptosis), lacrimal gland damage, dry eye syndrome, an asymmetric eyelid crease line, residual excess skin and subcutaneous tissue, eyelid furrow deformities, canthal webbing, and burns.

CONCLUSIONS: Blepharoplasty, despite being one of the most commonly performed plastic surgery procedures in the world, is not the easiest of procedures to perform. It is associated with a number of complications, which can have a major impact on the end result of the operation or even on the patient's quality of life. Knowledge of all the complications and how to prevent them is crucial for any surgeon who wants to achieve good postoperative results.

KEYWORDS

blepharoplasty, eyelid surgery, complications, plastic surgery

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STRESZCZENIE

WPROWADZENIE: Blefaroplastyka to zabieg chirurgiczny polegający na korekcie lub rekonstrukcji powiek górnych lub dolnych. Głównym celem wykonywania tych procedur jest zniwelowanie oznak starzenia się występujących w okolicy okołooczodołowej oraz poprawienie wyglądu nieestetycznych powiek. Plastyka powiek znajduje również zastosowanie w korekcji schorzeń o podłożu okulistyczno-funkcjonalnym. Celem niniejszego przeglądu jest opisanie najczęstszych powikłań po blefaroplastyce powiek górnych lub dolnych, analiza przyczyn powikłań oraz zaproponowanie metod zapobiegania im oraz ich korekcji.
PRZEGLĄD: Ważne jest zrozumienie, w jaki sposób i dlaczego dochodzi do powikłań po plastyce powiek. Większość powikłań pooperacyjnych należy do jednej z czterech kategorii: (1) niedokładna ocena przedoperacyjna, (2) niewłaściwa technika chirurgiczna, (3) zła ocena sytuacji śródoperacyjnej, (4) powikłania idiopatyczne. Do powikłań towarzyszących tego typu zabiegom należą: krwawienie, infekcje, urazy rogówki, podwójne widzenie, niedomykanie powiek (*lagophthalmos*), opadanie powieki (*ptosis*), uszkodzenie gruczołu łzowego, zespół suchego oka, asymetryczna linia załamania powieki, pozostały nadmiar skóry i tkanki podskórnej, deformacje bruzdy powiekowej, *canthal webbing* oraz oparzenia.
WNIOSKI: Blefaroplastyka, mimo że jest jednym z najczęściej wykonywanych zabiegów chirurgii plastycznej na świecie, nie należy do najłatwiejszych procedur. Wiąże się z licznymi powikłaniami, które mogą znacząco wpłynąć na ostateczny wynik operacji, a nawet na jakość życia pacjenta. Znajomość wszystkich możliwych powikłań oraz metod zapobiegania im jest kluczowa dla każdego chirurga, który chce osiągać dobre wyniki pooperacyjne.

SŁOWA KLUCZOWE

blefaroplastyka, chirurgia powiek, powikłania, chirurgia plastyczna

INTRODUCTION

Blepharoplasty is a surgical procedure to correct or reconstruct the upper or lower eyelids. The main purpose of performing these surgeries is to correct the signs of aging that occur in the periorbital region and to improve the appearance of unsightly eyelids [1]. Eyelid surgery is also used in the correction of ophthalmic conditions. Blepharoplasty of the upper eyelids is aimed at functional and cosmetic improvement, while the primarily purpose of procedures of the lower eyelids is cosmetic improvement [2]. As the population ages, the demand for both cosmetic and functional blepharoplasty is increasing [3,4]. This procedure, performed on the upper eyelid, involves excision of the excessive skin fold and, if necessary, removal of the corresponding portion of the eye's circular muscle and fat pads [2]. If the procedure involves the lower eyelids, the way it is performed depends on the patient's individual anatomical conditions [2].

REVIEW

Epidemiology

Eyelid surgery is one of the most commonly performed plastic surgery procedures in the world [5]. Blepharoplasty has been in the top 5 most commonly performed surgical procedures over the past 10 years, right next to rhinoplasty and facelift [1]. In 2021, it was ranked third by the International Society of Aesthetic Plastic Surgery (ISAPS) [6]. The frequency of performing blepharoplasty increased by 18.1% from the previous year [6]. Based on ISAPS data, it is estimated that 1,142,957 procedures were performed among women and 303,932 procedures were performed among men in 2021 worldwide [6].

Indications

The most common functional indication for upper eyelid blepharoplasty is upper eyelid excess skin (dermatochalasis), eyelid drooping (blepharoptosis). For cosmetic reasons, patients often want a more visible upper eyelid crease and filling of the superior palpebral furrow. Indications for lower eyelid blepharoplasty include a prominent nasolabial groove, lower eyelid asymmetry, bulging of upper eyelid fat (steatoblepharon), and lower eyelid protrusion exposing the eyelid conjunctiva [7,8]. Most of these indications are characterized by herniation of the orbital fat pads and protrusion of the lower orbital margin [8]. Although it is a minor surgical procedure, like any it carries the risk of complications [4].

Complications

It is important to understand how and why complications occur after eyelid surgery. Most postoperative complications fall into 1 of 4 categories: (1) inaccurate preoperative evaluation, (2) improper surgical technique, (3) poor intraoperative assessment, and (4) idiopathic complications [3]. Complications associated with this type of surgery include bleeding, infection, corneal injury, double vision, eyelid regurgitation (lagophthalmos), eyelid drooping (ptosis), lacrimal gland damage, dry eye syndrome, an asymmetric eyelid crease line, residual excess skin and subcutaneous tissue, eyelid furrow deformities, canthal webbing, and burns [3,4,7,9]. The purpose of this review is to describe the complications after

blepharoplasty of the upper and lower eyelids, to analyze the cause of the complications, and to propose methods of prevention and correction.

Bleeding

The eyelid and its surrounding areas have a rich blood supply, making bleeding during blepharoplasty inevitable. The patient's intake of anticoagulants [3] or uncontrolled increases in blood pressure during the preoperative and postoperative periods are risk factors for early, but also late, postoperative hematoma [10]. With blepharoplasty, the most common are preseptal hematoma as well as periorbital and extraocular hematoma. In the case of preseptal hematoma, blood from the ruptured vessel collects focally, or spills over into the surrounding tissues [3]. These hematomas usually pose no threat to vision, but can lead to varying degrees of scarring, eyelid misalignment, pigmentation abnormalities and discomfort [3]. It is recommended that ice cooling and compression be applied to the affected area.

The most feared hematoma after blepharoplasty, is an extraocular hematoma [7]. This is an extremely rare complication, occurring in about 0.055% of cases [10]. As the name suggests, it is an accumulation of blood in the space behind the eyeball. The volume of the orbit is 30 cm^3 [3], and it is designed to tolerate a small amount of fluid, but rapid hemorrhage is not well compensated. The pressure in the orbit increases causing venostasis, which raises intraocular pressure even more, resulting in a decrease in arterial blood flow, and as a result, orbital compartment syndrome [11,12]. In addition, there is a pushout of the eyeball forward manifested by proptosis. If the pressure inside the orbit exceeds the pressure in the central retinal artery, ocular perfusion is impaired. If this continues for more than 60 to 100 minutes, the patient is at the risk of permanent vision loss [13]. Extraocular hematoma manifests as decreased vision, a tense orbit, restricted eye movements and anisocoria [3]. The management of such a diagnosis is urgent lateral canthotomy and cantholysis. When the orbital pressure does not decrease or continues to increase, surgical control of bleeding and surgical decompression of the orbit should be performed [3].

Infection

Due to the good blood supply to the operated area, the rate of infection after blepharoplasty surgery is relatively low, ranging from 0.04% to 0.2% [14]. The most common is anterior blepharitis, which is confined to the eyelid itself [3]. It manifests as a red, tender and swollen eyelid. If not properly treated, the infection can spread to the orbit, causing orbital cellulitis and even necrotizing fasciitis [15], which are serious complications. Signs of orbital involvement include decreased vision, pupillary abnormalities, decreased eye movement and proptosis. The most common microbes are Staphylococcus and Streptococcus bacteria, and even atypical mycobacteria [3,16]. Treatment is based on oral antibiotic therapy, or in more severe cases, intravenous therapy. While antibiotics have increasingly limited therapeutic use against antibiotic-resistant strains, surgical antisepsis is still the best way to lower postoperative infections.

Corneal injuries

Corneal abrasion can be a complication of eye surface exposure during blepharoplasty [3]. It can occur through direct irritation of the cornea during surgery or during the postoperative period through irritation by surgical sutures [17]. Other corneal injuries associated with eyelid procedures are keratitis and partial or full--thickness corneal perforations. Corneal perforations involving the entire layer of the cornea are usually associated with the use of a laser during surgery or the preoperative administration of local anesthesia to the eyelid [18]. Patients with corneal damage usually report pain and reduced visual acuity. The Seidel test with fluorescein is used to assess the depth of corneal damage. The appearance of a trail of dye diluted by aqueous humor on the corneal surface indicates a full--thickness defect of the cornea. Most patients with corneal injuries as a complication of blepharoplasty are reported to have improvement in visual acuity in comparison to their preoperative condition. However, many develop corneal scarring, which does not enable the recovery of preoperative visual acuity [18]. The use of corneal shields in blepharoplasty procedures depends on the operator's preference. They have the advantage of a mechanical barrier to protect the cornea. Nonetheless, cases of corneal abrasions caused by the use of shields have been described in the literature [18].

Diplopia

When double vision occurs after blepharoplasty, it is important to determine whether it is monocular or binocular, and whether it is temporary or permanent. Monocular diplopia can result from the use of ointments and eye drops, interruption of the tear film or epithelial damage [3]. Temporary binocular diplopia can be caused by the penetration of local anesthetics into the extraocular muscles and impairment of them until the anesthetic is flushed out [3].

In the case of permanent monocular or binocular double vision, there are two main mechanisms of injury. The most common is decompensation through surgical interference of a pre-existing imbalance between the extraocular muscles [19]. Therefore, a thorough physical examination of the patient before surgery is crucial to maximally reduce the risk of complications. The second mechanism involves mechanical damage

by the operator to the inferior rectus or oblique muscles in lower eyelid blepharoplasty and the superior rectus or oblique muscles in upper eyelid blepharoplasty [3,19,20,21]. The trochlea of the superior oblique muscle tendon is located close to the supraorbital rim, during aggressive removal of the fat pad from the nasal side; it can be damaged, causing iatrogenic Brown syndrome [3]. The superior rectus muscle is connected by a fibrous membrane to the upper eyelid elevator muscle. In the case of partial resection of the upper eyelid levator muscle, the superior rectus muscle can mistakenly be damaged as well, hence intraoperative checking of ocular mobility is crucial [21]. If we talk about injuries during lower eyelid procedures, the main reason is the fact that the inferior oblique muscle separates the medial fat pad from the central one. It runs below the inferior rectus muscle. Therefore, the inferior oblique muscle is prone to injury during deep dissection of the medial or central fat pads, and the inferior rectus muscle during extensive dissection in the central fat pad. Aggressive dissection, the use of high coagulation energies, traction or hemorrhage at these sites can result in paresis or scarring with restriction, manifesting as double vision [20].

Lagophthalmos

Lagophthalmos is the patient's inability to close the eyelids completely, which is necessary to distribute the protective tear film throughout the eye. Failure to close the eyelid results in exposure of the cornea, which is associated with tear film evaporation or maldistribution, followed by exposure keratopathy, threatening corneal ulceration or perforation [22]. Clinically, lagophthalmos can be divided into temporary (lasting 2 to 3 weeks after surgery) and persistent chronic (longer than 3 months) [3]. Temporary can be associated with swelling and/or postoperative pain, injection of the anesthetic into the circular muscle of the eye, or traumatic myopathy [3]. When eyelid malfunction persists longer and does not resolve after a few weeks following surgery, we may suspect more serious causes for such a condition. The most common cause of chronic lagophthalmos is excessive eyelid skin resection. It is established that 20 mm of eyelid skin, measured from the center of the eyelid margin to the natural line of the eyebrow is sufficient to close the eyelid effortlessly [3]. Other causes of chronic lagophthalmos also include excessive resection of the eye's circular muscle, damage to the facial nerve (causing paralysis of the orbicularis muscle) and suturing of the orbital septum after it has been opened [3,4]. Treatment of this complication is based on maintaining an artificial protective layer on the cornea in the form of ointments and eye drops, and if the injury is permanent, reoperation and correction may be necessary [22].

Ptosis

The levator muscle of the upper eyelid and Muller's muscle are the two muscles responsible for lifting the upper eyelid [23]. Eyelid drooping can occur if they are damaged or if the levator aponeurosis, horns of the levator muscle complex or Whitnall's ligament are damaged during blepharoplasty. For direct damage to these structures to occur, the orbital septum must be opened, for example to reduce the fat pads. Eyelid drooping can also be caused by excessive postoperative swelling of the eyelid or bleeding, leading to separation of the aponeurosis [19]. To be certain that eyelid drooping is a complication of the surgery, and not pre--existent drooping such as involuntary ptosis, the patient should be carefully examined before qualifying for surgery [3]. It should be acknowledged that obscuring the upper eyelid margin due to excess skin (dermatochalasis) can mimic ptosis. The best way to confidently diagnose eyelid drooping is to measure the distance from the corneal light reflex to the edge of the eyelid in the primary gaze, known as the margin-reflex distance (MRD). Ptosis is defined by a MRD of 2.5 mm or less [3].

Dry eye syndrome

According to the definition established in 2017, dry eye syndrome is an ocular surface disease characterized by a loss of tear film function, with ocular symptoms present due to tear film instability, hyperosmolarity, inflammation or damage to the ocular surface and neurosensory abnormalities [24]. Contrary to previous beliefs, resection or incision of the ocular orbicular muscle does not correlate with increased dry eye syndrome symptoms [25,26,27]. The pathophysiology of dry eye syndrome symptoms is due to the surgical interference in the eyelid, tear film and ocular surface system. This affects the distribution of the tear film on the cornea, which is compounded by potential complications of the procedure, in the form of impaired eyelid closure caused by postoperative eyelid drooping, ectropion or dysfunction of the lateral canthus. All of these factors add up to cause postoperative dry eye disease [9]. The basis for avoiding this blepharoplasty complication is accurate patient classification before surgery, proper surgical technique and postoperative care. The patient should have a thorough medical history and a tear film break test or Schirmer's test before surgery to rule out the presence of dry eye syndrome already before the procedure. During the procedure, the main focus should be on protecting the cornea, establishing the borders of the surgery by marking the incision line and minimizing bleeding. Postoperative prevention of edema, inflammation and infection is recommended [9].

Lacrimal gland damage

Lacrimal gland damage is a serious complication of blepharoplasty. It can significantly affect the comfort as well as the health of the patient's eye. The gland is located behind the lateral orbital rim and can therefore be accidentally damaged or removed if mistaken for the lateral fat pad, significantly increasing the risk of complications [3]. Although blepharoplasty is mostly an aesthetic procedure, it carries the risk of serious functional complications such as permanent dry eye, foreign body sensation, corneal damage and even a loss of vision if the lacrimal gland is compromised [3,7]. In addition, damage to the gland can also lead to gland prolapse, which is characterised by displacement of the gland from its natural anatomical location, causing a visible bulge and functional impairment [3]. These changes not only affect the aesthetic appearance, but can also lead to chronic dry eye [7]. The cause of lacrimal gland prolapse may be aging of the orbital septum and weakening of the supporting ligaments, leading to changes in the anatomical structure of the eye [28]. Lacrimal gland prolapse is quite common, affecting approximately 15% of patients prior to blepharoplasty [4]. Misdiagnosis of this condition and inadvertent excision of the gland can lead to severe deterioration of corneal hydration [28]. If the gland is found to be prolapsed, repositioning of the gland using non-absorbable sutures is recommended as a treatment procedure to restore its normal function [3]. As many as 60% of patients who undergo blepharoplasty experience problems with tear gland prolapse, especially those with a history of multiple eyelid surgeries [9]. Failure to identify the gland and the unintentional removal of it rather than a fatty hernia can lead to severe dry eye [29]. These data highlight the importance of proper preoperative and intraoperative assessment in addition to the use of an appropriate surgical technique to avoid complications and ensure both aesthetic and functional surgical outcomes. Furthermore, in cases of gland prolapse after surgery, securing the gland with fine sutures to the periosteum is crucial to prevent future displacement [4]. In summary, ensuring a proper technique and management during surgery can reduce the risks associated with lacrimal gland damage as well as contribute to functional and aesthetic success after surgery [9].

Asymmetric eyelid crease

Asymmetry of the eyelid crease after blepharoplasty is an important post-operative complication that can occur in the early stages of recovery. Given that natural facial symmetry is rare, patients often have exaggerated expectations of achieving perfect symmetry after surgery. Thus, it is important to inform the patient before surgery that complete symmetry may not be achievable and that some degree of asymmetry is always possible [3]. The leading causes of asymmetry after surgery include inadequate intraoperative markings, ptosis not diagnosed before surgery, differences in eye protrusion and thyroid disorders affecting the eyelid structures [3].

Advanced methods of supporting the lower eyelids, such as lateral canthal fixation, preventive canthopexy or canthoplasty, used during lower eyelid blepharoplasty, effectively minimise the risk of asymmetry [30]. Reliable preoperative preparation, which includes accurate measurements and analysis of preoperative photographs, is crucial to prevent asymmetry [31,32]. However, if it occurs, there are various options for correction. For example, when the eyelid crease is too low, it is possible to make an incision above and fix it at a higher level. Conversely, if the crease is too high, it is recommended to make an incision at a lower level and use free fat beads to prevent it from attaching at too high a level [31,32]. Incorporating the aforementioned techniques into perioperative and operative procedures is important to minimize complications and increase patient satisfaction with the outcome of the procedure, the effects of which have both aesthetic as well as functional significance. It is also worth mentioning the necessity of photographic documentation both before any operation that alters the patient's appearance and in the event of abnormal healing symptoms.

Residual excess skin

Residual excess skin after blepharoplasty is a significant clinical problem resulting from postoperative asymmetry of the eyelid skin, particularly in the lateral and medial parts of the eyelids. Even despite carefully delineated areas of incision, such complications can occur. Before proceeding with any revision, the surgeon must ensure that sufficient skin remains for re-excision and that the patient does not have symptoms of dry eye or exposure keratopathy. In addition, careful assessment of the position of the eyebrows is crucial. If ptosis is present, it is advisable to restore the eyebrows to their natural anatomical position before deciding to remove the excess skin to avoid aggravating eyebrow sagging [3]. Corrective techniques depend on the amount of excess skin remaining. In situations of moderate excess skin, a 'skin pinching' procedure can be performed after blepharoplasty with volume preservation. In cases of significant skin excess, it may be more effective to lift and excise a flap of skin, particularly to eliminate excess skin extending along the entire length of the lower eyelid [33]. In the context of undercorrection of the upper eyelids, it is better to initially take too little skin rather than too much, as additional skin excision can easily be performed even under local anaesthesia.

It is very important to recognise previously undiagnosed cases of drooping eyebrows before surgery, which can simulate the appearance of excess upper eyelid skin [34]. Patients should be informed before surgery that approximately 5% to 10% of cases may require additional skin removal. In situations where concomitant brow drooping is present, a brow lift should be considered before proceeding with blepharoplasty correction to avoid unnecessary skin removal that could exacerbate brow drooping [35]. In addition, it is recommended to wait a period of at least 6 months after the original surgery before proceeding with any revision to allow the tissue to fully heal and to assess the long-term effects of the correction [3].

Sulcus deformity

Sulcus deformity is among the potential complications of blepharoplasty that can result from the mismanagement of upper eyelid fat tissue. The current surgical techniques favour fat preservation rather than fat resection as a change in approach to eyelid rejuvenation and the pursuit of a natural, youthful appearance. This represents a significant evolution from previous methods, which favoured fat resection and could lead to unaesthetic hollowing of the eyelid sulcus, giving the face an ageing appearance [35]. The upper eyelid contains two major fat pads, the nasal and middle one, which differ in chemical composition and structure, influencing their behaviour during ageing. Ageing causes the nasal fat pad to become more prominent, while the middle fat pad undergoes atrophy. This change in volume can contribute to deformation of the eyelid sulcus, which is visible as a depression on the eyelid. Therefore, it is necessary to prevent loss of periorbital volume [3]. Anatomical differences in the eyelid crease between patients require detailed consideration during surgical planning. It is important to discuss the anatomical features of the eyelid fold and the expected changes after surgery with the patient before the operation, as this is crucial to avoid complications such as repositioning of the eyelid fold or its obliteration [4]. In the surgical context, it is therefore necessary to avoid excessive fat resection in order not to result in unaesthetic hollowing. Instead, minimal sculpting of the nasal fat pad and strategic repositioning or fat grafting can be employed to restore symmetry and volume to the upper eyelid [3,35]. In addition, surgical and non-surgical revision options should be considered depending on the patient's individual expectations and aesthetic goals. For example, the use of hyaluronic acid fillers and manipulation of eyebrow position can correct minor irregularities and asymmetries that may occur after surgery [34]. In summary, a pivotal aspect of blepharoplasty is the prerequisite of not only a precise understanding of the functional internal anatomy, but also a thorough understanding of the delicate external structures. In turn, a detailed pre-operative consultation is crucial to establish realistic expectations of the patient and to ensure that the results of the operation are in line with the patient's aesthetic preferences [34].

Canthal webbing

As a complication of blepharoplasty, canthal webbing can occur on either side of the eyelid crease. Medially, it occurs when the incision line is too close to the edge of the eyelid, is at an abnormal angle, extends too far from the nasal direction, or too large a flap of skin has been excised [3]. It occurs laterally when the incision line of the upper eyelid extends below the lateral angle of the eyelid crevice or excess skin has been removed [36]. In both cases, the scar pulls flaccid skin from the upper and lower eyelids during the healing process, creating a skin bridge. This complication is difficult to remove and can generate further complications. When fixing canthal webbing, it is necessary to wait 6 months to a year after surgery for the wound to fully heal [3]. It should also be remembered that simple excision of the eyelid fold will not improve the situation and may even worsen it. The best method for skin transposition is the Z-plasty technique [36].

Burns

In lower and upper eyelid procedures, the main focus is placed on a surgical technique that spares the fat pads [37]. This is achieved by various methods, including the use of cauterization, which involves a thermal effect that can burn the periorbital area [3,38]. To reduce the risk of burns to a minimum, it is recommended to use bipolar cauterization, which allows more precise delivery of energy and heat than monopolar cauterization [38]. The technique of cutting with short, intermittent cuts is preferred over long, high-energy cuts. Covering the oxygen cannula with a surgical drape should also be avoided as an oxygen trap can result [3].

CONCLUSIONS

Blepharoplasty, despite being one of the most commonly performed plastic surgery procedures in the world is not the easiest of procedures to perform. It is associated with a number of complications, which can have a major impact on the end result of the operation or even on the patient's quality of life. Knowledge of all the complications and how to prevent them is crucial for any eyelid surgeon who wants to achieve good postoperative results.

Conflict of interest

The authors have no potential conflicts of interest to declare.

Ethics approval

Due to the nature of the research, the consent of the ethics committee was not required.

Authors' contribution

Study design – S. Kowalczyk, M. Guzikowski, M. Kokoszka, S. Sirek, D. Wyględowska-Promieńska
Data collection – S. Kowalczyk, M. Guzikowski, M. Kokoszka
Manuscript preparation – S. Kowalczyk, M. Guzikowski, M. Kokoszka, S. Sirek
Literature research – S. Kowalczyk, M. Guzikowski, M. Kokoszka, D. Wyględowska-Promieńska
Final approval of the version to be published – S. Sirek, D. Wyględowska-Promieńska

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OPIS PRZYPADKU
CASE REPORT

Long-term, complex orthodontic treatment of patient with Apert syndrome – from severe malocclusion to functional and aesthetic result

Długoterminowe, wieloetapowe leczenie ortodontyczne pacjentki z zespołem Aperta – od nasilonej wady zgryzu do funkcjonalnego i estetycznego rezultatu

Anna Ledwoń, Natalia Giża, Liudmyla Rodziewicz, Urszula Rojek

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ABSTRACT

This case report describes the orthodontic treatment of a 2-year-old female with Apert syndrome, initially admitted to the Clinic of Congenital Abnormalities in the University Dental Centre of Medical University of Silesia in Katowice in 2004. Following craniofacial surgery for premature skull fusion, the patient exhibited characteristic Apert syndrome features, including premature fusion of skull bones, midfacial hypoplasia, and syndactyly. Removable appliances were used between 2007 and 2013 to manage dental development and teeth loss, followed by craniofacial osteoplasty in 2013––2014 to correct significant maxillary underdevelopment. Fixed orthodontic treatment was initiated in December 2014, focusing on aligning teeth, correcting malocclusion, expanding the upper arch, and managing crowding. Despite treatment challenges, such as poor oral hygiene the 6-year orthodontic treatment yielded a satisfactory functional and aesthetic outcome. The patient achieved correct overjet and overbite, reduced crowding, and improved jaw relations, though some occlusal problems, including a residual posterior crossbite and minor crowding, persisted. Almost 4-year follow-up demonstrated stable results, although bruxism was developed, requiring a nightly splint. Continued follow-up is essential for managing long-term stability in this complex case.

KEYWORDS

Apert syndrome, orthodontic treatment, acrocephalosyndactyly, craniosynostosis, multidisciplinary treatment

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STRESZCZENIE

Prezentowany opis przypadku dotyczy leczenia ortodontycznego dziewczynki z zespołem Aperta, przyjętej do Poradni Wad Rozwojowych Uniwersyteckiego Centrum Stomatologii Śląskiego Uniwersytetu Medycznego w Katowicach w 2004 r. w wieku dwóch lat. Przed rozpoczęciem leczenia ortodontycznego u pacjentki przeprowadzono operację w celu korekty przedwczesnego zrośnięcia szwów czaszki. U pacjentki obserwowano charakterystyczne cechy zespołu Aperta, w tym przedwczesne zrośnięcie kości czaszki, niedorozwój środkowej części twarzy oraz syndaktylię. W latach 2007–2013 u pacjentki zastosowano aparaty ruchome w celu kontrolowania rozwoju zgryzu oraz uzupełnienia braków zębowych. W latach 2013–2014 wykonano osteoplastykę czaszkowo-twarzową w celu skorygowania znacznego niedorozwoju szczęki. Leczenie ortodontyczne aparatami stałymi rozpoczęto w grudniu 2014 r., koncentrując się na uszeregowaniu zębów, korekcie relacji przednio-tylnej szczęk, poszerzeniu górnego łuku zębowego oraz rozładowaniu stłoczeń. Pomimo trudności, takich jak niedostateczna higiena jamy ustnej, leczenie ortodontyczne przyniosło zadowalające efekty zarówno funkcjonalne, jak i estetyczne. Pacjentka uzyskała prawidłowy nagryz poziomy i pionowy, w znacznej mierze rozładowano stłoczenie zębów oraz poprawiono relacje szczęk. Niemniej jednak pewne problemy zgryzowe, w tym zgryz krzyżowy boczny oraz niewielkie stłoczenia, utrzymywały się po leczeniu. Prawie 4-letnia obserwacja efektów leczenia wykazała stabilne wyniki, choć u pacjentki rozwinął się bruksizm, co wymagało zastosowania nocnej szyny relaksacyjnej. Dalsza kontrola pacjentki jest niezbędna do utrzymania długoterminowej stabilności efektów leczenia.

SŁOWA KLUCZOWE

zespół Aperta, leczenie ortodontyczne, akrocefalosyndaktylia, kraniosynostoza, leczenie interdyscyplinarne

INTRODUCTION

Apert syndrome, also known as acrocephalosyndactyly type I, is a rare genetic disorder, with the incidence estimated to be 1 in 65.000 to 88.000 live births [1]. Apert syndrome is characterized by craniosynostosis (premature fusion of skull bones, which leads to deformation and disfunction of head structures) and syndactyly (fusion of fingers and toes). It was first described by French physician Eugène Apert in 1906. The condition is caused by mutations in the fibroblast growth factor receptor 2 (FGFR2) gene, leading to abnormal development of bones and other tissues during foetal development [2].

The primary clinical features of Apert syndrome include craniofacial abnormalities such as a high forehead, shallow eye sockets, midfacial hypoplasia, and underdeveloped maxilla, often resulting in restriction of airway and multiple dental problems [2]. Additionally, patients usually exhibit complex syndactyly, usually affecting all fingers and toes, which may significantly impair hand function. Neurological issues such as developmental delays and cognitive impairment can also be observed due to the premature fusion of the skull bones affecting brain growth [3].

The management of Apert syndrome is multidisciplinary. Diverse problems often require surgical intervention, e.g. to correct craniosynostosis, syndactyly, and other associated anomalies. Early diagnosis and treatment are essential to improve outcomes and quality of life for patients with Apert syndrome [4]. This case report discusses the clinical presentation and multidisciplinary treatment approach of a patient with Apert syndrome. The case report is emphasizing the challenges and long-term care considering malocclusions, functional and aesthetic outcomes during orthodontic treatment of individual with this rare congenital disorder.

CASE REPORT

A 2-year-old female was admitted to the Clinic of Congenital Abnormalities (Zabrze) in the University Dental Centre of Medical University of Silesia in Katowice in February 2004 to initiate diagnostic and orthodontic treatment due to Apert syndrome. Prior to the visit in Clinic of Congenital Abnormalities, patient had a craniofacial surgery in the Department of Plastic Surgery in Specialized Medical Centre in Polanica Zdrój (24 September 2003), to manage premature fusion of skull bones. Unfortunately, patient was not referred to Clinic of Congenital Abnormalities right after birth, so there was no medical history prior to February 2004, apart from hospital documentation provided by the parents. Initial examination revealed edentulous arches, pseudo-prognathism, concave profile and insufficient maxillary development. Characteristic features of Apert syndrome were observed: high forehead and midfacial hypoplasia as well as syndactyly, affecting both fingers and toes (Figure 1). Patient was under observation for several years, during early childhood and the period of deciduous teeth eruption (from 2004 to 2007). In May 2007 due to poor oral hygiene and numerous caries lesions patient was referred to paediatric dentist for general oral sanitation (Figure 2). After sanitation only canines and second molars were present in patient's mouth and it was decided to engage removable, child's prosthesis in the treatment process, which was replacing missing teeth. Patient was using removable prosthesis from 2007 to 2013. New appliances were created throughout that time in order to accommodate

patient's growth and eruption of permanent teeth. In February 2012, lower Schwarz appliance with Fisher's screw, Adam's clasps and short labial bow was included in treatment process. Patient's guardian was instructed to expand appliance once a week.

In 2013 and 2014 patient received series of two surgeries in Dallas, USA, in order to perform craniofacial osteoplasty. Serious maxillary under-development was corrected, facial features were significantly improved, and patient's profile was no longer concave (Figures 3 and 4).

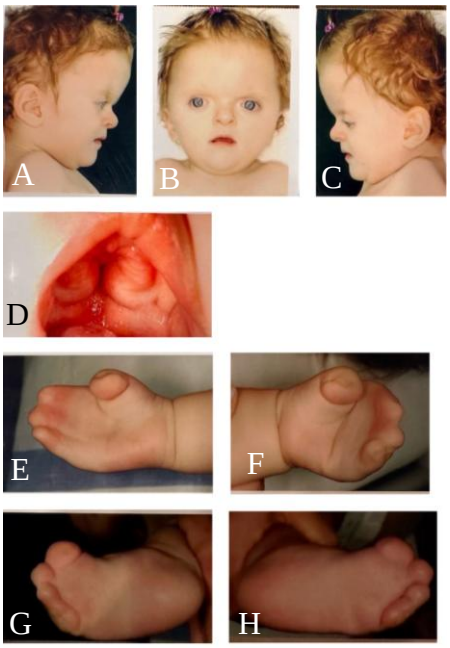

Fig. 1. Patient aged 2 years, during initial visit at Clinic of Congenital Abnormalities. Figures A–C present patient's face and profile before any orthodontic interventions, figure D presents cleft palate, figures E–H show hands and feet with syndactyly before surgical intervention.

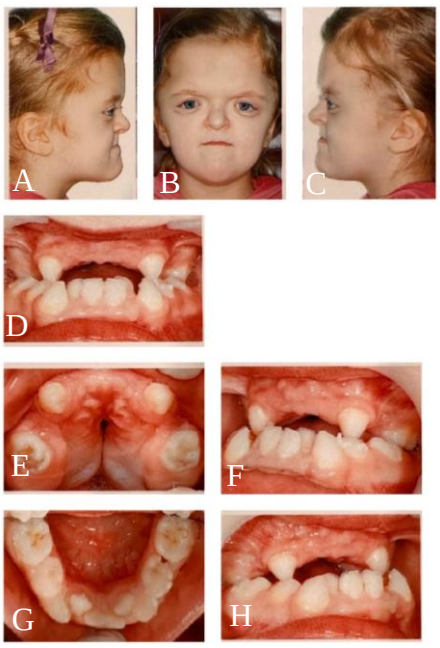

Fig. 2. Patient aged 5 years. Figures A–C present patient's face and profile in early childhood period, figures D–H show teeth and occlusion in deciduous dentition after general dental sanitation.

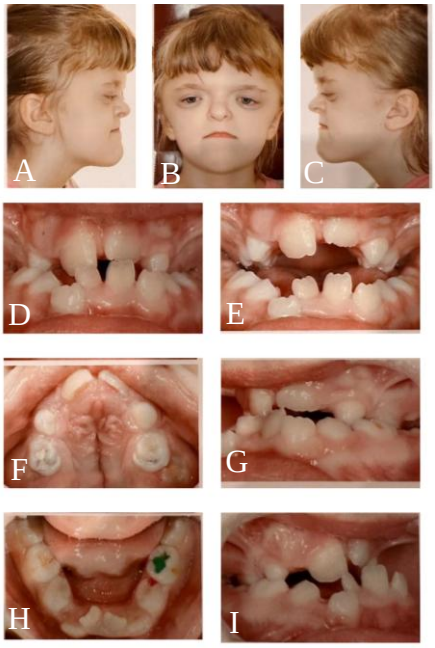

Fig. 3. Patient aged 10 years. Figures A–C present patient's face and concave profile before surgical interventions, figures D–I show teeth and occlusion in mixed dentition period, crossbite, severe crowding and reverse overjet is visible.

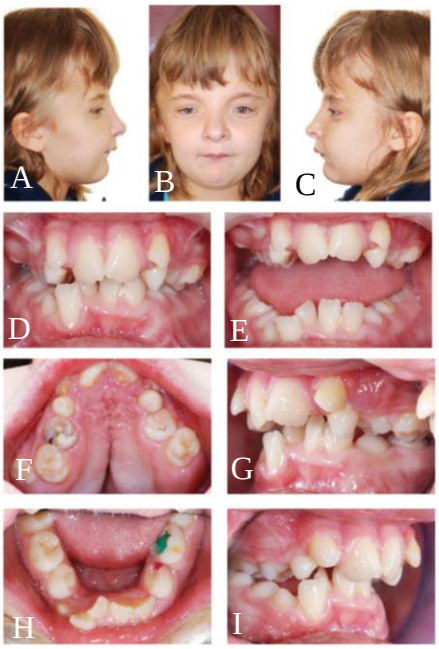

Fig. 4. Patient aged 12 years. Figures A–C present patient's face and convex profile after surgical interventions, figures D–I show teeth and occlusion in mixed dentition period, crossbite and severe crowding persist. However, correct overjet is now visible.

In December 2014 treatment plan was created based on panoramic radiograph, cephalometric radiograph and cephalometric analysis (according to Bjork's method), patient was 11 years 10 months old at the beginning of the treatment with fixed braces. The main treatment objectives were:

- aligning teeth in upper and lower arch
- correction of jaws relation, patient after surgical treatment (craniofacial osteoplasty) presented skeletal II class malocclusion
- space gain and management for severely crowded lower incisors
- expansion of upper arch and management of crowded and palatally erupted permanent teeth in maxilla, first left upper premolar in 180° rotation
- correction of right lateral crossbite
- correction of incisors relation: overjet and overbite
- aesthetical and functional improvement of patient's occlusion.

The treatment with fixed braces (0.022″ MBT (McLaughlin-Bennett-Trevisi) prescription) in the upper arch was initiated on 15 December 2014. The brackets on teeth 14, 12, 11, 21, 22, 24 and bands on 16, 26 were bonded. Fixed braces in lower arch were added on 25 February 2015, initially engaging also deciduous teeth present in patient's mouth, successively replaced with permanent dentition. The main objectives which determined the time of treatment were: complete lack of space and 180° rotation of first left upper premolar and palatally positioned right canine (Figures 5 and 6). Active treatment with fixed braces finished on 4 December 2020 and lasted almost 6 years. At the end of treatment patient aged 17 years 10 months. After removing fixed braces clear, removable retainers were created (Figure 7).

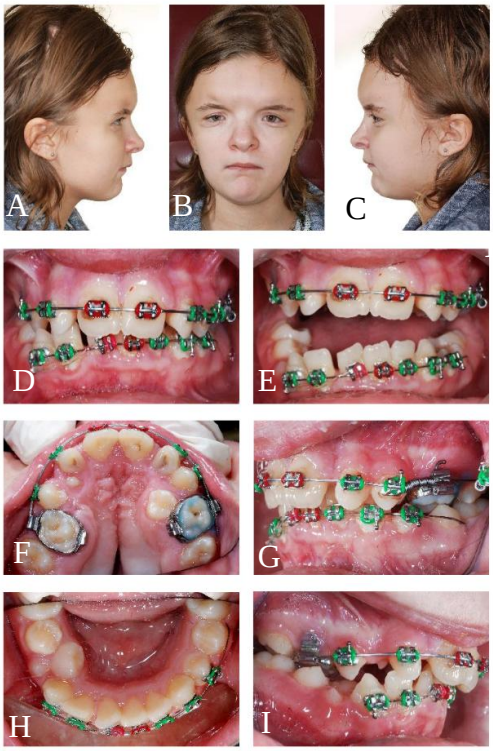

Fig. 5. Patient aged 13 years. Figures A–C present patient's face and profile after first few months of orthodontic treatment, figures D–I show teeth and occlusion after levelling phase.

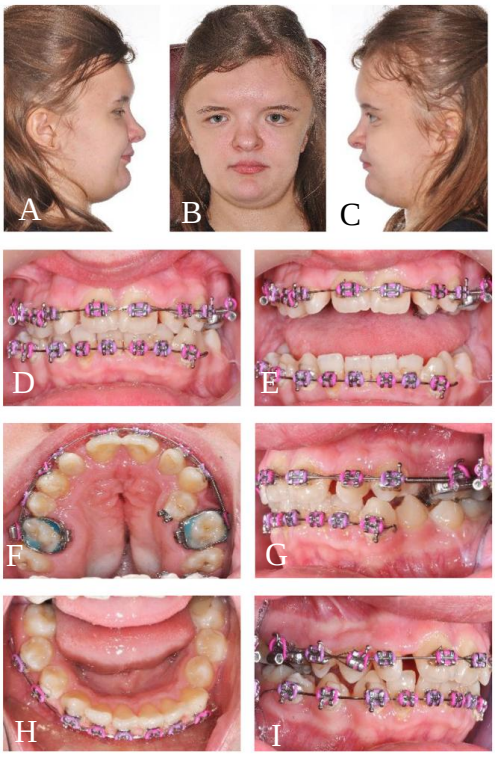

Fig. 6. Patient aged 16 years. Figures A–C present patient's face and profile during active orthodontic treatment with fixed braces, figures D–I show teeth and occlusion during finishing phase of orthodontic treatment.

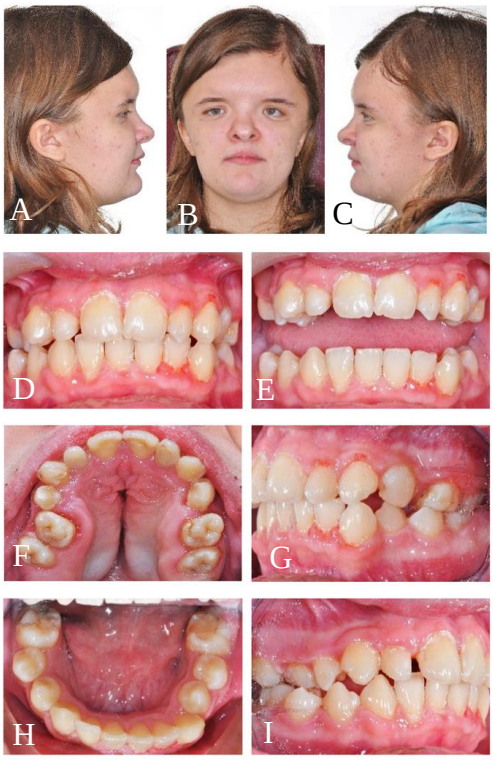

Fig. 7. Patient aged 17 years. Figures A–C present patient's face and profile after orthodontic treatment, figures D–I show teeth and occlusion with braces removed.

The outcome of the treatment is not ideal however, rather satisfying, considering all limitations and complexity of presented case. At the end of the treatment patient had correct overjet and overbite, moderate correction of right lateral crossbite (first right upper molar remained in crossbite), no severe crowding in upper and lower arch (however, some minor crowding still persist in lower arch), right canine aligned within upper arch, first left upper premolar partially derotated and aligned within upper arch, as well as acceptable jaws relation, satisfactory aesthetic and function. Nevertheless, due to the lack of second upper premolars, I Angle's class was impossible to achieve. The main impediment throughout treatment process was poor oral hygiene, despite numerous schoolings and oral hygiene instructions. Furthermore, frequent mechanic failures of bonded elements and wires leaded to elongation of active treatment process. Finally, orthodontic treatment was financed from the Polish National Health Fund (Narodowy Fundusz Zdrowia – NFZ). Patient was included in the governmental programme of orthodontic care for children with congenital defects of the facial skeleton. Even though the programme offered wider range of sponsored treatment methods compared to treatment of children who did not present any defects, some innovative solutions were not sponsored and therefore could not be included during treatment. NFZ financing was a serious limitation which played a key role during creation and realization of treatment plan which based on accessible appliances and protocols.

During almost 4-year follow-up occlusion and treatment results were stable. Patient had few sets of retainers done during retention period. Quick destruction of retainers indicated that bruxism may occur, especially during the night. In 2022 patients was diagnosed with bruxism and she is currently using nightly upper mouth splint. Patient is still visiting Clinic of Congenital Abnormalities every six months for follow-up.

DISCUSSION AND CONCLUSIONS

Apert syndrome is a rare congenital disorder characterized by craniosynostosis, syndactyly, and midface hypoplasia. It presents a significant challenge in orthodontic management. Patients with this condition typically exhibit a complex combination of craniofacial and dental anomalies, including severe class III malocclusion, narrow dental arches, often accompanied by a posterior crossbite, anterior open bite and crowding, necessitating a multidisciplinary approach to treatment [5]. The timing of orthodontic treatment in Apert syndrome is critical and must be well coordinated with planned surgical interventions [6]. Early orthodontic treatment is often delayed due to the need for cranial surgeries aimed at correcting craniosynostosis, which typically take priority during infancy and early childhood [7]. However, removable appliances used during early orthodontic treatment could be beneficial throughout treatment process, by modulating shape of arches and increasing patient's cooperation and systematicity [8]. Orthognathic surgery plays a pivotal role in managing the skeletal discrepancies in Apert syndrome. Maxillary advancement, often through Le Fort III osteotomy or distraction osteogenesis, is frequently required to correct midface retrusion, to advance the maxilla and improve facial aesthetics, airway function, and occlusion [9,10]. Intraoral management of crowding, crossbite and malposition of the teeth requires detailed diagnostics and often multi-annual treatment with fixed braces [11].

Due to the progressive nature of craniofacial growth in Apert syndrome, orthodontic treatment often extends over a long period, sometimes well into adulthood. Long-term retention is essential to prevent relapse. Fixed retainers or removable appliances may be employed depending on the severity of the case and the specific dental movements achieved during treatment. In presented case use of removable retainer might have been the reason why bruxism was developed. There are studies which indicate that disclussion caused by retainer may affect masticatory muscles and their response [12,13]. Nevertheless,

advanced malocclusion, complex treatment procedures and comprehensiveness of treatment often results in recurrence of some initial occlusal problems [14]. In presented case there was a relapse of right posterior crossbite. Moreover, continued follow-up is necessary as the craniofacial skeleton remains dynamic and can continue to change as the patient matures [15]. Beyond the physical challenges, patients with Apert syndrome also face significant psychosocial difficulties related to their appearance and speech. Orthodontic treatment can have a profound impact on a patient's quality of life by improving facial aesthetics and dental function, which in turn can enhance self-esteem and social interactions [16].

Apert syndrome often requires surgical intervention to address cranial, facial, and dental deformities. Early surgical management is crucial to prevent neurological complications, optimize appearance, and enhance function. Cranial vault remodeling is a cornerstone of surgical management, aimed at reducing the risk of increased intracranial pressure and improving neurodevelopmental outcomes. This procedure typically involves a frontal-orbital advancement to expand the skull, thus addressing craniosynostosis and preventing brain compression. Timing of surgery is critical, usually performed in infancy or early childhood, to facilitate optimal brain development. Distraction osteogenesis has also emerged as a valuable technique for facial reconstruction. This method involves the gradual lengthening of bones, particularly the maxilla, to correct midfacial hypoplasia and improve facial aesthetics and airway function. Distraction osteogenesis is often used in combination with other surgical approaches to address skeletal deformities and facilitate gradual, controlled expansion. This technique allows for better facial balance while minimizing the need for extensive bone grafting. Surgical management also involves correction of ocular anomalies and ear deformities. Timing and multidisciplinary coordination are essential for optimal outcomes in these patients [17,18,19,20].

The orthodontic treatment of patients with Apert syndrome is highly complex and requires a multidisciplinary approach that includes orthodontists, maxillofacial surgeons, and other healthcare providers. Timing of treatment, the use of advanced surgical techniques and long-term retention strategies are crucial for achieving successful outcomes. Despite the challenges, significant advancements in both orthodontic and surgical techniques have greatly improved the prognosis for these patients. Early diagnosis, careful planning, and ongoing collaboration between specialists remain key to optimizing both functional and aesthetic results in the orthodontic management of Apert syndrome.

In the presented case successful planning of surgical procedures and well-thought orthodontic treatment provided satisfying result for both the patient and the doctors. Despite numerous publications of successful management of Apert syndrome worldwide it is still challenging to achieve such a good result of treatment working only with the methods approved by governmental programme of orthodontic care for children with congenital defects of the facial skeleton of NFZ.

Authors' contribution

Study design – A. Ledwoń, N. Giża, L. Rodziewicz, U. Rojek
Manuscript preparation – A. Ledwoń, N. Giża, L. Rodziewicz, U. Rojek
Literature research – A. Ledwoń, N. Giża, L. Rodziewicz, U. Rojek
Final approval of the version to be published – A. Ledwoń, N. Giża, L. Rodziewicz, U. Rojek

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PRACA ORYGINALNA
ORIGINAL PAPER

Subtilisin/kexin type 9 protein convertase and interleukin 1 beta alterations in acute myocardial infarction

Zmiany ekspresji konwertazy białkowej subtylizyny/keksyny typu 9 oraz interleukiny 1 beta w ostrym zawale serca

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ABSTRACT

Lipids and inflammation are crucial components in acute myocardial infarction (AMI) pathophysiology. The aim of this study was to assess genetic expression of interleukin 1 beta (IL-1β) and subtilisin/kexin type 9 protein convertase (PCSK9) in AMI patients. 112 AMI patients – 55 with ST-segment elevation myocardial infarction (STEMI) and 57 with non-ST-segment elevation myocardial infarction (NSTEMI) – aged 35 to 92 (average age 65) were enrolled into the study. Control subjects were those with excluded coronary artery disease (CAD; n = 41) and with chronic coronary syndrome (CCS; n = 53). RNA extraction from peripheral blood mononuclear cells (PBMCs) using TRIzol Reagent (Invitrogen) method and genetic expression using quantitative real-time polymerase chain reaction (QRT PCR) method were performed. PCSK9 expression was higher ($p = 0.04$) and IL-1β lower ($p < 0.001$) in AMI subjects compared to controls. Higher PCSK9 transcriptional activity was found in more advanced stages of CAD, in male, in cases of increased body weight, decreased left ventricular ejection fraction (LVEF), and high-density lipoprotein (HDL) cholesterol concentration. Higher IL-1β expression was observed in patients with AMI and concomitant hypercholesterolemia. Thorough understanding of IL-1β and PCSK9 biology, key representatives of two basic pathophysiological links underlying myocardial infarction, is of great practical importance. This is particularly important due to currently wide availability of pharmacological intervention within metabolic pathways of these molecules.

KEYWORDS

protein convertase subtilisin/kexin type 9, interleukin 1 beta, acute myocardial infarction, gene expression, peripheral mononuclear blood cells

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STRESZCZENIE

Lipidy oraz zapalenie stanowią dwa fundamentalne ogniwa w patofizjologii ostrego zawału serca (*acute myocardial infarction* – AMI). Celem niniejszej pracy była ocena ekspresji genów interleukiny 1 beta (IL-1β) oraz konwertazy białkowej subtylizyny/keksyny typu 9 (*proprotein convertase subtilisin/kexin type 9* – PCSK9) u chorych z AMI. Do badania włączono 112 hospitalizowanych chorych z AMI, spełniających kryteria włączenia i wyłączenia – 55 z zawałem serca z uniesieniem odcinka ST (STEMI) oraz 57 z zawałem serca bez uniesienia odcinka ST (NSTEMI) – w wieku od 35 do 92 lat (średni wiek 65 lat). Grupę kontrolną stanowiły osoby z wykluczoną w koronarografii chorobą wieńcową (*coronary artery disease* – CAD; n = 41) oraz osoby z przewlekłym zespołem wieńcowym (*chronic coronary syndrome* – CCS; n = 53). Materiał RNA z komórek jednojądrzastych krwi obwodowej (*peripheral blood mononuclear cells* – PBMCs) uzyskano za pomocą metody TRIzol Reagent (Invitrogen), a ocenę ilościową ekspresji genów oceniano za pomocą metody reakcji łańcuchowej polimerazy w czasie rzeczywistym (*quantitative real-time polymerase chain reaction* – QRT PCR). Ekspresja PCSK9 była większa ($p = 0,04$), a IL-1β mniejsza ($p < 0,001$) u chorych z AMI w porównaniu z grupą kontrolną. Większą aktywność transkrypcyjną PCSK9 stwierdzono w bardziej zaawansowanych postaciach CAD, u mężczyzn oraz w przypadkach zwiększonej masy ciała, niższej frakcji wyrzutowej lewej komory (*left ventricular ejection fraction* – LVEF) i niższego stężenia cholesterolu frakcji HDL (*high-density lipoprotein*). Z kolei większą ekspresję IL-1β obserwowano u chorych z AMI i współistniejącą hipercholesterolemią. Dokładne zrozumienie biologii IL-1β i PCSK9, dwóch reprezentantów kluczowych ogniw patofizjologicznych w zawale serca, ma duże znaczenie praktyczne, szczególnie w kontekście szeroko aktualnie dostępnych metod farmakologicznej interwencji w ich szlaki metaboliczne.

SŁOWA KLUCZOWE

konwertaza białkowa subtylizyny/keksyny typu 9, interleukina 1 beta, ostry zawał serca, ekspresja genów, jednojądrzaste komórki krwi obwodowej

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains leading cause of morbidity and mortality in developed countries [1]. According to the most popular hypothesis, atherosclerosis is a chronic inflammatory process constituting a defensive response of vascular wall to damaging factors, especially hypercholesterolemia with the pivotal role of low--density lipoproteins (LDLs) [2]. Links between lipid metabolism and inflammation, key determinants in the pathophysiology of atherosclerosis, which is the main cause of acute myocardial infarction (AMI), are very complex and not fully understood. This paper aims to assess key molecules of these pathophysiological links, interleukin 1 beta (IL-1β) and subtilisin/kexin type 9 protein convertase (PCSK9), gene expression in AMI patients' peripheral mononuclear cells.

PCSK9 plays crucial role in the regulation of cholesterol homeostasis. It is a serine protease and ligand for the LDL receptor (LDLR). LDL binds to LDLR and is internalized being removed from circulation. It is then digested in lysosomes and LDLR is re-cycled to the surface, where continue its LDLs clearance. PCSK9 leads to lysosomal degradation of LDLR resulting in its decreased surface expression. It also inhibits recirculation of LDLR in hepatocytes. Abovementioned mechanisms result in lower LDLR expression and increased LDLs levels [3].

Inflammatory pathways drive atherosclerosis and are possible connection between conventional cardiovascular risk factors, atherosclerosis and its complications. The pivotal proinflammatory cytokine is IL-1β. It has become, in numerous clinical trials, the target of interventions aimed at inhibiting its action. Intracellular protein complex (NLR family pyrin domain containing 3 – NLRP3) forms a macromolecular structure called the NLRP3 inflammasome. Increased expression of NLRP3 inflammasome genes in human atherosclerotic plaques and their correlation with the severity of coronary artery disease (CAD) has been well proven [4,5].

Inflammation results in significant lipid and lipoprotein metabolism changes [6]. By reducing LDLR mRNA leads to an increase in very low (VLDLs) and LDLs and decrease of high-density lipoproteins (HDLs) cholesterol serum concentrations. Such a process has been well documented in an animal model with the use of lipopolysaccharide, which is often used as a model of infection and inflammation [7]. Moreover, it has been shown that reduced concentration of PCSK9 is associated with increased lipid clearance of pathogens by LDLR, reduced inflammatory response and better prognosis in patients with septic shock [8]. It was also shown that PCSK9 is present in atherosclerotic plaque and released from smooth muscle cells it is involved in the expression of LDLR in macrophages [9]. There is also some evidence for direct PCSK9 induction by inflammation [10].

Available data concern mainly the concentrations of studied molecules, which is not a simple, linear derivative of genetic expression. There is less data on gene expression itself, which is a very complex process. There are some data showing different expression and concentration levels of LDLR influenced by inflammatory process [11]. Links between the number

of gene transcripts and lipid profile are also unclear. The aim of the study was to assess mRNA levels of IL-1β and PCSK9 in peripheral blood mononuclear cells (PBMCs) of patients with AMI.

MATERIAL AND METHODS

The study protocol was approved by the Ethics Committee of Medical University of Silesia in Katowice (approval No. KNW/0022/KBI/98/15). All procedures were performed in accordance with the ethical standards formulated in the Helsinki Declaration. All participants have signed the informed consent.

112 patients, meeting the inclusion and exclusion criteria, admitted to the Department of Cardiology diagnosed with AMI (ST-segment elevation myocardial infarction – STEMI n = 55 and non-ST-segment elevation myocardial infarction – NSTEMI n = 57) were enrolled into the study. The inclusion criteria were: typical angina in the last 24 hours preceding admission to the hospital, abnormal electrocardiogram (ECG), biochemical evidence for cardiac necrosis, and CAD confirmed in coronary angiography. The exclusion criteria were: ongoing use of statins, lack of informed consent, previous severe heart failure (left ventricular ejection fraction – LVEF < 35%), malignancy, active infection, contact difficulties (stroke, mental disorders), and severe renal failure (estimated glomerular filtration rate – eGFR < 30 ml/min/m^2). Control group involved 53 patients with chronic coronary syndrome (CCS) and 41 subjects with excluded CAD, in whom no changes on coronary angiography were visualized (i.e. high risk occupation, myocardial bridge). Within 24 hours from admission, a detailed medical history was taken and following procedures were performed: physical examination, standard 12-lead ECG, echocardiography as well as blood samples were taken for biochemical and molecular analyses. Biochemical tests included: blood count cell, serum levels of electrolytes, creatinine, glucose, lipid profile and markers of myocardial necrosis: cardiac troponin T and creatine kinase MB (CK-MB) isoenzyme.

Material for molecular tests was peripheral venous blood. The research was carried out on easily available population of PBMCs, which is of key importance in the inflammatory process – lymphocytes and monocytes. RNA extraction was performed using TRIzol Reagent (Invitrogen). Evaluation of genetic expression of studied genes was performed using the quantitative real-time polymerase chain reaction (QRT PCR) method. Expression of studied genes was inferred from the mRNA copy number per 1 μg of total RNA.

Statistical analysis was performed using MedCalc and Statistica v.12.0 software. For quantitative variables number, arithmetic means, minimum and maximum value, and standard deviations (SD) of the estimated parameters were calculated. Qualitative variables were analyzed by calculating number and percentage of each value. The Shapiro-Wilk test was used to test the distribution of analyzed variables. Because the analyzed variables significantly differed from the normal distribution, non-parametric the Mann-Whitney U and Kruskal-Wallis tests were applied. Frequency analysis was conducted using Fisher's exact test or χ^2 test. The non-parametric Spearman correlation coefficient was used to analyze the correlation between selected parameters. A p-value of 0.05 or below was considered statistically significant.

RESULTS

General characteristics

Characteristics of the study group, taking into account demographic data, cardiovascular risk factors, and comorbidities is presented in Table I.

Majority of study group were men. Patients with myocardial infarction (MI) were more often current smokers and had positive family history for CAD compared to controls. They were also less frequent obese. There were no statistically significant differences between STEMI and NSTEMI individuals regarding demographic data, cardiovascular risk factors, and comorbidities occurrence.

The results of laboratory tests in the studied group are presented in Table II.

Table I. Characteristics of studied population of patients with acute myocardial infarction and controls including demographic data, cardiovascular risk factors and comorbidities

Entire studied group n = 206							
Parameter n; % of subgroup	MI n = 112 (100%)		CCS n = 53 (100%)		non-CAD n = 41 (100%)		p-value
Age [yrs] range mean	32–92 $\bar{x}$ 63.88		48–84 $\bar{x}$ 67.83		26–77 $\bar{x}$ 53.61		**0.004**
	number [n]	percentage [%]	number [n]	percentage [%]	number [n]	percentage [%]	
Sex	W = 32	28.6	W = 19	35.8	W = 19	46.3	0.114
Cardiovascular risk factors							
FH	29	26	5	9.4	6	14.6	**0.03**
Current smokers	47	42	9	17	3	7.3	**< 0.005**
Ex-smokers	37	33	22	41.5	15	36.6	0.567
Obesity	27	24	37	69.8	18	43.9	**0.002**
Comorbidities							
AH	86	77	46	86.8	25	61	**0.014**
DM/IFG/IGT	42	37.5	26	49	10	24.4	**0.049**
PAD	11	10	9	17	0	0	**0.029**
AF	13	12	16	30	8	19.5	0.104
CAD	28	25	41	77	0	0	**< 0.005**

MI – myocardial infarction; CCS – chronic coronary syndrome; non-CAD – patients without coronary artery disease; W – women; FH – family history positive for cardiovascular disease; AH – arterial hypertension; DM – diabetes mellitus; IFG – impaired fasting glycaemia; IGT – impaired glucose tolerance; PAD – peripheral artery disease; AF – atrial fibrillation; CAD – coronary artery disease history.

Table II. Results of laboratory tests in studied group

Parameter	non-CAD n = 41		MI n = 112		CCS n = 53		p-value
	$\bar{x}$	± SD	$\bar{x}$	± SD	$\bar{x}$	± SD	
Total cholesterol [mg/dl]	152.38	32.15	189.34	47.97	171.33	46.30	**0.026**
HDL cholesterol [mg/dl]	47.25	16.68	40.52	12.4	52.13	25.32	0.0569
LDL cholesterol [mg/dl]	76.75	28.79	120.91	46.88	93.67	39.45	**0.001**
Triglycerides [mg/dl]	143	50.72	150.0	69.86	135.75	96.49	0.141
Troponin T on admission [ng/ml]	0.0088	0.004	0.56	1.20	0.015	0.009	**< 0.001**
Troponin T – control [ng/ml]	0.0045	0.002	1.52	1.20	0.015	0.09	**< 0.001**
Glucose [mg/dl]	104.78	21.28	140.91	59.81	114.76	35.23	**< 0.001**
Creatinine [mg/dl]	0.96	0.22	0.93	0.26	0.96	0.31	0.870

n – number; $\bar{x}$ – average; SD – standard deviation; non-CAD – patients without coronary artery disease; MI – myocardial infarction; CCS – chronic coronary syndrome; HDL – high-density lipoprotein; LDL – low-density lipoprotein.

In MI patients higher values of total cholesterol and LDLs were found, as well as lower levels of HDLs cholesterol compared to individuals with CCS and those with excluded CAD. There was also higher serum glucose concentration.

In STEMI compared to NSTEMI slightly higher glucose level was observed (143 mg/dl vs 131 mg/dl; p = 0.004). No other significant differences were observed in basic laboratory tests in the group of patients with AMI, taking into account the type of diagnosed MI (STEMI vs NSTEMI).

PCSK9 and IL-1β expression

IL-1β and PCSK9 gene expression in studied group are shown in Figure 1.

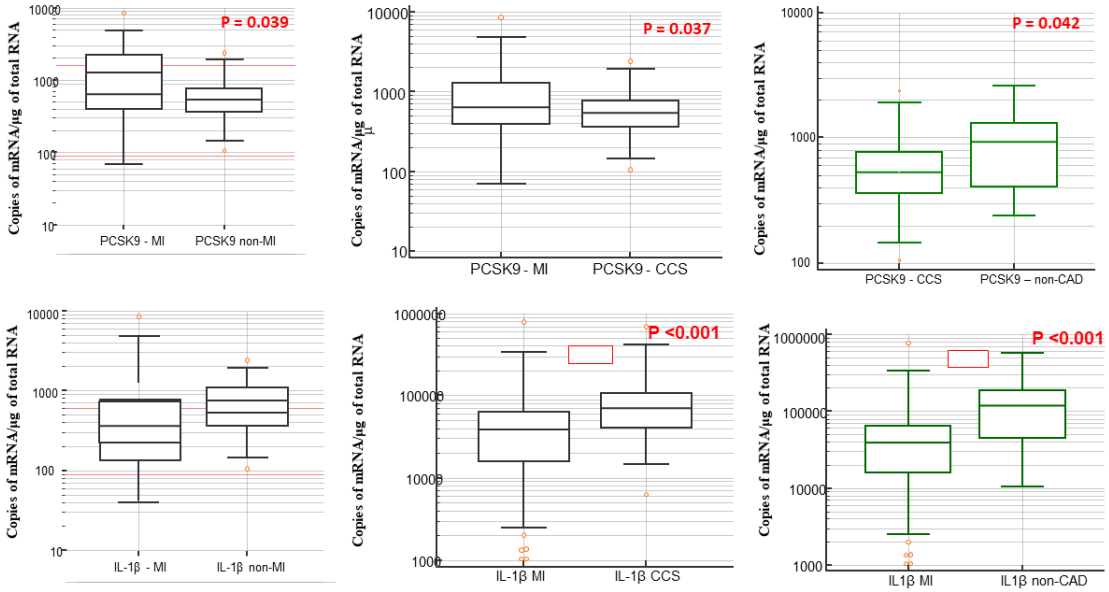

Fig. 1. Subtilisin/kexin type 9 protein convertase and interleukin 1 beta gene expression in patients with coronary artery disease. MI – myocardial infarction; CCS – chronic coronary syndrome; non-CAD – excluded coronary artery disease; PCSK9 – subtilisin/kexin type 9 protein convertase; IL-1β – interleukin 1 beta. Data analyzed using the Mann-Whitney U test.

AMI patients had higher expression of PCSK9 gene compared to the patients with CCS and those with excluded CAD (p = 0.037 and p = 0.042 respectively; Mann-Whitney U test). In turn, expression of IL-1β gene was lower in the AMI group compared to the group with stable form of CAD (p < 0.001) as well as those in whom CAD was excluded (p < 0.001). There were no significant differences in both, PCSK9 and IL-1β, gene expression regarding type of MI – STEMI vs NSTEMI (p = 0.1881 and p = 0.6858 for PCSK9 and IL-1β respectively).

In patients with AMI number of significant artery narrowings was related to higher PCSK9 gene expression (p = 0.038), but no such relationship was found in case of IL-1β (p = 0.416). Significantly higher PCSK9 mRNA level was found within patients burdened with poor prognosis factors, such as: male sex (p = 0.006), increased body weight (p = 0.05), reduced HDL cholesterol concentration (p = 0.04), and reduced LVEF (p = 0.210; ns).

Abnormal lipid profile was associated with increased expression of IL-1β gene in patients with MI compared to the controls (p = 0.025). Results of genetic expression analysis of IL-1β and PCSK9 in patients with MI, taking into account inappropriate lipid profile according to the current guidelines of the European Society of Cardiology on the management of dyslipidemias (total cholesterol > 190 mg/dl and/or LDL > 55 mg/dl and/or HDL < 45 mg/dl in women and < 40 mg/dl in men and/or triglycerides > 150 mg/dl) [12] are presented in Table III. The subjects belonged to the group of high or very high cardiovascular risk categories.

Within AMI patients elevated triglycerides and total cholesterol levels were connected with increased IL-1β expression (p = 0.027 and p = 0.056, respectively). PCSK9 expression was higher among men with lower HDL concentration (p = 0.044). Increased expression of both molecules – IL-1β and PCSK9 was demonstrated in cases of atherogenic dyslipidemia. These results are presented in Figure 2.

Table III. Subtilisin/kexin type 9 protein convertase and interleukin 1 beta genetic expression in studied group of patients regarding coexistence of abnormal lipid profile

Parameter	Subgroup	PCSK9	IL-1β
Triglycerides	MI_TG_n vs MI_TG_a	0.320	0.027
Total cholesterol	MI_TC_n vs MI_TC_a	0.488	0.056
HDL (women)	MI_HDL_W_n vs MI_HDL_W_a	0.807	0.387
HDL (men)	MI_HDL_M_n vs MI_HDL_M_a	0.044	0.940
LDL	MI_LDL_n vs MI_LDL_a	0.834	0.066

PCSK9 – subtilisin/kexin type 9 protein convertase; IL-1β – interleukin 1 beta; HDL – high-density lipoprotein; LDL – low-density lipoprotein; MI – myocardial infarction; _n – normal value; _a – abnormal value; TG – triglycerides; TC – total cholesterol; W – women; M – men. Data analyzed using the Kruskal-Wallis test.

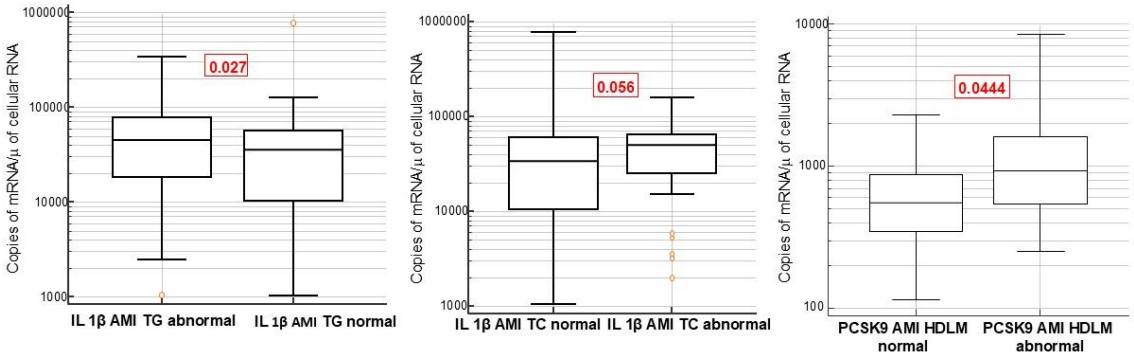

Fig. 2. Expression of interleukin 1 beta and subtilisin/kexin type 9 protein convertase genes in patients with acute myocardial infarction regarding lipid profile. IL-1β – interleukin 1 beta; AMI – acute myocardial infarction; TG – triglycerides; TC – total cholesterol; PCSK9 – subtilisin/kexin type 9 protein convertase; HDLM – high-density lipoproteins in men. Data analyzed using the Mann-Whitney U test.

DISCUSSION

PCSK9 plays a pivotal role in cholesterol metabolism by affecting the LDLR and reducing its levels on the plasma membrane [13]. In our study higher expression of PCSK9 was found in the group of patients with AMI compared to patients with CCS and those with excluded CAD ($p = 0.037$ and $p = 0.042$ respectively). This is consistent with the results obtained by other authors [14]. Available results of experimental studies indicate that inflammation can induce PCSK9 gene expression [15]. PCSK9 expression is not only restricted to the liver, but also occurs in the vascular wall and in inflammatory cells. The expression of PCSK9 was also demonstrated in atherosclerotic plaques [16]. Increase in PCSK9 concentration results in increased LDLR degradation, consequently leading to increased serum cholesterol levels. We have demonstrated increased expression of PCSK9 gene in case of atherogenic dyslipidemia. Additionally, it turned out that higher expression of PCSK9 gene occurred in the group of men and was associated with lower HDL concentration. This may be responsible for their worse prognosis. Further studies are needed to determine the influence of PCSK9 gene expression on lipid metabolism abnormalities and MI patient outcomes. PCSK9 expression may turn out to be valuable prognostic marker in that group of patients.

Atherosclerosis is considered to be an inflammatory disease. Atherosclerotic plaque formation is lipoprotein-dependent disease characterized by inflammation, proliferation, necrosis, and calcification in arterial wall [17]. Various inflammatory mediators and scavenger receptors have been implicated in inflammatory response in atherosclerosis. Plaque macrophages are able to modify, by oxidation, accumulated LDL to form ox-LDL [18]. LDLRs are not required for endocytosis of ox-LDL by monocytes/macrophages. Different scavenger receptors, like SRA, CD36, and LOX-1, are involved in this phenomenon. Their expression in highly increased by inflammatory stimuli [19]. There is evidence supporting direct relationship between PCSK9 and inflammation response. Ding et al. [20] demonstrated that in an inflammatory milieu, elevated levels of PCSK9 potently stimulate the expression of scavenger receptors and ox-LDL uptake in macrophages, and thus contribute to the process of atherogenesis. Human recombinant PCSK9 has been shown to directly activate macrophages as indicated by macrophage migration and release of proinflammatory cytokines [21]. There are also data confirming direct links between PCSK9 and IL-1β expression. Ding et al. [22] demonstrated that NLRP3 inflammasome induction via IL-1β induces PCSK9 secretion.

IL-1β is prototypical proinflammatory cytokine produced by macrophages, endothelial and smooth muscle cells. It is mainly activated by tumor necrosis factor alpha (TNF-α) as response to inflammation and plays multiple functions in blood vessel wall. Its atherosclerotic effect has been proven in experiments with the mouse model [23]. Due to its numerous and potent atherosclerotic effects on a number of cells, IL-1β appears to be one of the most important cytokines involved in inflammatory vascular diseases, especially atherosclerosis resulting in MI. IL-1β gene is located in chromosome 2. Gene expression is very complex process that depends on many factors. The pro IL-1β gene consists of seven exons with a primary transcription product length of 7008 nucleotides. IL-1β is formed as a precursor and is then activated in the inflammasome by caspase 1 with a significant contribution of NLRP3. It was shown that deletion of the IL-1 receptor was protective against ischemia and reperfusion injury in AMI models, resulting in smaller infarct size, reduced left ventricular enlargement and reduced left ventricular dysfunction [24]. It has also been shown that a single nucleotide polymorphism mutation in the IL-1β gene is associated with lower expression of basal C-reactive protein (CRP) concentration in healthy subjects. Elevated basal

CRP levels are, in turn, associated with increased cardiovascular risk [25]. Inflammasome and consequently production of active IL-1β form is stimulated by pathogen-related molecular patterns (PAMPs) and alarmins – damage-related molecular structures (DAMPs), which include cholesterol crystals. Ischemia and reperfusion related myocardial damage leads to impaired function of the viable myocardium, inducing an intense inflammatory response expressed by inflammasome activation, maturation of IL-1β and other proinflammatory cytokines [26]. Furthermore, IL-1β aggravates the dysfunction of myocardium resulting in its subacute damage, impaired contractility and a decrease in reactivity of beta adrenergic receptors. This leads to the stimulation of apoptosis, dilatation of the left ventricle and reduced response of beta adrenergic receptors [27]. There are many possibilities of pharmacological IL-1β blocking at different levels of its action.

We showed lower number of IL-1β gene transcripts in the group with AMI compared to the controls. However, majority studies conducted so far have shown an increased concentration of that cytokine in the post-infarction period [28,29]. These discrepancies can result from several issues. Firstly, in the majority of studies concentration of IL-1β and not, as in our study, gene expression, was assessed. Gene expression is the starting point for the formation of final product – protein. This is a multistage process. Even very high gene expression does not have to translate into a high concentration of the protein. Translation is controlled at many levels, starting with gene expression, its secretion and extracellular processing. In addition, it should be noticed that protein serum concentration applies to its entire pool, regardless of the source of its origin. In turn, gene expression (number of transcripts) refers to a specific population of cells – in this case, peripheral blood mononuclears, important for inflammation.

It is well known that the role of IL-1β is crucial in the postinfarction period, taking part in the inflammatory response, infarct healing and myocardial remodeling, which take place somewhat later [30]. In the AMI mouse model, it was shown that IL-1β genetic expression increases mostly in the first hours of acute ischemia, peaking at 6 hours since first symptoms, and then significantly decreases [31]. In our study blood samples for molecular testing were taken within the first 24 hours from hospital admission (not clinical presentation) which may explain lower expression of IL-1β in our study group. It seems that possible anti--inflammatory treatment in AMI should be ordered at the very beginning. This requires further clinical investigation.

In patients with AMI, increase in IL-1β gene expression was demonstrated in the groups with increased level of triglycerides ($p = 0.0564$) and total cholesterol ($p = 0.0444$). Available data regarding IL-1β gene expression and lipid profile in patients with AMI are scarce and often inconsistent.

Human atherosclerotic plaques are inflammatory lesions in which immune cells and inflammatory molecules are detectable in large levels. CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) confirmed the inflammatory theory of atherosclerosis and shed new light on the role of IL-1β in determining cardiovascular risk [32]. Canakinumab, an IL-1β blocking antibody, prevented the recurrence of ischemic events in patients who had experienced AMI in a study of 10,061 patients. Also phase II clinical trial showed promising data with anakinra, a recombinant IL-1 receptor antagonist, in patients with STEMI or heart failure with a reduced ejection fraction [33]. Unlike other anti-inflammatory drugs, in CANTOS, canakinumab did not affect cholesterol but slightly increased triglycerides, so that cardiovascular prophylactic effects were not dependent on any lipid effects related to IL-1β function.

Statins have become pillars of prevention and treatment of atherosclerotic cardiovascular disease. In addition to the lipid lowering effect, statins have various pleiotropic effects that include modulation of the inflammatory response [34]. Statins can increase PCSK9 expression thus in our study patients on statin therapy were not included into the study. Since the use of statins was an exclusion criterion, the recruitment process of patients and the control group was relatively long (about 2 years) – these were not patients subsequently hospitalized (all comers) due to MI, which is a certain limitation of this study. Abovementioned CANTOS study caused IL-1β has recently become an effective and relatively safe target for secondary cardiovascular prevention in patients with residual inflammation. Statins, although generally perceived as anti-inflammatory drugs, may have different effects on the synthesis of IL-1β in different cells, and some studies even show a paradoxical increase in its concentration after treatment with statins [35]. Given the deleterious role of IL-1β in the pathophysiology of MI, the addition of canakinumab to statins in these patients may provide a stronger inhibition of the IL-1β mediated inflammatory response.

It is commonly accepted that concentration of PCSK9 in AMI is increased, the data on the behavior of PCSK9 in the context of the advancement of CAD are inconclusive. We demonstrated that transcriptional activity of the PCSK9 in AMI patients increased along with advancement of CAD (number of significant coronary artery changes), but the difference turned out to be statistically insignificant. Interesting data in this regard was provided by Almontashiri et al. [14], which is an analysis of two independent, large, angiographic retrospective studies. Based on data analysis from

Ottawa Heart Genom Study (OHGS), it is known that in carefully selected 18 patients (without diabetes and without previous lipid-lowering treatment) with angiographically confirmed coronary heart disease, PCSK9 levels were not associated with the advancement of the disease. The same study found that PCSK9 levels were increased in the case of acute, but not previous, myocardial infarction. On the other hand, in the EmCB (The Emory Cardiology Biobank) study, in a similar group of patients, the concentration of PCSK9 was higher in the group of patients with angiographically proven coronary disease – the concentration of PCSK9 turned out to be an independent predictor of its occurrence. As in the OHGS group, also in the EmCB study, increased levels of PCSK9 were found in patients with acute, but not previously suffered, myocardial infarction.

Our study is not devoid of several limitations. In the field of study material, a significant limitation is the number of patients examined and overrepresentation of men in the studied group. The study is also limited by the single stage of genetic expression measurement – blood samples were taken within first 24 hours from admission. As mentioned above it could influence obtained results regarding especially IL-1β expression which can be time dependent in case of AMI. Finally, there is also lack of PSCK9 and IL-1β blood concentration assessed. However, this is the first step of research aimed to asses PSCK9 and IL-1β genetic expression in real-world AMI patients. Further exploring of PSCK9 and IL-1β expression and their relationship in cell models are planned.

CONCLUSIONS

Thorough understanding of IL-1β and PCSK9 biology, key representatives of two basic pathophysiological elements underlying MI, inflammation and lipid abnormalities, is of great practical importance. Known poor prognostic value of lipid disorders, such as increased concentration of total and reduced of HDL cholesterol, are reflected in the expression of PCSK9 and IL-1β. Further research is needed to assess the importance of predictive determination of IL-1β and PCSK9 genetic expression. This is particularly important due to currently wide availability of pharmacological intervention within metabolic pathways of these molecules.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Medical University of Silesia, Katowice, Poland (approval No. KNW/0022/KBI/98/15).

Conflict of interest

The authors declare no conflict of interest.

Authors' contribution

Study design – M. Majewski, J. Dąbek, Z. Gąsior
Data collection – M. Majewski, J. Głogowska-Ligus
Data interpretation – J. Dąbek, Z. Gąsior, A. Kułach
Statistical analysis – J. Głogowska-Ligus
Manuscript preparation – M. Majewski, A. Kułach
Literature research – M. Majewski, A. Kułach

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OPIS PRZYPADKU
CASE REPORT

Laparotomy and hysterectomy performed due to massive hemorrhage in patient with cervical pregnancy – case report

Laparotomia i histerektomia wykonane z powodu masywnego krwotoku u pacjentki z ciążą szyjkową – opis przypadku

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ABSTRACT

A 40-year-old woman, gravida 5, para 3, at an estimated 9 weeks gestation, after three caesarean sections, was admitted to the Department of Gynaecology, Obstetrics and Oncological Gynaecology due to an ectopic pregnancy located in the cervix. On the fifth day of hospitalization, massive vaginal hemorrhage occurred. An unsuccessful attempt was made to evacuate the gestational sac via the vaginal route, ending with an urgent laparotomy and hysterectomy.

KEYWORDS

cervical pregnancy, ectopic pregnancy, hysterectomy

STRESZCZENIE

40-letnia kobieta, w dziewiątym tygodniu ciąży piątej, po trzech porodach przez cesarskie cięcie, została przyjęta na Oddział Ginekologii, Położnictwa i Ginekologii Onkologicznej z rozpoznaniem ciąży pozamacicznej zlokalizowanej w szyjce macicy. W piątej dobie hospitalizacji wystąpił masywny krwotok z dróg rodnych. Podjęto nieskuteczną próbę ewakuacji jaja płodowego drogą pochwową, zakończoną pilną laparotomią i histerektomią.

SŁOWA KLUCZOWE

ciąża szyjkowa, ciąża ektopowa, histerektomia

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INTRODUCTION

Cervical pregnancy (CP) is extremely uncommon, accounting for less than 1% of all ectopic pregnancies (EPs). In course of CP, the embryo implants and grows below the internal opening of the cervix [1]. Despite the rarity of CP, its prevalence is on the rise owing to the increased infertility treatments and invasive procedures, such as curettage and caesarean sections *(*CSs) [2,3]. Patients typically report painless vaginal bleeding. A higher level of beta-human chorionic gonadotropin (B-hCG) may indicate an abnormally located pregnancy, but the diagnosis requires further diagnostics, primarily imaging. Ultrasound (transvaginal and transabdominal) is commonly employed, and in cases of ambiguity, magnetic resonance imaging is utilized. Treatment of CP can be divided into conservative and surgical. Conservative includes pharmacological treatment (systemic or intra-amniotic methotrexate, with or without intra-amniotic potassium chloride) or expectancy [4]. This type of treatment can be chosen only if the patient consents to this method, is pain free, hemodynamically stable, serum B-hCG before treatment is less than 5000 mUI/ml, ectopic mass size is less than 4 cm in largest diameter, there is no ultrasound evidence of fetal heart activity, no concomitant intrauterine pregnancy, and no known sensitivity to methotrexate [4,5]. Curettage due to the risk of hemorrhage is most often used in combination with mechanical methods (cervical artery ligation, tamponade) [4]. Resection of CP is also possible using hysteroscopic or laparoscopic techniques with or without hemostatic management and laparoscopic uterine artery embolization [1]. Hysterectomy remains the method of choice in case of uncontrolled hemorrhage [4].

We report a case of a patient with EP in the area of cervix or CS scar, who failed hysteroscopic resection and underwent an urgent laparotomy and hysterectomy due to massive hemorrhage.

CASE REPORT

A 40-year-old woman, gravida 5, para 3, with three previous CSs and history of one spontaneous abortion was admitted to the Department of Gynaecology, Obstetrics and Oncological Gynaecology. The reason for admission was the diagnosis and treatment of an unspecified EP, which was suspected to be present in either the CS scar or the cervix. The patient's medical history included curettage of the uterine cavity after a miscarriage. There were no chronic diseases, allergies, alcohol consumption and nicotine addiction in patient's history. Body mass index was normal. B-hCG level primary was 14.879 IU/l, whereas two days later, it was 16.948 IU/l. There were no abnormalities in laboratory tests. The peripheral blood count revealed a hemoglobin (Hb) level of 13.5 g/dl, red blood cells (RBC) 4.57 mln/µl, white blood cells (WBC) 7.2 G/l, and hematocrit (HCT) 39.2%. Electrolyte levels and coagulation parameters were normal. On the second day of hospitalization, the patient reported painless bleeding. The transvaginal ultrasound showed the presence of a gestational sac (GS) with an embryo located in the cervical canal at the level of the internal os. The crown--rump length (CRL) was 28 mm. Gestational age calculated from the GS was estimated at 9 weeks and 4 days. Embryo cardiac activity was present with fetal heart rate (FHR) 132 bpm. Because of the proximity of the CS scar and cervical canal, the implantation of pregnancy within a CS scar was not possible to exclude. The cervix was found to be distended, numerous hypoechoic spaces were observed around the GS, and there was a significant increase in microvascular flow imaging (MV-Flow) around the GS (Figures 1 and 2). As the patient initially did not consent to the termination of the pregnancy, she was informed about possible complications. On the fifth day of hospitalization, heavy vaginal bleeding occurred. An ultrasound examination of the uterus revealed a distorted GS with an abnormal shape in the cervical area with no FHR. A significant vascularization with vascular invasion was evident in the area of CS scar and cervix. The cervix was dilated to 5.5 × 4.7 cm. A small amount of free fluid was observed in the pouch of Douglas. No fluid was detected in the Morrison's pouch, left renal lining, spleen, or between intestinal loops. The patient was qualified for surgery. Urgently, an attempt to hysteroscopic removal of the CP was made. Approximately 1000 ml of blood with clots was evacuated from the vagina. A distended, cyanotic, actively bleeding cervix was found. Due to the significant bleeding and difficulties in evacuation, which indicate a significant infiltration of the GS into the cervix, and the deteriorating general condition of the patient, it was decided to perform an urgent laparotomy and hysterectomy. The embryo was found to be growing into the cervical smooth muscles. A total of 100 ml of blood was present in the pouch of Douglas. There was a small amount of endometriosis on the surface of the left ovary, which had been coagulated. A cyst measuring 3 cm in diameter was surgically removed from the right ovary.

The fallopian tubes remained unchanged bilaterally. Adhesions were dislodged, the fallopian tubes and uterus were surgically removed. The material (fallopian tubes, uterus, right ovarian cyst) was examined histopathologically and the GS was collected for genetic testing at the patient's request.

The patient exhibited a favorable general state subsequent to the surgical procedure. The morphology at that time was: Hb level 9.0 g/dl, RBC 3.02 mln/µl,

WBC 19.9 G/l, and HCT 26.6%. She received three units of packed red blood cells. The Hb level increased to 11.9 g/dl, RBC 4.23 mln/µl, HCT 37.1%, and WBC decreased to 8.8 G/l. The following drugs were administered: paracetamol, morphine, metamizole, pethidine, ceftazidime, tranexamic acid, lutein, ethamsylate and enoxaparin. The patient was discharged and continued to receive enoxaparin 40 mg daily. Histopathological examination revealed that the cervical canal contained fragments consistent with embryo, which confirmed CP. The microscopic description of a right ovarian cyst revealed a hemorrhagic corpus luteum. The endometrium displayed signs of dyshormonosis, with focal transformation of the decidua stroma. Genetic testing revealed male genetic sex.

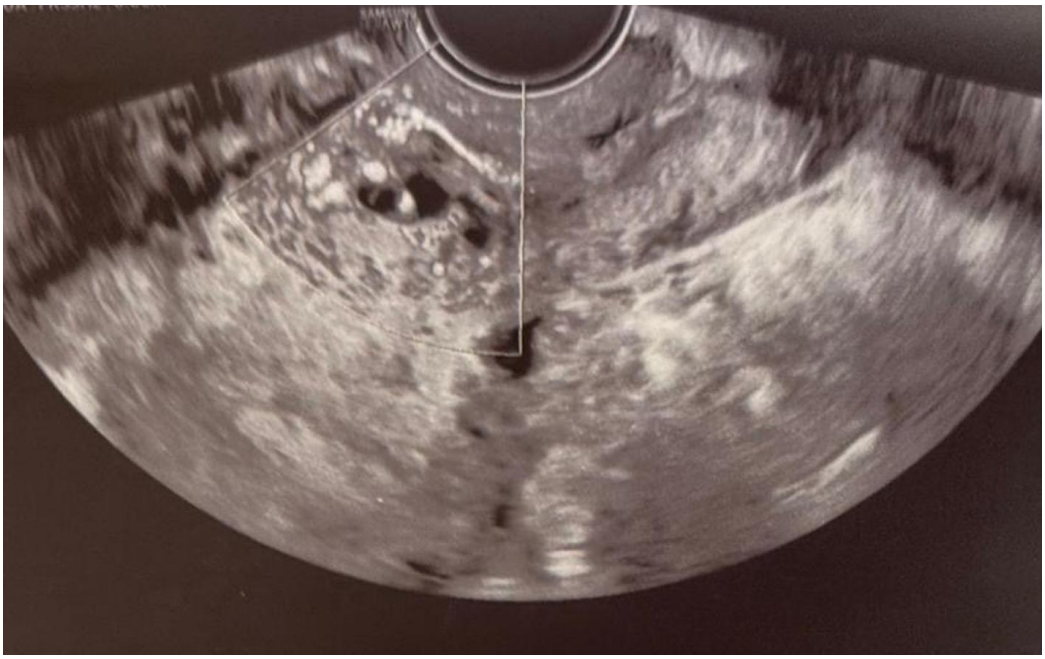

Fig. 1. Microvascular flow imaging around the gestational sac located next to the internal opening of the cervix.

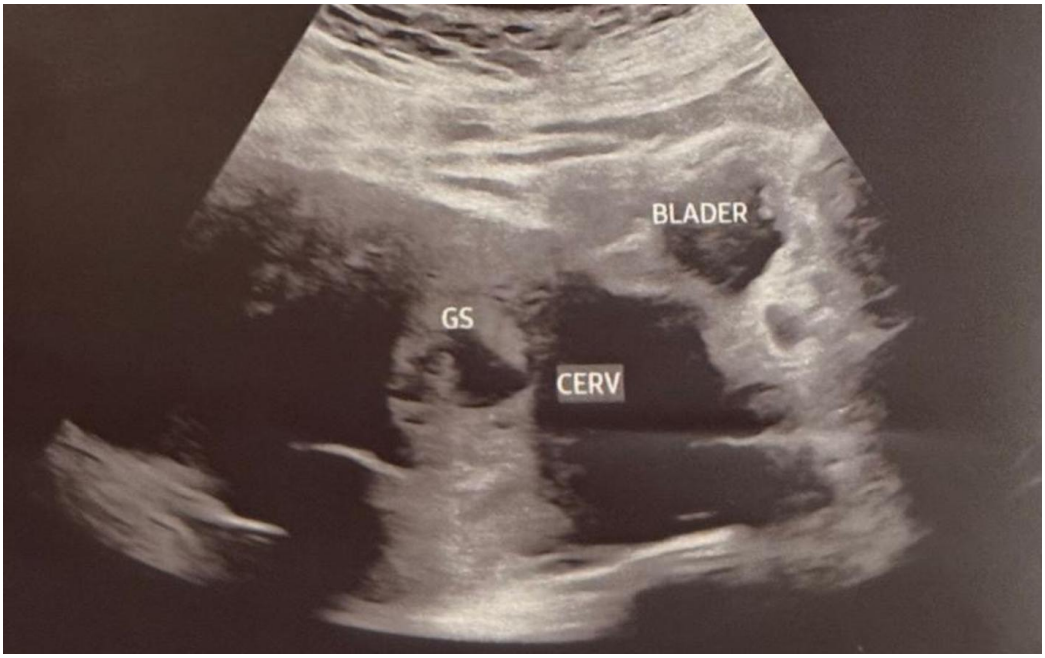

Fig. 2. The gestational sac in the area of caesarean section scar and the cervix. GS – gestational sac; CERV – cervix.

DISCUSSION

The patient's case presented two risk factors of EP – history of three previous CSs and curettage of the uterine cavity [3]. She was asymptomatic before hospitalization. The typical symptom of EP (painless bleeding) was not observed until the second day of hospitalization. However, patient's clinical condition deteriorated rapidly and massive bleeding occurred. Obstetric hemorrhage remains the leading cause of maternal mortality and morbidity [6]. EP, including CP, is one of the causes that may lead to massive hemorrhage [7]. This creates the need for a rapid diagnosis and initiation of appropriate treatment. At present, the optimal treatment for CP remains uncertain. Management should be based on international guidelines that consider the patient's medical condition. According to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommendations, conservative treatment was not appropriate for our patient [4]. Due to the deteriorating condition, after obtaining her consent, a decision was made to terminate the pregnancy by hysteroscopy. Unfortunately, this attempt was unsuccessful. Heavy bleeding led to life-saving laparotomy and hysterectomy.

There are cases similar to the one described [6,8] in which hysteroscopic resection of CP was not possible due to large blood loss. These patients most often required hysterectomy, traditionally performed abdominally. Alammari et al. [7] described the case of a patient with a CP and vaginal hysterectomy was chosen as the method of treatment. Bartosch et al. [8] reported the case of a woman with painless vaginal bleeding who was diagnosed with CP and underwent abdominal hysterectomy due to placenta accrete. The placenta was entirely located in the cervix and the scar from the previous CS had nothing to do with the EP. Cases of CP complicated by hemorrhage treated without hysterectomy have been described in the literature [9,10]. Hemorrhage from the implantation site was controlled by placing and inflating a Foley catheter balloon in the cervix after dilatation and curettage [9]. There was a case of undiagnosed CP complicated by extensive, painless vaginal bleeding followed by birth of a child and hysterectomy [11].

CONCLUSIONS

CP, although rare in obstetrics, is a serious clinical condition. Rapid diagnosis and treatment are essential due to the risk of sudden deterioration of the patient's condition – from no symptoms to massive uncontrolled hemorrhage. In such cases, urgent surgical intervention is necessary, and hysterectomy remains the method of choice. This case highlights the importance of using international guidelines that enable appropriate management of rare but dangerous cases of CP.

Authors' contribution

Study design – A. Spyra, A. Sierpińska, Ł. Witek, A. Marzec, A. Olejek
Manuscript preparation – A. Spyra, A. Sierpińska, Ł. Witek, A. Marzec, A. Olejek
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PRACA POGLĄDOWA
REVIEW

Modern treatment approaches for erectile dysfunction – review

Nowoczesne podejścia terapeutyczne w leczeniu dysfunkcji erekcyjnej – przegląd

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ABSTRACT

Erectile dysfunction (ED) is a significant public health issue that affects both patients' quality of life and their intimate relationships. While phosphodiesterase type 5 inhibitors (PDE5-Is) are the standard first-line treatment, a substantial proportion of patients fail to achieve satisfactory results. Growing interest in alternative treatment approaches has led to the exploration of novel therapies, including botulinum neurotoxin (BoNT). BoNT increases penile tissue blood supply by relaxing corpora cavernosa smooth muscle by inhibiting the release of acetylcholine. In this review, BoNT as a new agent in the treatment of ED and comparison with the safety and efficacy of advanced techniques like endovascular therapy, stem cell therapy, platelet-rich plasma therapy, and low-intensity shockwave therapy is discussed. The mechanisms of action, clinical trial results, and possible limitations of these approaches are discussed. According to recent research, BoNT is a potential alternative for ED patients who are not responsive to traditional treatments. Additional studies, however, are required to establish optimal dosing regimens and determine the long-term benefits of these new therapeutic approaches.

KEYWORDS

erectile dysfunction, modern treatment, botulinum toxin, sexual health

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STRESZCZENIE

Zaburzenia erekcji (*erectile dysfunction* – ED) są istotnym problemem zdrowia publicznego, wpływającym zarówno na jakość życia pacjentów, jak i ich relacje intymne. Chociaż inhibitory fosfodiesterazy typu 5 (*phosphodiesterase type 5 inhibitors* – PDE5-Is) stanowią standardowe leczenie pierwszego rzutu, znaczna część pacjentów nie osiąga zadowalających rezultatów. Rosnące zainteresowanie alternatywnymi metodami leczenia doprowadziło do eksploracji nowych terapii, w tym neurotoksyny botulinowej (*botulinum neurotoxin* – BoNT). BoNT zwiększa dopływ krwi do tkanek prącia poprzez rozluźnienie mięśni gładkich ciał jamistych dzięki hamowaniu uwalniania acetylocholiny. W niniejszym przeglądzie omówiono BoNT jako nowy środek w leczeniu ED oraz porównano bezpieczeństwo jej stosowania i skuteczność z zaawansowanymi metodami, takimi jak terapia endowaskularna, terapia komórkami macierzystymi, terapia osoczem bogatopłytkowym oraz terapia falą uderzeniową o niskiej intensywności. Omówiono mechanizmy działania, wyniki badań klinicznych oraz możliwe ograniczenia tych metod. Według najnowszych badań BoNT jest obiecującą alternatywą dla pacjentów z ED, którzy nie reagują na tradycyjne leczenie. Konieczne są jednak dodatkowe badania w celu ustalenia optymalnych schematów dawkowania oraz określenia długoterminowych korzyści nowych podejść terapeutycznych.

SŁOWA KLUCZOWE

dysfunkcja erekcyjna, nowoczesne leczenie, toksyna botulinowa, zdrowie seksualne

Introduction

Erectile dysfunction (ED) is a condition characterized by persistent difficulties in achieving or maintaining an erection sufficient for satisfactory sexual intercourse. This issue has a significant impact on public health and the quality of life of men worldwide. According to estimates, ED currently affects over 150 million men globally, and by 2025, this number could increase to approximately 300 million [1].

ED is particularly common in older age groups – affecting approximately 20% of men aged 40–50, with its prevalence increasing to 50% among men over the age of 70 [2].

Importance of the problem

ED is not limited to physiological aspects – it also has a significant impact on mental health, interpersonal relationships, and overall life satisfaction. Numerous studies indicate that individuals suffering from ED are more likely to experience depression, anxiety, and low self-esteem [3].

The partners of men struggling with ED often experience dissatisfaction in their relationships, which can negatively affect the quality of the relationship. Additionally, ED can be an indicator of underlying cardiovascular diseases, such as atherosclerosis, hypertension, or diabetes [4]. Both the direct costs associated with the treatment and diagnosis of ED and the indirect costs, including loss of work productivity and social burdens, have a significant impact on healthcare system budgets [5].

Current treatment methods

Traditional treatment of ED is primarily based on pharmacotherapy using phosphodiesterase type 5 inhibitors (PDE5-Is), such as sildenafil, tadalafil, vardenafil and the newest such as avanafil or udenafil. These medications work by increasing the availability of nitric oxide (NO) in the smooth muscles of the corpora cavernosa, promoting their relaxation and improving blood flow [6]. Although these medications are effective for most patients, they do not provide the expected improvement in approximately 30–40% of cases. Additionally, side effects such as headaches, vision disturbances, or nasal congestion may lead some patients to discontinue therapy. Alternative treatment methods include prostaglandin injections (e.g. alprostadil), vacuum pumps, and surgical procedures such as penile prosthesis implantation. While these options can be effective in certain cases, they are often considered invasive, costly, and difficult to use on a daily basis.

New therapeutic approaches

In recent years, increasing attention has been given to innovative methods for treating ED. One of the most promising solutions is the use of botulinum neurotoxin (BoNT). Primarily known for its applications in aesthetic medicine and neurology, BoNT works by relaxing smooth muscles through the inhibition of acetylcholine release at neuromuscular junctions [7].

Additionally, BoNT affects the regulation of the autonomic nervous system, which may support the mechanisms responsible for the erection process. Current studies indicate that BoNT may be particularly effective in patients who do not respond to PDE5-Is and in cases of ED with mixed etiology. Due to its minimal side effects and long-lasting therapeutic effect (up to six months), BoNT could serve as a viable alternative to more invasive treatment options.

Aim of the study

The aim of this review is to present the potential use of BoNT in the treatment of ED and to compare it with other modern therapeutic approaches. This article will discuss the mechanisms of action of BoNT, findings from preclinical and clinical studies, as well as the

potential benefits and limitations of this approach. Additionally, the review will explore innovative ED treatment strategies, including platelet-rich plasma (PRP) therapy, stem cell therapy, low-intensity shockwave therapy (LI-SWT), endovascular treatment methods, and the impact of regular physical activity, particularly aerobic exercise, on erectile function. The goal is also to identify areas requiring further research to improve the understanding and optimization of novel ED therapies.

The analysis included clinical studies, randomized controlled trials, and case series focusing on BoNT and the range of modern therapeutic approaches to ED discussed above. Studies that did not directly address these therapies or their effects on erectile mechanisms were excluded, as well as research focusing solely on traditional treatments, such as PDE5-Is, without reference to innovative therapeutic approaches.

Causes of ED

ED is a multifactorial condition. It can result from both organic and psychogenic causes. Below are the most significant organic factors:

1. Vascular factors: Atherosclerosis of the penile arteries and other circulatory disorders can significantly reduce blood flow to the corpora cavernosa [8].
2. Neurogenic factors: Spinal cord injuries, diabetic neuropathy, or pelvic surgeries can lead to impaired nerve signal transmission, preventing a proper response to sexual stimulation [9].
3. Hormonal factors: Testosterone deficiency, hyperprolactinemia, and thyroid dysfunction can lead to decreased libido and the inability to achieve an erection [10].

Psychological factors, such as stress, depression, relationship difficulties, or fear of failure, play a significant role in the development of ED, especially in young men. Stress activates the sympathetic nervous system, which can hinder the parasympathetic responses necessary for achieving an erection. Depression is associated with decreased levels of key neurotransmitters, including dopamine and serotonin, which are crucial for experiencing pleasure and sexual motivation. Additionally, reduced oxytocin levels, which play a role in emotional bonding and sexual function, may further contribute to erectile difficulties, particularly in the context of relationship distress [11]. Relationship problems, such as a lack of emotional intimacy, can exacerbate these issues, creating a vicious cycle of mutual tension and withdrawal [12].

The role of smooth muscles in ED

Smooth muscles of the corpora cavernosa play a crucial role in the erection process. Their relaxation allows proper blood flow and penile engorgement. Excessive smooth muscle tension, often associated with autonomic nervous system dysfunctions, is one of the main pathophysiological mechanisms in ED.

The autonomic nervous system, which regulates smooth muscle tension, operates based on a balance between the sympathetic and parasympathetic systems. A disruption of this balance, caused, for example, by diabetic neuropathy, can prevent proper vasodilation and blood flow to the penis [13].

Treatment using new technologies in the context of ED

Treatment with BoNT

Botulinum neurotoxin type A (BoNT-A) may play a significant role in the treatment of ED, especially in patients with excessive smooth muscle tension. BoNT-A works by blocking the release of acetylcholine at neuromuscular synapses, leading to muscle relaxation. In the context of ED, BoNT-A can restore autonomic balance and improve blood flow by relaxing the vessels in the corpora cavernosa [10]. A summary of all available studies on the use of BoNT-A is presented in Table I.

Table I. Publications investigating treatment with botulinum toxin type A

Publication	Study population	Applied treatment	Conclusions
Giuliano et al. [14]	A total of 85, 44, and 23 men received two, three, and four doses of BTX/A ic, respectively.	This retrospective case series evaluates the effectiveness of repeated off-label X/A injections (onabotulinumtoxinA 100 U, incobotulinumtoxinA 100 U, or abobotulinumtoxinA 500 U) in men with ED unresponsive to PDE5-Is or PGE1-ICIs, defined by an IIEF-EF score < 26.	The overall response rate was 77.5%, with higher rates in mild (85.7%) and moderate (79%) ED. Response increased with repeated injections: 67.5%, 87.5%, and 94.7% after the second, third, and fourth injections. Changes in IIEF-EF were similar across injections. Four men reported mild penile pain, and one experienced a burning sensation. Repeated BTX/A injections with PDE5-Is or PGE1-ICIs resulted in effective, sustained responses and acceptable safety.
Abdelrahman et al. [15]	A double-blind, randomized, placebo-controlled study involving 70 patients with PDE5I-resistant ED collected data on EHS, PSV, EDV, SHIM, and SEP-2&3 at the start.	The treatment group (n = 35) received 100 units of BoNT-A in 2 ml saline via ICI, while the control group (n = 35) received 2 ml saline. EHS, PSV, and EDV were assessed at 2 weeks, and SHIM, SEP-2, SEP-3, and GAQ-Q1&Q2 at 2, 6, and 12 weeks post-treatment.	Two weeks after treatment, the treated group showed significant improvements in EHS, PSV, EDV, and GAQ-Q1 ($p < 0.001$) compared to the control. After 6 and 12 weeks, the treated group also showed improvements in SHIM scores, SEP-2, and GAQ-Q1 and Q2. At 6 weeks, the treated group had a 5-point increase in SHIM, with 53% achieving erections sufficient for vaginal penetration. BoNT-A is a safe and effective treatment for PDE5I-resistant ED.
Giuliano et al. [16]	Data from a retrospective, uncontrolled study conducted at a single center were analyzed, involving 47 patients with ED, consecutively recruited, who were insufficiently responsive to existing pharmacological treatment.	Patients treated with PDE5-Is or IC PGE1 injections received additional IC abobotulinumtoxinA (250 or 500 U) as a free combination with their existing therapy.	The response rate to IC abobotulinumtoxinA with prior pharmacological treatment was 54% at 6 weeks. Two patients experienced mild penile pain. Effectiveness was not influenced by ED etiology or risk factors, but less severe ED had a higher response rate. Preliminary evidence suggests IC abobotulinumtoxinA may be a safe adjunctive therapy for ED unresponsive to standard treatment, pending confirmation in clinical trials.
El-Shaer et al. [17]	A prospective, randomized, double-blind, placebo--controlled study was conducted from July 2016 to February 2019, involving 176 patients who were randomly assigned (1:1:1) to one of the treatment sequences, with follow-up for 6 months.	The Botox 100 U group (BTX-100; 62 patients), the Botox 50 U group (BTX-50; 59 patients), or the placebo group (55 patients).	Both the BTX-100 and BTX-50 groups showed significant improvements in SHIM, EHS, SEP, GAS, and Doppler parameters ($p < 0.001$), with maximal improvement at 3 months. Approximately 40% of patients were able to engage in sexual intercourse. No significant improvement was observed in the placebo group ($p = 0.264$). At 6 months, BTX-100 showed a statistically significant advantage over BTX-50 ($p < 0.01$).
Giuliano et al. [18]	66 men with difficult-to--treat ED.	IncobotulinumtoxinA 100 U ICI as an adjunctive therapy.	The response rate to incobotulinumtoxinA ICI was 52%, with no impact from ED etiology or severity (except spinal cord injury). A clinically significant response to the first injection predicted the need for a second (OR = 5.6). Three men experienced mild penile pain during the injection.
Abdel Raheem et al. [19]	A prospective, double-blind, randomized study involving 70 patients with ED unresponsive to PDE5-Is and ICI therapy.	Patients were randomly assigned to treatment (100 units BoNT-A) or control (1 mL saline) groups, with 35 patients in each. Penile duplex ultrasound and EHS were assessed at baseline and 2 weeks post-treatment. SHIM, SEP, and GAQ questionnaires evaluated outcomes at 6 and 12 weeks.	In the treated group, significant improvements were observed in peak systolic velocity, end-diastolic velocity, EHS, and SHIM score ($p < 0.001$). SEP-1 and SEP-2 responses were higher in the treated group, as were GAQ-1 and GAQ-2 responses. No adverse events occurred, and improvements were sustained at the 12-week follow-up.

BTX/A, X/A, BoNT-A – botulinum toxin type A (alternative abbreviations used in some studies); ED – erectile dysfunction; PDE5-Is – phosphodiesterase type 5 inhibitors; PGE1 – prostaglandin E1; ICI – intracavernosal injection; IIEF-EF – International Index of Erectile Function – Erectile Function domain; EHS – Erection Hardness Score; PSV – peak systolic velocity; EDV – end-diastolic velocity; SHIM – Sexual Health Inventory for Men; SEP-2&3 – Sexual Encounter Profile questions 2 and 3; GAQ-Q1&Q2 – Global Assessment Questionnaire questions 1 and 2; IC – intracavernosal; GAS – Global Assessment Score.

Other innovative treatment methods for ED

Table II presents publications on other innovative treatment methods for ED.

Table II. Publications investigating other innovative treatment methods for erectile dysfunction

Publication	Study population	Applied treatment	Conclusions
1	2	3	4
Platelet rich plasma			
Masterson et al. [20]	61 men with mild to moderate ED (IIEF score 11–25).	Two injections of PRP or placebo, administered one month apart.	PRP was safe but showed no significant difference in efficacy compared to placebo.
Poulios et al. [21]	The study included 60 sexually active male patients aged 40––70 years with mild to moderate ED. Participants were required to be in stable heterosexual relationships and refrain from using other ED treatments during the study.	Participants were randomly assigned to receive two ICIs of either PRP or a placebo (normal saline), with a one-month interval between treatments. PRP was prepared using an FDA-approved separation system.	The study found that PRP injections significantly improved erectile function compared to the placebo. At the six-month follow-up, 69% of PRP-treated patients showed a clinically meaningful improvement, compared to 27% in the placebo group. No adverse effects were reported, indicating that PRP may be a safe and effective treatment for mild to moderate ED.
Shaher et al. [22]	The study included 100 men aged 45–65 with mild to moderate ED. Participants were randomly assigned to two groups: one receiving PRP treatment and the other receiving a placebo (saline injections).	The PRP group received three ICIs (3 mL per corpus cavernosum) at 15-day intervals. The placebo group received the same volume of saline injections. Follow-up assessments were conducted at 1, 3, and 6 months.	PRP treatment significantly improved erectile function compared to placebo, with the highest improvement observed at the 3-month follow-up. At 6 months, 70% of PRP patients achieved a clinically meaningful improvement, compared to 16% in the placebo group. No major adverse effects were reported, suggesting PRP is a safe and promising treatment for mild to moderate ED.
Saltzman et al. [23]	The study enrolled 60 men aged 30–80 with mild to moderate ED (IIEF-EF score 12–25), all in stable heterosexual relationships and providing informed consent.	Participants were randomly assigned to receive either PRP injections and low-intensity SWT or placebo (saline injections and sham SWT). The treatment lasted five weeks, with PRP and SWT in weeks 1 and 5, and additional SWT sessions in weeks 2–4.	The study aims to evaluate the safety and efficacy of combined PRP and SWT therapy for ED. The primary outcome focuses on adverse events, while secondary outcomes include improvements in erectile function based on the IIEF-EF score and reduction in the need for PDE5-Is. If successful, this approach could offer a regenerative treatment option for ED.
Zaazaa et al. [24]	80 patients with ED who had a refractory response to PDE5-Is for at least 6 months.	Patients were randomly assigned to four groups: saline (placebo), PRFM injection, PGE-1 injection, and PRFM + PGE-1 combination. Intracorporeal injections were given weekly for 8 weeks, with follow-ups at 1, 2, 3, and 6 months.	The combination of PRFM and PGE-1 showed significant improvement in erectile function scores compared to the other groups. However, despite the improvements, patients still had mild to moderate ED. The treatment is not recommended as a standalone therapy for ED but may enhance response to ICI home therapy in patients resistant to oral PDE5-Is.
Aerobic exercises			
Leitão et al. [25]	45 men (aged 40–59) with ADAM, experiencing ED and low testosterone levels.	Participants were divided into four groups: (1) control + placebo, (2) control + *Eurycoma longifolia* (200 mg daily), (3) concurrent training + placebo, and (4) concurrent training + *Eurycoma longifolia*. The interventions lasted for 6 months, with exercise performed 3 times a week.	The combination of *Eurycoma longifolia* supplementation and concurrent training led to the most significant improvements in erectile function and testosterone levels. While both interventions had benefits separately, their combined effect was superior, suggesting a synergistic impact on male sexual health.
Rislanu et al. [26]	30 men (aged 25–65) diagnosed with ED. Participants were randomly assigned to two groups.	One group received electrical stimulation therapy, and the other performed aerobic exercise for six weeks (two sessions per week). Erectile function was assessed using the IIEF-5 before and after treatment.	Both treatments improved erectile function, but electrical stimulation showed significantly better results compared to aerobic exercise. This suggests that electrical stimulation may be a more effective non-invasive option for managing ED.
La Vignera et al. [27]	50 middle-aged men (48––62 years) with arterial ED. A control group of 20 men was also included.	A structured aerobic physical activity program: 150 minutes of moderate-intensity aerobic exercise per week for 3 months. The control group did not participate in the exercise program.	Aerobic physical activity significantly improved erectile function, endothelial health, and metabolic parameters. The exercise group showed higher IIEF-5 scores, better penile vascular function, and reduced endothelial apoptosis compared to the control group.

cd. tab. II

1	2	3	4
		Stem cell therapy	
Al Demour et al. [28]	4 male patients (aged 49–60) with diabetes-related ED resistant to standard treatments.	Two consecutive ICIs of autologous BM-MSCs were administered, with follow-ups over 12 months to assess safety and efficacy.	The treatment was well tolerated, with no significant adverse effects. Patients showed improvements in erectile function, with increased IIEF-15 and EHS. The results suggest that BM-MSC therapy may be a promising option for diabetic patients with refractory ED.
Levy et al. [29]	8 men aged 40–70 with chronic ED who did not respond to oral treatments.	Injection of PM-MSCs into the corpora cavernosa. Patients were monitored for 6 months.	Stem cell treatment led to a significant increase in penile blood flow. Three patients achieved erections without medication, while others required lower doses. Further studies with larger samples are needed to confirm effectiveness.
You et al. [30]	10 men with ED due to radical prostatectomy or diabetes mellitus, unresponsive to PDE5-Is.	Injection of autologous BMSCs into the corpus cavernosum. Patients were monitored for 12 months.	The treatment was safe, with no severe adverse events directly related to BMSC injection. Some patients showed an improvement in erectile function, but further research is needed to confirm long-term efficacy.
Koga et al. [31]	38 men with ED, aged 31–79, including patients with diabetes, hypertension, or a history of priapism.	Injection of a cultured conditioned medium derived from exfoliated deciduous dental pulp stem cells (SHED-CM) into the corpus cavernosum, administered in three sessions over several weeks.	97.4% of patients showed improved erectile function, with an average IIEF-5 score increase of 64.4%. Nearly half achieved scores indicating no ED. No adverse events were reported. Further studies are needed to confirm long-term efficacy.
		Low-intensity shockwave therapy	
Kennady et al. [32]	33 men with organic ED were randomized to shockwave therapy (n = 17) or sham treatment (n = 16). After one month, the sham group crossed over to receive shockwave therapy.	Participants received LiSWT for ED, with efficacy evaluated using the SHIM score and EHS at 1 month. Erectile function was further assessed at 1, 3, and 6 months post-treatment.	LiSWT significantly improved erectile function, with a mean SHIM score increase of 5.5 points at 6 months ($P < .001$). 54.6% of men showed clinically significant improvement, and 68% of those with an initial EHS < 3 improved to ≥ 3. The study supports LiSWT's long-term effectiveness in organic ED.
De Oliveira et al. [33]	The study included 25 ED patients, divided into two groups: 13 with ED ≤ 24 months and 12 with ED > 24 months.	Patients received LiSWT for ED, with effectiveness assessed using the IIEF-5 questionnaire at baseline, 6 weeks, and 3 months. Penile Doppler ultrasound was done before and 6 weeks after treatment to evaluate vascular changes.	LiSWT is a safe, non-invasive, and repeatable treatment for ED, showing significant improvements in erectile function and penile vascular parameters. The results indicate that the duration of ED does not negatively impact the effectiveness of the therapy.
Kalyvianakis et al. [34]	48 men with severe vasculogenic ED were randomized to LiST plus tadalafil (n = 34) or sham therapy plus tadalafil (n = 17) in a double-blind trial. 3 patients were excluded (n = 3).	Participants received 12 LiST sessions (three times weekly) and daily tadalafil 5 mg for four weeks. Erectile function was assessed via IIEF-EF and SEP diary at 1 and 3 months. Primary outcome: IIEF-EF at 3 months. Secondary outcomes: IIEF-EF at 1 month, SEP responses, and adverse events.	LiST plus tadalafil significantly improved IIEF-EF scores vs. sham plus tadalafil at 1 and 3 months ($P \leq .002$). More patients achieved a clinically important IIEF-EF improvement, though SEP responses were not statistically significant. No adverse events were reported, suggesting added benefit of LiST in severe vasculogenic ED.
Kalyvianakis et al. [35]	This randomized study included 97 PDE5 inhibitor users with vasculogenic ED, divided into four groups based on LiST frequency and EFD. Groups received LiST twice or three times weekly. 89 patients completed the 6-month follow-up.	Participants underwent 12 LiST sessions (two or three times weekly) with EFD 0.05 or 0.10 mJ/mm². Erectile function was assessed via IIEF-EF, SEP diary, and penile ultrasonography. Primary outcome: erectile function improvement. Secondary outcomes: MCID achievement and PSV changes at 3 months.	All groups showed significant improvement in IIEF-EF, SEP3, and PSV ($p < 0.001$), with no difference between session frequencies. Higher EFD (0.10 mJ/mm²) showed a trend toward better efficacy but lacked statistical significance. No adverse effects were reported. Further research is needed.

cd. tab. II

1	2	3	4
Olsen et al. [36]	This randomized, placebo--controlled study included 112 men with organic ED. Participants were assigned to LI-ESWT (n = 51) or placebo (n = 54), with both patients and clinicians blinded. After 10 weeks, the placebo group received active treatment.	LI-ESWT participants received five treatment sessions over five weeks. ED was assessed at screening and at 5, 12, and 24 weeks using interviews, EHS, and IIEF-15. The placebo group initially received sham treatment but later underwent active therapy after 10 weeks.	At five weeks post-treatment, 57% of men in the LI-ESWT group achieved erection sufficient for intercourse without medication vs. 9% in the placebo group (p = 0.0001). While EHS showed significant improvement, no statistical difference was noted in the IIEF-EF domain. After 24 weeks, 19–23% maintained this effect. Larger, long-term studies are needed to confirm LI-ESWT's potential as a cure.
		Endovascular treatment methods	
Aschenbach et al. [37]	This study retrospectively analyzed 29 men diagnosed with ED caused by veno--occlusive dysfunction. Diagnosis was confirmed through pharmacocaverno-sometry and cavernosography. All participants underwent endovascular embolization therapy via a transfemoral approach.	The procedure involved catheter placement at the target vascular sites, followed by embolization using N-butyl-2-cyanoacrylate (Histoacryl®). The primary endpoints included technical success, clinical improvement, and the occurrence of complications.	Endovascular embolization demonstrated a high technical success rate (93.1%), with failure occurring in two patients due to anatomical challenges. Clinically, 88.8% of successfully treated patients experienced improvement in erectile function. Specifically, 40.7% progressed from poor tumescence and no rigidity (E1) to good tumescence with intermediate rigidity (E4), while 29.6% regained normal rigidity (E5), and 18.5% achieved improved tumescence with poor rigidity (E3). Only 11.1% showed no change in erectile function. The procedure was performed without complications, making it a safe and effective therapeutic approach for veno-occlusive ED.

ED – erectile dysfunction; IIEF – International Index of Erectile Function; PRP – platelet-rich plasma; FDA – Food and Drug Administration; ICI – intracavernosal injection; IIEF-EF – International Index of Erectile Function – Erectile Function domain; SWT – shockwave therapy; PDE5-Is – phosphodiesterase type 5 inhibitors; PRFM – platelet-rich fibrin matrix; PGE-1 – prostaglandin E1; ADAM – androgen deficiency in the aging male; BM-MSCs, BMSCs – bone marrow--derived mesenchymal stem cells; EHS – Erection Hardness Score; PM-MSCs – placental matrix-derived mesenchymal stem cells; SHED-CM – stem cells from human exfoliated deciduous teeth – conditioned medium; LiSWT, LiST, LI-ESWT – low-intensity shockwave therapy (alternative abbreviations used in some studies); SHIM – Sexual Health Inventory for Men; SEP – Sexual Encounter Profile; EFD – energy flux density; MCID – minimal clinically important difference; PSV – peak systolic velocity.

Discussion

The management of ED has evolved significantly over the past decades, shifting from traditional pharmacological approaches to innovative therapeutic strategies targeting the underlying pathophysiology of the disorder. This discussion critically evaluates the potential of BoNT as an emerging treatment for ED and juxtaposes its efficacy and safety profile against other novel interventions.

Challenges in current treatment approaches

Despite the widespread use of PDE5-Is such as sildenafil and tadalafil, approximately 30–40% of patients fail to achieve satisfactory therapeutic outcomes [16]. The limited efficacy of PDE5-Is in certain patient populations, particularly those with endothelial dysfunction, diabetes mellitus, or neurogenic ED, underscores the need for alternative treatment options [15]. Additionally, common side effects, including headaches, visual disturbances, and nasal congestion, often lead to discontinuation of therapy [17]. More invasive solutions, such as penile prosthesis implantation, while effective, are associated with surgical risks and high costs [18], further highlighting the necessity of exploring less invasive, yet efficacious alternatives.

Botulinum toxin: a paradigm shift in ED management

BoNT, primarily recognized for its neuromuscular blockade properties, has emerged as a promising agent in the treatment of ED by modulating smooth muscle tone in the corpora cavernosa [10]. Its mechanism of action involves inhibition of acetylcholine release at neuromuscular junctions, leading to prolonged smooth muscle relaxation and improved penile blood flow [14]. Clinical studies demonstrate encouraging outcomes, with significant improvements in Erection Hardness Score (EHS), peak systolic velocity (PSV), and Sexual Health Inventory for Men (SHIM) scores in BoNT--treated patients resistant to PDE5-Is [15]. Notably, repeated injections appear to enhance therapeutic efficacy, with response rates improving from 67.5% after the second injection to 94.7% after the fourth [14]. However, BoNT therapy is not without its limitations. While adverse effects are generally mild, including transient penile pain and burning sensations [17], the optimal dosing regimen and long-term safety profile require further elucidation [18]. Additionally, the lack of standardized administration protocols presents

a challenge in achieving consistent therapeutic outcomes across different patient populations [10].

Comparative analysis of emerging therapies

Several other innovative therapeutic modalities have been explored for ED management, including:

1. PRP therapy
   PRP therapy has gained attention for its regenerative properties, promoting angiogenesis and tissue repair [21]. Clinical studies indicate that PRP injections result in significant improvements in erectile function, with approximately 69% of treated patients experiencing clinically meaningful benefits at six--month follow-up [22]. However, some trials report no significant difference compared to placebo [20], necessitating further research to clarify its efficacy.
2. Stem cell therapy
   Stem cell-based approaches aim to restore erectile function through cellular regeneration and neoangiogenesis [28]. Preliminary trials involving mesenchymal stem cell (MSC) injections have demonstrated promising results, particularly in diabetic and post-prostatectomy patients [29]. Nevertheless, concerns regarding the scalability, cost, and ethical considerations of stem cell therapy remain unresolved [30].
3. LI-SWT
   LI-SWT has been shown to stimulate neovascularization and improve penile hemodynamics [32]. Randomized controlled trials indicate significant improvements in erectile function, with a mean SHIM score increase of 5.5 points at six months [33]. Notably, combination therapy with LI-SWT and PDE5-Is has yielded superior results compared to monotherapy [34].
4. Endovascular techniques
   Penile artery stenting and embolization procedures have emerged as viable options for patients with vasculogenic ED refractory to medical therapy [37]. Studies suggest that endovascular embolization can restore erectile function in up to 88.8% of patients with veno-occlusive dysfunction [37]. However, these techniques require specialized expertise and are associated with procedural risks [37].

Future research directions and clinical implications

While current findings underscore the potential of BoNT as an effective treatment for ED, several key questions remain unanswered. Future research should focus on optimizing dosing regimens, refining patient selection criteria, and evaluating long-term outcomes [18]. Additionally, investigating synergistic treatment strategies – such as combining BoNT with LI-SWT or regenerative therapies – may enhance therapeutic efficacy [15]. Large-scale, multicenter randomized controlled trials are essential to establish evidence--based guidelines for integrating BoNT into clinical practice [17].

Conclusions

Based on the analysis of available clinical studies, BoNT-A appears to be a promising and safe therapeutic option for patients with ED, particularly those unresponsive to conventional treatments such as PDE5-Is. The reviewed evidence suggests that BoNT-A may offer significant improvements in erectile function with a favorable safety profile, especially when used as an adjunct to other therapies. However, due to the heterogeneity of study designs and limited long-term data, further well-designed randomized trials are necessary to establish standardized dosing protocols, assess durability of effect, and define optimal patient selection criteria.
In addition, regenerative and neuromodulatory approaches such as PRP, stem cell therapy, LI-SWT, and endovascular techniques also show potential but require further validation. In our opinion, the future of ED management lies in a personalized, multimodal strategy that combines pharmacological, procedural, and lifestyle-based interventions, tailored to the etiology and severity of the condition.

Authors' contribution

Study design – K. Nikel
Data collection – J. Smolarczyk, M. Piegza
Manuscript preparation – K. Nikel, M. Stojko
Literature research – K. Nikel, M. Stojko

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PRACA ORYGINALNA
ORIGINAL PAPER

Impact of COVID-19 visitation restrictions on hospitalized patients and their families – a dual perspective

Wpływ ograniczeń odwiedzin w szpitalach podczas pandemii COVID-19 na hospitalizowanych pacjentów i ich rodziny – perspektywa dwustronna

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ABSTRACT

INTRODUCTION: To slow the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the pandemic, healthcare institutions worldwide implemented rules to restrict hospital visitation, poising significant challenges for the entire healthcare system. The presence of relatives often facilitates communication and exchange of information between patients and healthcare professionals.
MATERIAL AND METHODS: The study involved 203 adult, independent patients and 198 relatives. Conducted in a rehabilitation outpatient clinic between November 2021 and March 2022, the study aimed to evaluate how patients and their relatives perceived visitation restrictions in hospitals during the coronavirus disease 2019 (COVID-19) pandemic. Patients and their relatives were divided into two groups based on their positive or negative assessment of the restrictions.
RESULTS: Among the patients, 44% (N = 90) evaluated the visitation restrictions positively, while 56% (N = 113) viewed them negatively. Among relatives, 41% (N = 82) gave a positive assessment, while 59% (N = 116) expressed dissatisfaction with the restrictions.
CONCLUSIONS: The study found that the hospital visitation ban during the pandemic primarily evoked negative emotions among both patients (56%) and their relatives (59%). Despite the restrictions, most patients and their families maintained daily contact through alternative communication methods, highlighting the need for further development of remote communication options in hospitals. Additionally, hospitals provided effective procedures for delivering personal belongings and sharing information about patients' conditions, which was positively evaluated by respondents. In the future, a more flexible approach to visitations should be considered, for example, allowing visits in exceptional cases.

KEYWORDS

patients, coronavirus, relatives

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STRESZCZENIE

WSTĘP: Aby spowolnić rozprzestrzenianie się wirusa SARS-CoV-2 (*severe acute respiratory syndrome coronavirus 2*) podczas pandemii, instytucje opieki zdrowotnej na całym świecie wprowadziły zasady mające na celu ograniczenie odwiedzin pacjentów przebywających na oddziałach szpitalnych, co stworzyło ogromne wyzwania dla całego systemu zdrowotnego. Obecność bliskich często ułatwia komunikację i wymianę informacji między pacjentami a pracownikami służby zdrowia.

MATERIAŁ I METODY: W badaniu wzięło udział 203 pełnoletnich, samodzielnych pacjentów oraz 198 osób bliskich. Badanie prowadzono w jednej placówce medycznej, tj. w poradni rehabilitacyjnej, od listopada 2021 r. do marca 2022 r. i miało na celu ocenę, jak pacjenci i ich bliscy postrzegali ograniczenia odwiedzin w szpitalach w trakcie pandemii COVID-19 (*coronavirus disease 2019*). Pacjentów i ich osoby bliskie podzielono na dwie grupy – na podstawie pozytywnej lub negatywnej oceny ograniczeń.

WYNIKI: Spośród pacjentów 44% (N = 90) pozytywnie oceniało wprowadzenie ograniczeń, podczas gdy 56% (N = 113) postrzegało je negatywnie. Z kolei spośród osób bliskich pozytywną ocenę wystawiło 41% (N = 82), a 59% (N = 116) wyraziło niezadowolenie z ograniczeń.

WNIOSKI: Badanie wykazało, że zakaz odwiedzin w szpitalach podczas pandemii wywoływał głównie negatywne emocje zarówno u pacjentów (56%), jak i ich bliskich (59%). Mimo restrykcji większość pacjentów i ich rodzin utrzymywała codzienny kontakt za pomocą alternatywnych metod komunikacji, co podkreśla potrzebę dalszego rozwoju zdalnych form kontaktu w szpitalach. Ponadto szpitale zapewniły skuteczne procedury dostarczania rzeczy osobistych oraz udostępniania informacji o stanie pacjentów, co zostało pozytywnie ocenione przez respondentów. W przyszłości należy rozważyć bardziej elastyczne podejście do odwiedzin, na przykład zezwalając na wizyty w wyjątkowych przypadkach.

SŁOWA KLUCZOWE

pacjenci, koronawirus, osoby bliskie

INTRODUCTION

During the coronavirus disease 2019 (COVID-19) pandemic, in order to contain the spread of the virus, hospitals around the world introduced visiting restrictions for patients staying in wards, which created huge challenges for medical staff as well [1]. Although some restrictions on visitors have long existed, such as the introduction of specific visiting hours in hospitals and are a recognised common practice, the extent of restrictive restrictions, including a complete ban on the presence of patients' relatives, introduced especially at the beginning of the pandemic, was unprecedented [2,3,4].

On the one hand, the use of restraints reduced the risk of transmission of infections to hospitalised patients and thus to the wider community, protected patients from increased morbidity, especially those with comorbidities or immunocompromised patients, and safeguarded the health of staff [3]. Patient- and family--centered care, on the other hand, includes, in addition to ongoing communication, visits, the participation of the family directly in the care of the patient, accepting that this approach improves medical and psychological outcomes in patients [5]. For healthcare providers, the introduction of visitation restrictions may have caused anxiety and difficulties in ensuring patient autonomy or holistic patient-centered care [6].

The exact extent and nature of the support provided by a close relative depends on the patient's clinical situation, degree of independence, age, and the nature of the relationship between the close relative and the patient [3]. According to Article 3(1)(2) of the Act on Patients' Rights and the Patients' Ombudsman (*Ustawa z dnia 6 listopada 2008 r. o prawach pacjenta i Rzeczniku Praw Pacjenta*) [7], a close relative is a spouse, a relative up to the second degree, or a relative up to the second degree in a straight line, a legal representative, a person in cohabitation, or a person indicated by the patient.

The study aimed to find out the evaluation among patients and their relatives of the introduction of visitation restrictions in hospitals during the COVID-19 pandemic.

The lack of access to personal care and support provided by visitors to patients negatively affected the well-being of those hospitalised and the overall experience of the attention they received [8,9]. Some patients, to prevent separation from their loved ones, may have made decisions that adversely affected their health, such as refusing or delaying medical care, which may have accelerated the deterioration of their health, both physically and psychologically [3,8].

In turn, patients' use of technology to communicate (video calls, phone calls, social media) with loved ones depended on the hospitalised patients' access to these devices, experience, skills, and familiarity with using them. During the pandemic, medical staff had to adapt to other ways of communicating with patients' loved ones and supporting patients, families to access and use technology [4,10], but phone or video calls were often not a sufficient substitute for direct contact with loved ones [11]. The psychological impact of the introduced restrictions on hospitalised patients and their families is still poorly understood [4].

MATERIAL AND METHODS

Participants

A total of 203 adult, independent patients and 198 relatives took part in the survey. Participation in the study of patients and relatives was voluntary and anonymous. Only independent patients and their relatives participated in the study, i.e. patients who do not require care from other people, e.g. in the areas of mobility, nutrition, or care. Patients and their relatives were divided into two groups: related to both positive and negative assessments of the introduction of visitation restrictions at the hospital during the pandemic. Respondents who rated the introduction of visitation restrictions as definitely good and rather good were assigned to the group that rated the introduction of restrictions positively. In contrast, respondents who assessed the introduction of visitation restrictions strongly badly, rather badly or had no opinion on the subject were assigned to the group that assessed the introduction of restrictions negatively.

In the patient group, 65% (N = 132) were female and 35% (N = 71) were male. On the other hand, among relatives, 52% (N = 102) were women and 48% (N = 96) were men (Table I). The mean age of the patients was 55.5 years (19.0–87.0 years), among women, the mean age was 55.0 years, and among men 56.5 years. The mean age of relatives was 49.5 years (23.0–78.0 years), among women the mean age was 47.0 years, and among men 52.0 years.

Among the patients surveyed, most respondents had secondary education – 44.4% (N = 90), 3% (N = 6) of people had primary education, 25.6% (N = 52) had vocational education, and 27% (N = 55) had tertiary education. On the other hand, among relatives, 51% (N = 101) of respondents had secondary education, 1.5% (N = 3) of respondents had primary education, 14.2% (N = 28) had vocational education, and 33.3% (N = 66) had tertiary education.

Most patients resided in a medium-sized city (20,000––100,000 inhabitants) – 53.7% (N = 109), in a large city (> 100,000 inhabitants) 20.2% (N = 41), in a small city 19.2% (N = 39) and in a village 6.9% (N = 14). Among relatives, the largest number of respondents also lived in a medium-sized city – 59.6% (N = 118), in a large city 21.2% (N = 42), in a small city 13.1% (N = 26) and in a village 6.1% (N = 12; Table I).

Table I. Characteristics of studied group of patients and relatives

Variable		Group	
		patients N = 203 (%; N)	**relatives** N = 198 (%; N)
Gender	women	65%; 132	52%; 102
	men	35%; 71	48%; 96
Education	professional	25.6%; 52	14.2%; 28
	basic	3%; 6	1.5%; 3
	medium	44.4%; 90	51%; 101
	higher	27%; 55	33.3%; 66
Place of residence	village	6.9%; 14	6.1%; 12
	city up to 20,000	19.2%; 39	13.1%; 26
	city of 20,000–100,000	53.7%; 109	59.6%; 118
	city over 100,000	20.2%; 41	21.2%; 42

Patients were hospitalized in various hospital wards in Silesia (98%; N = 199), 2% (N = 4) of respondents were hospitalized in Opole, Lesser Poland, Subcarpathian, and Lower Silesian. 18% (N = 36) were treated in the orthopaedic ward, 14% (N = 29) in the gynaecological ward, 14% (N = 29) in the cardiology ward, 11% (N = 23) in the neurological ward, 9% (N = 18) in the general surgery ward, 7% (N = 14) on the rehabilitation ward, 6% (N = 12) on the urology ward, 6% (N = 13) on the internal medicine ward, 3% (N = 7) on the rheumatology ward, 3% (N = 7) on the pulmonology ward. Otherwise, single hospitalisations were in otolaryngology (ENT), ophthalmology, nephrology, diabetology, psychiatry, dermatology, endocrinology, oncology, and pregnancy pathology departments.

Regarding the degree of relatedness of the relatives to the hospitalised patient, most respondents 64% (N = 127) were spouses, 28% (N = 55) were children, 4.5% (N = 9) were siblings, 1.5% (N = 3) were parents, partner 1% (N = 2), guardian 0.5% (N = 1), daughter--in-law 0.5% (N = 1).

According to the Statistics Poland (Główny Urząd Statystyczny), in 2022 there were 6,895,900 people hospitalised in Poland, after calculating a fraction size of 0.9, a maximum error of 5%, and the minimum sample size with a confidence level of 95% a sample size of 138 people was obtained, which justifies that

a sample size of 203 and 198 is appropriate to conduct research.

Study design

It should be noted that the greatest increase in incidence in the fourth wave of the pandemic occurred in the second half of November 2021, admission to hospitals was restricted during this period for outsiders. The study was conducted in one medical facility, i.e. a rehabilitation clinic, from November 2021 to March 2022, to which patients and their relatives reported. Respondents in the study indicated the date and hospital department where they were hospitalized during the pandemic. The dynamics in the rehabilitation clinic differ from those in the hospital, as patients from different hospital wards are referred to the rehabilitation clinic, making it easier to collect data and assess the introduction of visitation restrictions among patients and their relatives.

Ethical consideration

The study design did not require the approval of the local bioethics committee (Decision of the ŚUM Bioethics Committee No. PCN/CBN/0052/KB/187/22), and the study was conducted in accordance with the provisions of the Declaration of Helsinki.

Instrument

The present study was a cross-sectional study in which the authors used specially designed questionnaires aimed at patients and their relatives as the data collection method (Appendix 1). Patients and their relatives gave informed consent to participate in the study. The primary criteria for inclusion in the study were health status to participate and being over 18 years of age.

The first part of the questionnaires consisted of questions on demographic data, including gender, age, place of residence. The second part of the questionnaires consisted of individual factors such as level of education, hospital wards in which patients stayed, provinces in which people were hospitalised, periods in which patients were hospitalised, chronic diseases accompanying the patients, or the relationship that the patient had with the relative.

The last part of the questionnaire consisted of 26 closed questions addressed to patients and nine questions addressed to relatives. The questionnaires consisted mainly of single-choice questions and were formulated on the basis of the patient's rights under the Act on Patients' Rights and the Patients' Ombudsman.

Statistical analysis

Statistical analysis was performed with Statistica version 13.3 (TIBCO Software Inc.). The chi-square test was used to compare the frequency of occurrence of a trait across groups, or subgroups. In turn, the frequency of occurrence of traits, qualitative variables, was expressed as percentages and N significant values. Microsoft Excel was used for data collection.

To assess the internal consistency of the questionnaire, the Cronbach's alpha test was used in the section evaluating the introduction of visitation restrictions. The Cronbach's alpha value was 0.84, which indicates high reliability of the tool. This value falls within the acceptable range for social research, where a value of 0.7 or higher is considered sufficient to establish question consistency. This means that the questions included in the questionnaire were internally consistent and measured the same construct, which was the evaluation of the introduction of visitation restrictions.

RESULTS

56% (N = 113) of respondents were hospitalised due to a planned procedure, 39% (N = 80) due to a sudden deterioration in health, 4% (N = 8) due to rehabilitation, and one case each of risk of premature birth and liver disease were the reasons for hospitalisation.

91.4% (N = 181) of visitors indicated that they had the opportunity to contact the patient daily, 5.6% (N = 11) of visitors contacted the patient once a week, 2.5% (N = 5) of respondents did not contact the patient, 0.5% (N = 1) of visitors contacted the patient less than once a week. Among patients, 93.5% (N = 190) of respondents had daily contact with a relative, 2.5% (N = 5) of people contacted a relative once a week, and 4% (N = 8) of patients did not contact a relative.

In the group of visitors, 88% (N = 175) of the respondents did not need help to contact the patient, 8% (N = 15) of the respondents indicated that the medical staff helped to contact the patient, 2% (N = 4) of the relatives did not contact the hospitalised person, 1% (N = 2) of the respondents had no opinion on the subject and 1% (N = 2) of the respondents indicated that the medical staff did not help to contact. In contrast, 89% (N = 180) of patients also did not need help to contact the visitor, 6.5% (N = 13) of respondents felt that medical staff helped to contact, 3% (N = 7) of respondents did not contact the visitor and 1.5% (N = 3) of respondents had no opinion on the subject.

94.5% (N = 187) of visitors indicated that they had the possibility to give personal items necessary during hospitalisation to the patient, which was negated by 4% (N = 8) of respondents, and 1.5% (N = 3) of respondents had no opinion on the subject. In contrast, 93% (N = 189) of patients indicated that they had the possibility to receive personal items necessary during hospitalisation, which was negated by 3.5% (N = 7) of respondents, and 3.5% (N = 7) of respondents had no opinion on the subject.

Although the survey included respondents who were hospitalised at different times, most, 97% (N = 192) of visitors, indicated that patient visits were prohibited due to the pandemic, 2% (N = 4) of people did not visit the hospitalised person, 0.5% (N = 1) of respondents indicated that visits were allowed, another 0.5% (N = 1) of people that visits were possible but on presentation of a certificate of vaccination. Among patients, 94% (N = 191) of respondents indicated that visits were prohibited due to the pandemic, 3% (N = 6) of people indicated that they were not visited by relatives, 1% (N = 2) of respondents indicated that visits were allowed and 2% (N = 4) of respondents that visits were possible but only in special situations.

The authors conducted a study on the same study group regarding the evaluation of the introduction of restrictions on visiting patients by relatives and the well-being of hospitalised patients during the pandemic [9,12]. 57% (N = 113) of respondents, in the visitor group, rated the introduction of hospitalised visiting restrictions badly, 41% (N = 82) of respondents rated the introduction of these restrictions well and 2% (N = 3) had no opinion on the subject. In the patient group, 52% (N = 105) of people rated the introduction of in-patient visiting restrictions badly, 44% (N = 90) of respondents rated the introduction of these restrictions well and 4% (N = 8) of people had no opinion on the subject (Figure 1).

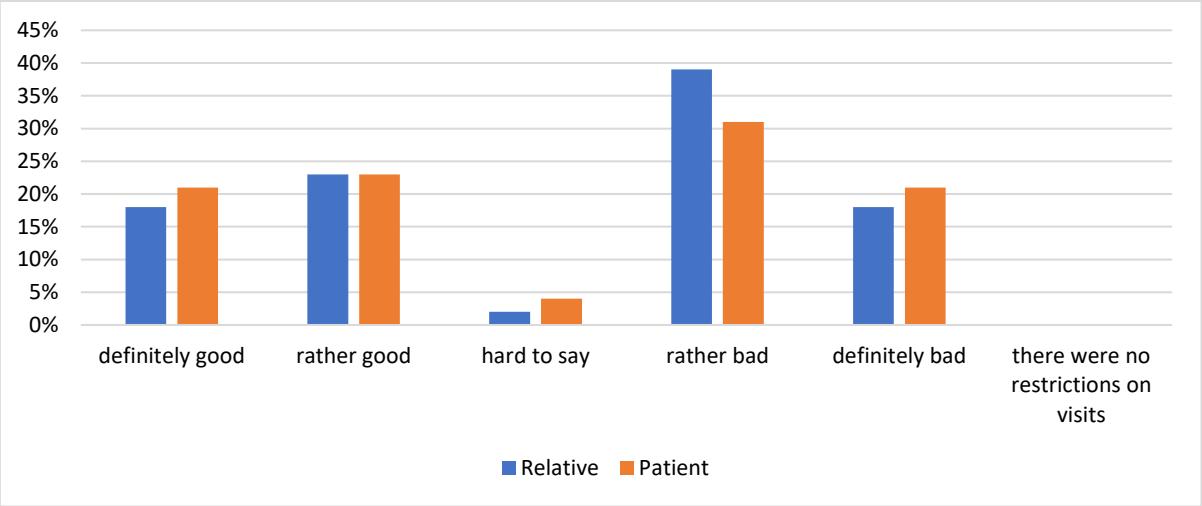

Fig. 1. Assessment of visitation restrictions in hospital wards by relatives and patients.

Regarding the way medical staff communicate information about the patient, 58% (N = 115) of people did not contact medical staff in this regard, 39% (N = 77) of people gave a good assessment of the way medical staff communicate this information and 3% (N = 6) of respondents gave a bad assessment of the way medical staff communicate this information.

The frequency of obtaining patient information from medical staff was also analysed among the respondents. Most visitors did not contact medical staff – 57.6% (N = 114), 24.2% (N = 48) of respondents received patient information from medical staff once a day, 13.6% (N = 27) of respondents received such information several times a day and 4.6% (N = 9) of respondents received such information less than daily.

In addition, 58.1% (N = 115) of relatives did not contact medical staff about receiving patient information over the phone, 40.4% (N = 80) of respondents received such information after verifying the identity of the person calling the medical facility, 1.5% (N = 3) of respondents did not receive information about the hospitalised person, because medical staff did not provide it over the phone.

The positive and negative evaluation of the introduction of visiting restrictions among patients was influenced by factors such as gender: more women – 65% (N = 73) than men – 35% (N = 40) negatively evaluated the introduction of restrictions; education: 32% (N = 36) of patients with a vocational education negatively evaluated the introduction of restrictions in hospitals, compared to patients with a higher education – 22% (N = 25), the highest proportion of patients with a secondary education negatively evaluated the introduction of restrictions – 41% (N = 46); place of residence: patients from a small city – 28% (N = 32) evaluated the introduction of restrictions worse than patients living in a large city – 15% (N = 17), the highest proportion of patients living in a medium-sized city negatively evaluated the introduction of visit restrictions – 50% (N = 56; Table II).

Furthermore, in the group of patients who negatively assessed the introduction of visitation restrictions, 91% (N = 103) of them had the possibility of daily contact with relatives, 82% (N = 93) of them did not need help to contact relatives, 93% (N = 105) of the respondents indicated that visitation was prohibited due to the

pandemic and, according to 89% (N = 101) of the respondents, relatives were able to give them personal items necessary during hospitalisation. In contrast, in the group of patients who were positive about the introduction of visitation restrictions, up to 97% (N = 87) of them were able to have daily contact with relatives, 97% (N = 87) of the respondents did not need assistance in contacting relatives, 96% (N = 86) of the respondents indicated that visits were prohibited due to the pandemic and according to 98% (N = 88) of the patients, relatives were able to give them personal items necessary during hospitalization (Figure 2).

Table II. Characteristics of surveyed group of patients divided into groups with positive and negative opinions of introduction of visitation restrictions

Variable		Total N = 203 (%; N)	Patient group	
			positive assessment of visitation reduction N = 90 (%; N)	negative assessment of reduction in visits N = 113 (%; N)
Gender	women	65%; 132	66%; 59	65%; 73
	men	35%; 71	34%; 31	35%; 40
Education	basic	3%; 6	0%; 0	5%; 6
	professional	25.6%; 52	18%; 16	32%; 36
	medium	44.4%; 90	49%; 44	41%; 46
	higher	27%; 55	33%; 30	22%; 25
Place of residence	village	6.9%; 14	7%; 6	7%; 8
	city up to 20,000	19.2%; 39	8%; 7	28%; 32
	city of 20,000–100,000	53.7%; 109	59%; 53	50%; 56
	city over 100,000	20.2%; 41	26%; 24	15%; 17

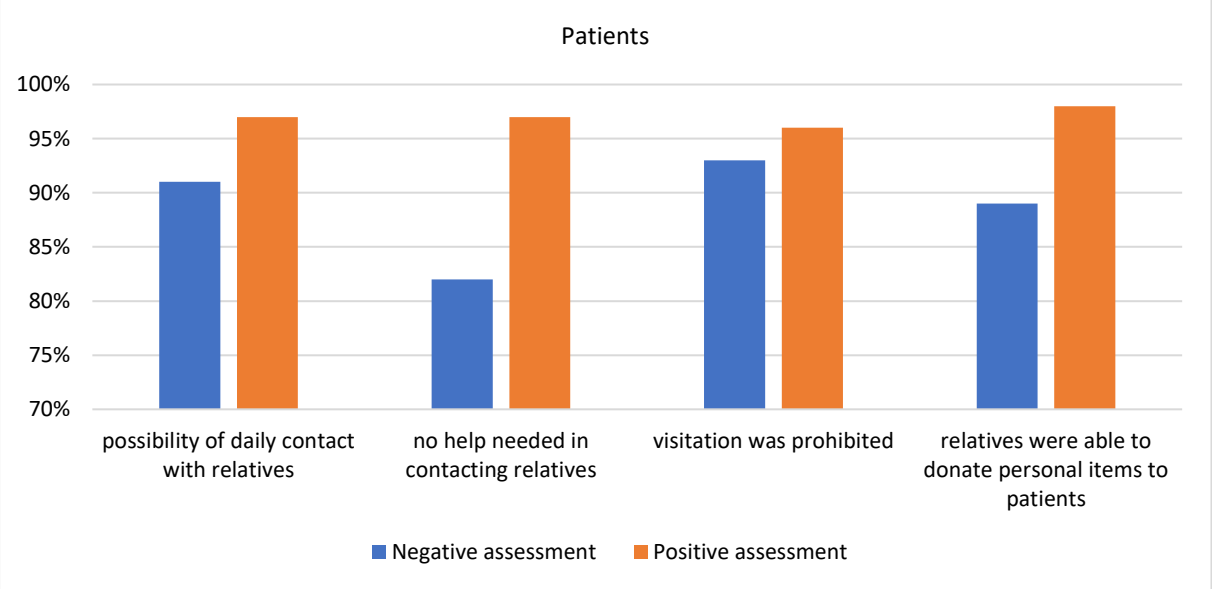

Fig. 2. Characteristics of surveyed group of patients divided into groups positively and negatively assessing introduction of visitation restrictions.

Positive and negative evaluations of the introduction of visiting restrictions among relatives were also influenced by factors such as gender: more women – 55% (N = 64) than men – 45% (N = 52) negatively evaluated the introduction of restrictions; education: the highest number of relatives with a secondary education negatively evaluated the introduction of hospital restrictions – 58% (N = 67), while the highest number of respondents with a tertiary education positively evaluated the introduction of these restrictions – 48% (N = 39); place of residence: relatives living in a medium-sized city evaluated the introduction of visitation restrictions the worst – 62% (N = 72; Table III).

Furthermore, in the group of relatives who negatively assessed the introduction of visitation restrictions, 90% (N = 104) of them had the possibility of daily contact with the patient, 84% (N = 98) of them did

not need help to contact the hospitalised person, 92% (N = 107) of the respondents in this group had the possibility to give the patient personal items necessary during hospitalisation, 97% (N = 113) of the respondents indicated that visiting the hospitalised person was prohibited due to the pandemic. In contrast, among the relatives who viewed the visitation restrictions positively, 94% (N = 77) were able to maintain daily contact with the hospitalised patient, and the same proportion – 94% (N = 77) did not require assistance in establishing this contact. Additionally, 99% (N = 81) were able to deliver personal items needed during the hospital stay. According to 96% (N = 79) of respondents, hospital visits were prohibited due to the pandemic (Figure 3).

Table III. Characteristics of surveyed group of relatives with division into groups positively and negatively assessing introduction of visitation restrictions

Variable		Total N = 198 (%;N)	Group of relatives	
			positive assessment of visitation reduction N = 82 (%; N)	negative assessment of reduction in visits N = 116 (%; N)
Gender	women	52%; 102	46%; 38	55%; 64
	men	48%; 96	54%; 44	45%; 52
Education	basic	1.5%; 3	1%; 1	2%; 2
	professional	14,2%; 28	10%; 8	17%; 20
	medium	51%; 101	41%; 34	58%; 67
	higher	33.3%; 66	48%; 39	23%; 27
Place of residence	village	6.1%; 12	9%; 7	4%; 5
	city up to 20,000	13.1%; 26	6%; 5	18%; 21
	city of 20,000–100,000	59.6%; 118	56%; 46	62%; 72
	city over 100,000	21.2%; 42	29%; 24	16%; 18

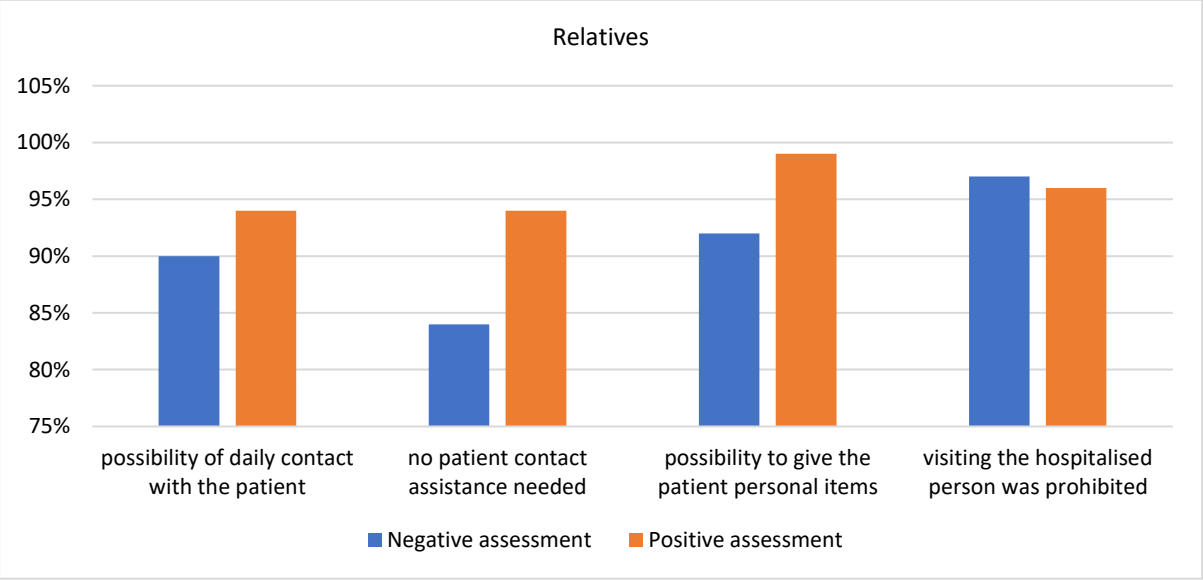

Fig. 3. Characteristics of surveyed group of relatives divided into groups positively and negatively assessing introduction of visitation restrictions.

DISCUSSION

Most countries, during the COVID-19 pandemic, introduced temporary restrictions on visiting patients in hospital wards, due to the potential for visitors to transmit the disease [13,14]. To understand the concept of visitation restriction, it is important to discern the mechanisms of relatives' involvement in the care of the hospitalised person and the impact of visitation on patient outcomes [13].

An overwhelming number of patients and their relatives understood the necessity of the visitation restriction, but the consequences of its introduction may have had an impact on the psychological state of hospitalised patients and their relatives [4]. The very contact with the healthcare system is often a source of great stress for the patient and their relatives, and the introduction of restrictions on patients' visitation could have significantly exacerbated their anxiety [1]. Greater psychological stress among relatives may also have resulted from the fact that they were unable to form their own opinion about the patient's health due to their absence from the patient [4].

As indicated in Article 33(1) of the Act on Patients' Rights and the Patients' Ombudsman [7], a patient of a health care entity that performs therapeutic activity of 24-hour and inpatient health care services within the meaning of the regulations on health care activity has the right to personal, correspondence, telephone contact with other persons. The so-called right of visitation, i.e. the right of contact with other persons, is part of the patient's broader right, i.e. the right to respect for family and private life, and is assumed to cover not only patients but also their relatives. Furthermore, the legislator has guaranteed patients the right to contact other persons without specifying the meaning of the term 'other persons', so that only the patient has the right to decide on the persons who visit him or her [15]. On the other hand, according to Article 5 of the Act on Patients' Rights and the Patients' Ombudsman [7], the head of an entity that provides health services or a doctor authorised by him or her may restrict the exercise of a patient's right in a situation where an epidemic threat arises or for reasons of patients' health safety and, in the case of the right to contact other persons, also for reasons of the entity's organisational capacity. During the pandemic, there were recommendations issued by the Ministry of Health and the Chief Sanitary Inspectorate on visiting relatives [16,17].

When introducing visitation restrictions, it was crucial to maintain the principle of proportionality, so that the harm to visitors and patients that might result from implemented restrictions was commensurate with the expected public health benefits, which could be influenced by a number of factors, such as the possibility, mode of transmission, severity of illness, incubation period and duration of infectivity, or community burden of disease [3,18]. Also, exemptions for visitation restrictions should be justified by the benefit-harm ratio, which in some countries has included, for example, pediatric patients, newborns, infants in intensive care units, people with disabilities, or people at the end of life [3,19,20,21]. Regardless of the circumstances, rules regarding visitation restrictions should be transparent and clear, with clear justification for their application, and decisions and exceptions for visitors should be based on general ethical principles such as trust, autonomy, proportionality, or minimisation of harm, in turn, a number of local factors should also be taken into account when making these decisions, including the current burden of infection in the community, new variants of the virus, vaccination rates, or available resources to combat it in the community [3,18,21]. Determining the benefits and burdens of restrictions on visitors is an important issue in view of the still rapidly spreading viruses, or the potential for further outbreaks in the future [1].

A study conducted in a hospital in the Valais region (Switzerland) found that visitation restrictions were not well received by either relatives or patients, especially those at the end of life or with cognitive impairment, with whom conversations other than face-to-face, including video, were difficult or impossible [13,22]. Families of some patients noted psychological as well as physical regression in these patients, which was also due to the lack of stimulation usually guaranteed by direct contacts. For other patients, especially those who were independent, it was welcome to compensate for the prohibition of visits with conversations, e.g. by telephone or video [13]. Virtual visits have been shown to have a positive effect on patients' recovery, reduce distress for relatives, and may also improve morale among medical staff. It seems responsible and rational for hospitals to continue to invest in telehealth, digital tools regardless of the circumstances [23].

Although the efforts of healthcare professionals and digital solutions that led to maintaining adequate distance between family members and patients were appreciated, these methods cannot replace the direct presence of loved ones [14,24,25]. Alternative means of visits, such as multimedia and digital applications, limited the ability to maintain social relationships, as well as often failing to allow loved ones to understand the patient's overall condition. The need to trust medical facilities, the inability to see what care was actually being offered to patients, and the often unclear and inconsistent rules for implementing restrictions may have caused discouragement in relatives, especially in the elderly, and contributed to their search for effective communication, especially face-to-face communication [13,22]. The presence of relatives

facilitates communication and the exchange of information between patients and health professionals, which increases the satisfaction of hospitalised patients, their families and the restriction of these visits may put more of a workload on medical staff, who often wanted to compensate patients during the pandemic for the care that visitors provided, also decision-making and communication with relatives is more difficult and time-consuming when visitors cannot be present with patients [3,4,13,26].

According to the self-reported survey, which included only independent patients and their relatives, the majority of hospitalised patients and relatives were able to contact each other on a daily basis, the respondents did not need assistance in this contact from the medical staff, and they were also able to hand over personal items necessary during hospitalization. Furthermore, respondents reported that hospital ward visits were prohibited due to the pandemic, a measure that generated considerable dissatisfaction among many. In addition, most visitors did not reach out to medical staff for updates on the patient's condition.

A study conducted during the first wave of the COVID-19 pandemic among patients in a hospital in Valais found that the lack of physical presence of relatives resulted in anxiety, decreased mood, and a greater need for up-to-date information about the patient's condition. A significant proportion of the relatives participating in the study felt that they were well informed by the medical staff, but some respondents expressed concerns about the limitations of visiting and felt less or no involvement in the patient care provided. Significant differences were observed in some wards, most notably in gynaecology or obstetrics. In the study, 69% of respondents acknowledged that they had regular contact with hospitalised patients (at least once a day), but the attempt to replace physical visits by digital means was associated with clear limitations, related to reduced understanding by those close to the patient of the patient's overall condition, which was also a source of emotional distress and a greater burden for medical staff [13]. The authors of the referenced study recommend a more flexible, tailored, and patient-centered approach to visit limitations depending on the patient's clinical situation [13].

The results of a study of the consequences of visitation restrictions in health care services during the COVID-19 pandemic, based on a literature review [24], indicate that they had many negative consequences for patients as well as family members, despite efforts made to use technical solutions to replace face-to-face visits. Restrictions on visitation have increased mental health problems and caused distress among patients as well as relatives. Despite this, other studies have shown that family members approved of and adhered to visitation restrictions to inhibit the spread of COVID-19, even when their well--being may have been affected [14,24,27].

A study that included hospitalised patients and their relatives, carried out at the outpatient clinics of the University Medical Centre Rostock, found that the reduction in hospital visits to control the COVID-19 pandemic was an additional stress factor for both patients and their relatives. This study showed that relatives were more psychologically stressed than hospitalised patients, and the desire to visit hospitalised patients was more pronounced among relatives than among patients [4].

A study conducted among relatives of patients hospitalized during the COVID-19 pandemic in general surgery and internal medicine departments across three hospitals in northern and central Portugal found that visitation restrictions led to a detachment of families from the hospital environment. This, in turn, negatively impacted the healthcare process by hindering the involvement of family members in patient care. This study also showed that medical teams often went to great lengths to ensure the well-being of hospitalised patients [28]. Patients' families know their health history best, are attentive to emerging needs, and have the opportunity to collaborate with medical staff in the observation and supervision of the patient. As these studies indicate, assessing each circumstance in detail and making the decision to allow visits on this basis, despite the visitation restrictions in place, demonstrates a patient- and family-centered approach and, according to emerging evidence, the presence of the family alongside the patient positively influences patient outcomes and the overall process of care involved [28]. It is difficult to determine whether visit restrictions have effectively prevented the spread of COVID-19. It is reasonable to argue that these restrictions have slowed the spread of the disease [13], although other studies indicate that the family has not played a significant role in the transmission of SARS-CoV-2 virus [1], undoubtedly in the future, should further threats arise, consideration of the introduction of visit restrictions should be done with consideration of the potential benefits and harms to patients and their relatives.

CONCLUSIONS

1. Almost all visitors and patients indicated that hospital ward visits were prohibited due to the pandemic. For more than half of the respondents in both groups, this was a source of dissatisfaction, emphasizing the importance of physical contact with loved ones for both groups surveyed. The inability to receive visitors may have negatively affected patients' emotional well-being, causing

feelings of loneliness and stress, especially among elderly and chronically ill individuals.
2. Despite the pandemic restrictions, most independent patients and their relatives had daily contact with each other through alternative communication methods, without requiring assistance from medical staff in this regard. The ability to maintain daily contact via phone or online was crucial for preserving family bonds and mitigating the negative effects of visitation restrictions. This may indicate the need for further development and improvement of remote communication methods in hospitals.
3. The majority of patients and their relatives believed that despite visitation restrictions it was possible to deliver essential personal items to the hospitalized individual, highlighting that hospitals provided appropriate means for their transfer.
4. More than half of the relatives did not contact the medical staff to obtain information about the patient's condition. However, those who took advantage of this opportunity positively assessed the way the information was provided. Most often, the information was conveyed by the medical staff over the phone once a day, after prior verification of the caller's identity by the medical facility. Positive feedback on the way medical staff communicated information may indicate that hospitals successfully adapted to new challenges.
5. Differentiating patients and their relatives into two groups in relation to a positive or negative assessment of the introduction of visitation restrictions, in both groups more women than men negatively assessed the introduction of visitation restrictions, with most respondents with a secondary education and living in a medium-sized city giving negative assessments of the introduction of restrictions.
6. In the future, in the event of new epidemics, it may be worth considering a more flexible approach to visitations, such as allowing them in exceptional cases (e.g. for critically ill patients) or implementing protective measures that enable safe contact.

Limitations

The amount of evidence related to the impact of the introduction of visiting restrictions in hospitals on patients' and relatives' assessment of the implementation of these restrictions is low, and further research is definitely needed in this area, in view of the still dynamic spread of new diseases and the viruses that cause them, including dependants. Given the small number of studies conducted on this topic, it was not easy to compare the results of our own study with other available results. Limitations of the study were the collection of results in a single medical facility, i.e. a rehabilitation clinic, the sample size, the smaller number of relatives (198) than patients (203) surveyed, the study's focus on independent persons only, the failure to distinguish between relatives and patients infected with COVID-19 and patients hospitalised for another reason and visitors. The delay between the hospitalisation of the patients and the completion of the questionnaire by them and their relatives was also a limitation.

Practical implementation

In the event of further outbreaks occur in the future, the development of the next hospital ward visitation policies should take into account the already known benefits and burdens of the previously implemented visitation restrictions for patients and their relatives and the exemptions regarding these restrictions and the families or essential carers of the patients could be involved in the development of the strategies [1].

Funding

This research recived no external funding.

Institutional Review Board Statement

This research complies with the provisions of the Helsinki Declaration and local regulations of the Bioethical Commission of the Medical University of Silesia, Katowice, Poland; the Committee on Publication Ethics (COPE) regulations were followed in the study.

Data Availability Statement

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

Authors' contribution

Study design – K. Jaroń, M. Grajek, J. Kobza
Data collection – K. Jaroń
Data interpretation – K. Jaroń, M. Grajek, J. Kobza
Statistical analysis – K. Jaroń, M. Grajek
Manuscript preparation – K. Jaroń, M. Grajek, J. Kobza
Literature research – K. Jaroń

Appendix 1

DEPARTMENT OF PUBLIC HEALTH
FACULTY OF PUBLIC HEALTH IN BYTOM
MEDICAL UNIVERSITY OF SILESIA, KATOWICE, POLAND

Dear Sirs,

I kindly request you to participate in a survey on medical staff-patient communication in the context of patient rights during the COVID-19 pandemic. Participation in the survey is voluntary and completely anonymous. The material collected will be used for research purposes only. We kindly ask for your assistance in the survey. The survey consists of 2 parts. The first part of the survey consists of 26 short questions, will take approximately 15–20 minutes to complete and is aimed at hospitalised patients. The second part of the survey is aimed at the patient's relatives and consists of 9 short questions, it will take approximately 10–15 minutes to complete.

The term 'hospital' as used in the survey includes hospitals and other inpatient units.

The term 'COVID-19', as used in the survey, refers to the respiratory disease caused by the SARS-CoV-2 coronavirus.

QUESTIONNAIRE FOR PATIENTS' RELATIVES

AGE: ..... years

GENDER: ☐ K (woman) ☐ M (man)

EDUCATION:
a) primary
b) vocational
c) secondary
d) higher

PLACE OF RESIDENCE:
a) rural area/village
b) small town up to 20,000 inhabitants
c) medium town with 20,000 to 100,000 inhabitants
d) large city with more than 100,000 inhabitants
e) very large city with more than 200,000 inhabitants

RELATIONSHIP TO THE PERSON HOSPITALISED
.....

HOSPITAL WARD WHERE YOUR CLOSE RELATIVE IS STAYING
.....

VOIVODESHIP WHERE YOUR RELATIVE IS STAYING IN THE HOSPITAL WARD
.....

PERIOD WHERE YOUR NEARLY RELATIVE STAYED IN HOSPITAL SITUATION (please give the approximate time of the beginning and end of stay in hospital ward, day/month/year)
☐☐-☐☐-☐☐☐☐ -- ☐☐-☐☐-☐☐☐☐

1. **For what reason was your loved one admitted to hospital?**
   a) planned operation and/or treatment
   b) sudden deterioration of health
   c) rehabilitation after illness or injury
   d) complications after an illness
   e) other (which?) .....
2. **Did you have any opportunity to contact your loved one (including by telephone) during your stay in hospital?**
   a) YES, every day
   b) YES, once a week
   c) YES, less than once a week
   d) I have not contacted my relative

3. **Did the medical staff assist you in contacting (also by phone) your loved one?**
   a) definitely yes
   b) rather yes
   c) hard to say
   d) rather no
   e) definitely not
   f) I did not need help to contact a relative
   g) I did not communicate with my relatives
4. **Were you able to give your personal items necessary for your hospitalization to your relatives?**
   a) definitely yes
   b) rather yes
   c) difficult to say
   d) rather no
   e) definitely not
5. **Were you allowed to visit your relative during his/her stay in the hospital ward?**
   a) YES, visits to your relatives were allowed
   b) YES, visits to a relative were possible but only in special situations
   c) NO, visits of a relative were forbidden due to the pandemic
   d) I did not visit a relative
   e) other (which ones?) .....
6. **How would you rate the restriction on visiting a loved one in hospital during the pandemic?**
   a) definitely good
   b) rather well
   c) difficult to say
   d) rather bad
   e) definitely bad
   f) there were no restrictions on visiting a relative
7. **How would you rate the way in which medical staff provided information about your relative staying in hospital?**
   a) definitely good
   b) rather well
   c) hard to say
   d) rather bad
   e) definitely bad
   f) I did not contact medical personnel
8. **How often have you been able to get information about your loved one from medical personnel?**
   a) several times a day
   b) once a day
   c) less than daily
   d) I have not been in contact with medical personnel
9. **Did you receive information about a loved one over the phone from medical personnel?**
   a) YES, always
   b) YES, after the medical staff had verified the identity of the person calling the medical facility
   c) NO, the medical personnel did not give information about a relative over the phone
   d) I did not contact the medical personnel
   e) other (which?) .....

THANK YOU VERY MUCH FOR FILLING IN THE QUESTIONNAIRE

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PRACA POGLĄDOWA
REVIEW

Heart failure with preserved left ventricular ejection fraction – clinical perspectives

Niewydolność serca z zachowaną frakcją wyrzutową lewej komory – perspektywy kliniczne

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is an increasingly recognized subtype of heart failure, particularly affecting older adults and women. It accounts for approximately 51–63% of heart failure cases, and its prevalence continues to rise, largely due to aging populations and an increasing burden of comorbidities such as hypertension, diabetes, obesity, and chronic kidney disease. The European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines emphasize a combination of clinical symptoms, preserved left ventricular ejection fraction (LVEF ≥ 50%), elevated natriuretic peptides, and echocardiographic markers of diastolic dysfunction for diagnosis. Additionally, diagnostic algorithms such as the HFA-PEFF score and H_2FPEF score aid in differentiating HFpEF from other cardiovascular and non-cardiovascular diseases. Until recently, HFpEF treatment focused mainly on symptom relief and comorbidity management. However, newer pharmacological therapies have demonstrated benefits in reducing hospitalizations and improving cardiovascular outcomes. Prognosis in HFpEF remains poor, with a 5-year mortality rate of approximately 75%. Thus patients with HFpEF require comprehensive management that includes lifestyle modifications, optimized pharmacotherapy, and rigorous control of comorbid conditions. Currently presented review summarizes practical aspects of HFpEF diagnosis, pathophysiology, treatment and prognosis focusing on multidisciplinary approaches and early intervention strategies may improve outcomes for patients affected by this challenging condition.

KEYWORDS

heart failure, heart failure with preserved ejection fraction, diastolic dysfunction

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STRESZCZENIE

Niewydolność serca z zachowaną frakcją wyrzutową (*heart failure with preserved ejection fraction* – HFpEF) jest coraz częściej rozpoznawanym podtypem niewydolności serca, dotykającym głównie osoby starsze i kobiety. Odpowiada za około 51–63% przypadków niewydolności serca, a jej częstość występowania nadal rośnie, głównie ze względu na starzenie się populacji oraz wzrastające obciążenie chorobami współistniejącymi, takimi jak nadciśnienie tętnicze, cukrzyca, otyłość i przewlekła choroba nerek. Wytyczne Europejskiego Towarzystwa Kardiologicznego (European Society of Cardiology – ESC) oraz Amerykańskiego Towarzystwa Kardiologicznego (American Heart Association – AHA) wskazują konieczność spełnienia kryteriów diagnostycznych obejmujących objawy kliniczne, zachowaną frakcję wyrzutową lewej komory (*left ventricular ejection fraction* – LVEF ≥ 50%), podwyższony poziom peptydów natriuretycznych oraz echokardiograficzne markery dysfunkcji rozkurczowej. Ponadto algorytmy diagnostyczne, takie jak skale HFA-PEFF i H_2FPEF, wspomagają różnicowanie HFpEF z innymi chorobami sercowo-naczyniowymi i pozasercowymi. Do niedawna leczenie HFpEF koncentrowało się głównie na łagodzeniu objawów oraz kontrolowaniu chorób współistniejących. Jednak nowsze terapie farmakologiczne wykazały korzyści w zakresie redukcji liczby hospitalizacji oraz poprawy wyników sercowo-naczyniowych. Rokowanie w HFpEF pozostaje niekorzystne; 5-letnia śmiertelność wynosi około 75%. Dlatego pacjenci z HFpEF wymagają kompleksowego postępowania obejmującego modyfikację stylu życia, optymalizację leczenia farmakologicznego oraz ścisłą kontrolę chorób współistniejących. Niniejszy przegląd podsumowuje praktyczne aspekty diagnostyki, patofizjologii, leczenia i rokowania HFpEF, koncentrując się na podejściu interdyscyplinarnym i strategiach wczesnej interwencji, które mogą poprawić wyniki leczenia pacjentów dotkniętych tym wymagającym schorzeniem.

SŁOWA KLUCZOWE

niewydolność serca, niewydolność serca z zachowaną frakcją wyrzutową, dysfunkcja rozkurczowa

Introduction

The estimated incidence of heart failure in the population of developed countries is 10,000 to 20,000 cases per million people [1]. It is believed that 51–63% of these cases are heart failure with preserved ejection fraction (HFpEF), and this percentage is constantly increasing relative to heart failure with reduced ejection fraction (HFrEF) [2,3,4,5,6,7]. This increase is particularly visible in the older age group [8]. In people over 60 years of age, HFpEF affects up to 5% of the population [9].

Women are more often affected [1]. The age of people who develop HFpEF is on average 6 years older than in people with HFrEF [10]. The incidence of hospitalization due to HFpEF is increasing and is one of the main causes of hospitalization in patients with acute heart failure [11]. In the African-American population, HFpEF accounts for 70% of all heart failure cases [12].

It is assumed that comorbidities are more common in HFpEF than HFrEF, and this is particularly true for conditions such as hypertension and obesity [13,14]. Arterial hypertension is also the most common cardiovascular disease that occurs in the majority of patients with HFpEF [8]. Although coronary artery disease is more often associated with HFrEF, it is worth emphasizing that it also co-occurs in 30–60% of HFpEF cases [15]. When a patient with HFpEF has coronary artery disease, the risk of a progressive decline in left ventricular ejection fraction (LVEF) increases, as does the risk of mortality [16].

The numerous comorbidities associated with HFpEF that may influence its development include: diabetes (incidence 20–40% of cases), chronic renal failure (20–30% of cases), obesity (50% of cases) and atrial fibrillation [15]. Mortality among patients with HFpEF is comparable to that observed in people with HFrEF, but some studies have shown that it may be slightly lower in HFpEF [5,7,17].

For effective treatment of HFpEF, a thorough understanding of its pathophysiology and etiology is necessary. In recent years, significant progress has been made in understanding the hemodynamic and cellular processes that contribute to the development of HFpEF. The development of HFpEF begins with diastolic dysfunction, manifested by incomplete relaxation of the myocardium and increased passive stiffness of the heart walls, which leads to left atrial enlargement. Arterial hypertension, as the most common comorbid disease, is one of the key factors contributing to this process. The increase in arterial wall stiffness increases the filling pressure of the left ventricle. Combined with the relatively normal function of the mitral valve, this leads to increased pressure in the left atrium. In the later stages of the disease, pulmonary hypertension develops, which leads to damage to the right side of the heart. Moreover, changes in the lungs result in a reduction of the gas exchange surface, remodeling of pulmonary vessels and impairment of lung function. Additionally, overhydration, often associated with comorbidities such as kidney disease, can lead to right ventricular overload, increasing filling pressure and contributing to disease progression. These processes have a significant impact on hemodynamic changes in the heart. At the cellular level, the theory of systemic inflammation is a promising direction of research. Increased production of inflammatory factors resulting from many comorbidities leads to damage to inflammatory vessels, which in turn affects the

bioavailability of nitric oxide, cyclic guanosine monophosphate (cGMP) concentration and titin phosphorylation in the myocardium. Changes in cellular metabolism, including anaerobic glycolysis and switching to less favorable metabolic pathways, also affect cardiac cell function. These processes rarely occur in isolation. They often coexist, enhancing each other, which affects the entire heart muscle [18]. As a result, the etiology and pathophysiology of HFpEF is a complex set of processes that interact to lead to cardiac dysfunction. Understanding these mechanisms is crucial for further progress in the treatment and improvement of the quality of life of patients with HFpEF [1]. The scheme of development of right ventricular failure in HFpEF is presented in Figure 1.

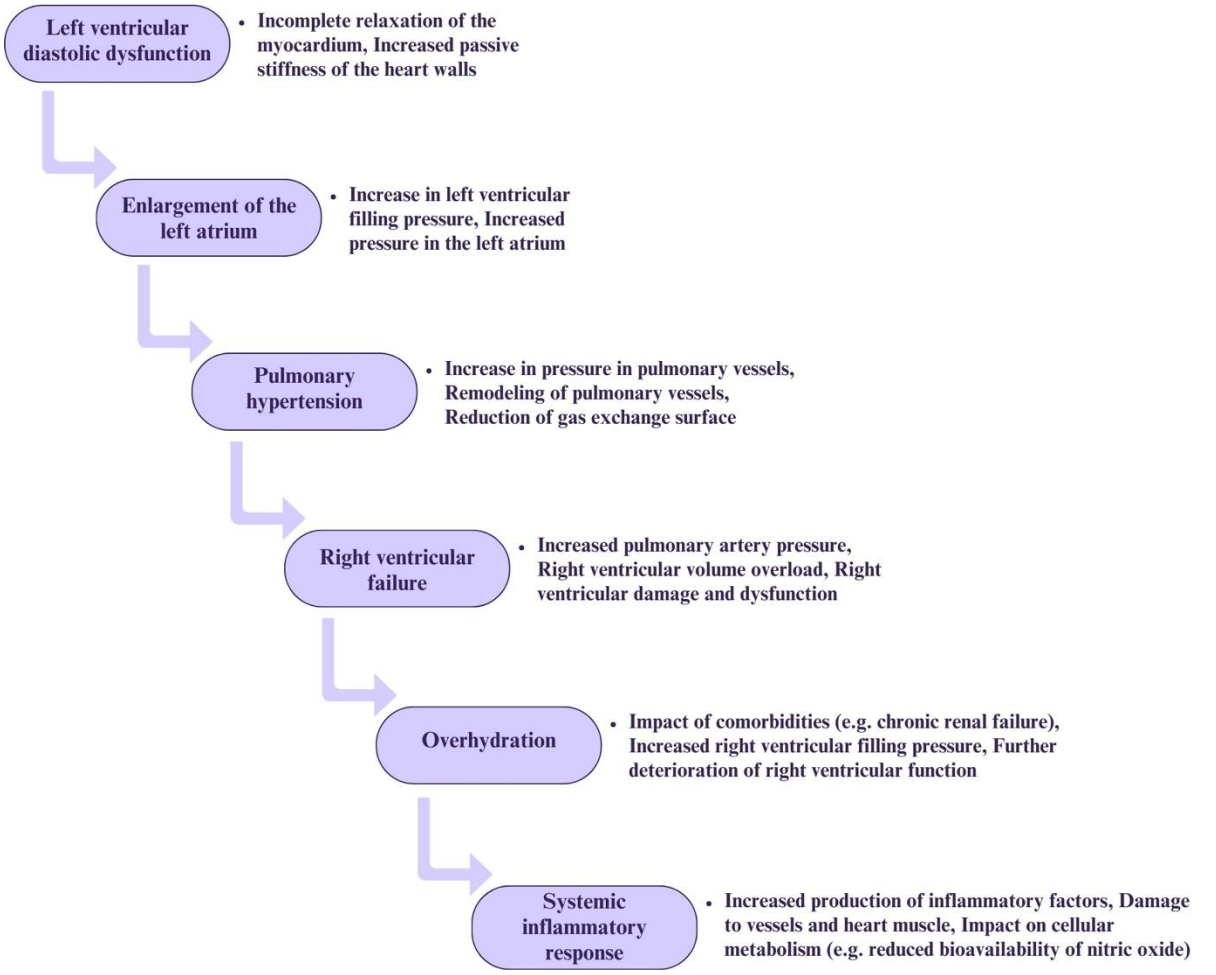

Fig. 1. Diagram of development of right ventricular failure in heart failure with preserved ejection fraction.

Clinical characteristics of patients with HFpEF

The diagnosis of HFpEF is based on the identification of symptoms and signs in patient with LVEF ≥ 50%. Patients with HFpEF often report dyspnea on exertion, which interferes with daily functioning. There is also fatigue and reduced exercise tolerance. Characteristic symptoms include orthopnoea, i.e. shortness of breath when lying down, and paroxysmal nocturnal dyspnea, manifested by sudden episodes of shortness of breath during sleep. Patients may also experience heart rhythm disturbances.

During physical examination in patients with HFpEF, symptoms mainly include: peripheral edema, especially of the lower limbs, pulmonary rales, dilated jugular veins and hepatojugular reflux. A third heart sound, which suggests increased left ventricular end-diastolic pressure, may also be present in HFpEF. Cardiac apex enlargement, i.e. a change in the position or enlargement of the heart apex palpable, is also possible. Moreover, increased jugular venous pressure is typical in patients with HFpEF [19,20].

One of the invasive tests assessing the level of B-type natriuretic peptide (BNP), used to exclude heart failure

in patients with shortness of breath and preserved ejection fraction (> 50%), revealed the following symptoms: dyspnea on exertion in 91% of patients, orthopnea in 48%, paroxysmal nocturnal dyspnea in 29%, increased pressure in the jugular veins (average 10.4 ± 2.8 cm H_2O) in 72% and lower limb edema in 66%. The patients included in the study also had echocardiographic abnormalities consistent with HFpEF [9,21,22,23].

The quality of life in patients with HFpEF is as low or even worse than in patients with HFrEF. The level of physical activity in these patients is similarly limited to that in people with moderate to severe chronic obstructive pulmonary disease (COPD) [24].

Table I. Structural and functional parameters of heart in diagnosis of heart failure with preserved ejection fraction

Parameter	Threshold
LV mass index	≥ 95 g/m² (female) / ≥ 115 g/m² (male)
Relative wall thickness	> 0.42
LA volume index	> 34 mL/m² (SR)
E/e' ratio at rest	> 9
NT-proBNP	> 125 (SR) or > 365 (AF) pg/mL
BNP	> 35 (SR) or > 105 (AF) pg/mL
PA systolic pressure	> 35 mmHg
TR velocity at rest	> 2.8 m/s

LV – left ventricle; LA – left atrium; NT-proBNP – N-terminal pro-B-type natriuretic peptide; BNP – B-type natriuretic peptide; PA systolic pressure – pulmonary artery systolic pressure; TR velocity – tricuspid regurgitation velocity; SR – sinus rhythm; AF – atrial fibrillation.

Diagnosis of HFpEF

The diagnosis of HFpEF is complex due to its nonspecific symptoms and multifactorial etiology. Various algorithms and guidelines have been developed to facilitate the identification of this form of heart failure.

The first step in diagnosing HFpEF in patients presenting with symptoms should involve ruling out other non-cardiac causes of dyspnea and/or edema [25]. Non-cardiac causes include lung diseases, kidney diseases, liver diseases, neuromuscular disorders, anemia, depression, and others.

The next diagnostic step, based on the European Society of Cardiology (ESC) guidelines, requires fulfilling the following diagnostic criteria for HFpEF (all these criteria must be met to confirm the diagnosis of HFpEF) [26,27]:

- presence of subjective and/or objective symptoms of heart failure
- preserved left ventricular systolic function with LVEF ≥ 50%
- elevated levels of natriuretic peptides: BNP ≥ 35 pg/ml and/or N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 125 pg/ml
- evidence of structural heart disease (e.g. left atrial enlargement or left ventricular hypertrophy) or diastolic dysfunction.

Structural and functional parameters of the heart in the diagnosis of HFpEF are presented in Table I.

Elevated NT-proBNP levels are a key diagnostic criterion, but their interpretation in HFpEF requires caution due to variability. Factors influencing NT-proBNP levels include:

- reduced natriuretic peptide release (e.g. associated with obesity or diabetes)
- increased NT-proBNP levels in atrial fibrillation, pulmonary hypertension, or primary right ventricular dysfunction
- the effects of certain medications, such as angiotensin receptor-neprilysin inhibitors (ARNIs) [21,28,29,30,31,32,33,34, 35,36].

Echocardiography remains a cornerstone in diagnosing HFpEF. Key echocardiographic findings include an increased left atrial volume index (LAVI > 34 ml/m²), left ventricular hypertrophy (LV wall thickness > 11 mm), diastolic dysfunction (e.g. E/e' ratio > 9), and mitral valve abnormalities such as severe atrial functional mitral regurgitation [28,29,30,31,32].

The further step in clinical evaluation is to assess the cardiac diseases imitating HFpEF – among others: cardiomyopathies, sarcoidosis, cardiac amyloidosis, other storage and infiltrative diseases, pericardial diseases, and more.

The diagnostic process can be further supported by tools such as the Heart Failure Association–Preserved Ejection Fraction (HFA-PEFF) algorithm and the H_2FPEF (Heavy, Hypertensive, atrial Fibrillation,

Pulmonary hypertension, Elder, Filling pressure) score, which assess the probability of HFpEF [33].

The HFA-PEFF algorithm includes four steps:

1. Pretest assessment (P):
   - evaluation of heart failure symptoms (subjective and/or objective)
   - identification of comorbidities and risk factors
   - standard laboratory tests, including natriuretic peptides
   - resting electrocardiogram and exercise tests (e.g. 6-minute walk test)
   - preliminary echocardiography.
2. Echocardiography and natriuretic peptides (E):
   - advanced echocardiographic assessment (e.g. left atrial volume index, diastolic function)
   - measurement of natriuretic peptides (BNP ≥ 35 pg/ml or NT-proBNP ≥ 125 pg/ml).
3. Functional and hemodynamic assessment (F):
   - functional echocardiography (e.g. E/e' ratio, tricuspid regurgitation velocity)
   - hemodynamic evaluation using invasive techniques (e.g. pulmonary capillary wedge pressure, left ventricular end-diastolic pressure)
   - additional tests such as cardiac magnetic resonance imaging, positron emission tomography, or myocardial biopsy in challenging cases.
4. Etiological assessment (F2):
   - comprehensive analysis to determine the etiology of HFpEF
   - use of genetic testing, biomarkers, and advanced imaging techniques.

The H_2FPEF score is another valuable simple tool to assess the likelihood of HFpEF in patients with HF symptoms. This scoring system includes the following parameters:

H: Heavy (obesity, BMI > 30 kg/m²) – 2 points
H: Hypertension (≥ 2 antihypertensive medications) – 1 point
A: Atrial fibrillation (paroxysmal or persistent) – 3 points
P: Pulmonary hypertension (PASP > 35 mmHg) – 1 point
E: Elderly (age > 60 years) – 1 point
F: Filling pressure (E/e' > 9) – 1 point.

Patients with an H_2FPEF score ≥ 6 have a high likelihood of HFpEF. For intermediate scores (2––5 points), invasive hemodynamic testing may be necessary, including:

- right heart catheterization (RHC) to evaluate pulmonary artery pressure
- assessment of pulmonary artery wedge pressure (PAWP): PAWP > 18 mmHg confirms HFpEF, while PAWP < 11 mmHg excludes it [36,37,38,39,40].

The diagnosis of HFpEF involves a comprehensive evaluation of clinical, laboratory, imaging, and functional findings. Diagnostic algorithms such as HFA-PEFF and scoring systems like H_2FPEF assist in distinguishing HFpEF from other conditions and identifying underlying etiologies. In complex cases, advanced echocardiographic and invasive assessments may be required to confirm the diagnosis and guide treatment [9,33,38,39,40,41,42,43,44].

A summary of the steps in diagnosing HFpEF is presented in Table II.

Table II. Summary of steps in diagnosing heart failure with preserved ejection fraction

Step	Assessment	Elements
1	Non-cardiac causes	COPD, obesity, anemia, chronic kidney disease, pulmonary embolism, cirrhosis
2	Heart failure definition	symptoms + cardiac dysfunction + response to treatment
3	Heart failure mimics	pericardial diseases, muscular, neurological disordes
4	H_2FPEF score	H: Heavy (obesity, BMI > 30 kg/m²), H: Hypertension (≥ 2 antihypertensive medications), A: Atrial fibrillation, P: Pulmonary hypertension (PASP > 35 mmHg), E: Elderly (age > 60 years), F: Filling pressure (E/e' > 9)
5	HFA-PEFF score	structure, diastolic, biomarkers

COPD – chronic obstructive pulmonary disease; BMI – body mass index; PASP – pulmonary artery systolic pressure.

Treatment of HFpEF

Until recently, there was no effective therapy specifically designed for HFpEF. Current guidelines emphasize the importance of managing comorbid conditions as the primary treatment strategy. The management of HFpEF is generally divided into pharmacological and non-pharmacological approaches [45].

Pharmacological treatment

Pharmacological treatment of HFpEF focuses primarily on symptom reduction, hemodynamic stabilization, and the reduction of cardiovascular risk factors. The main classes of drugs used in the treatment of HFpEF according to the latest American guidelines that have shown benefits include:

Sodium-glucose cotransporter-2 inhibitors (Class I recommendation)

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, such as empagliflozin and dapagliflozin, have received Class I recommendations for reducing heart failure hospitalizations and cardiovascular mortality. These drugs are particularly effective in patients with diabetes or chronic kidney disease. Initially developed for glycemic control in type 2 diabetes mellitus (T2DM), SGLT2 inhibitors have shown significant cardiovascular benefits in patients with and without T2DM, particularly in heart failure. They reduce hospitalization and cardiovascular death across all ejection fraction subgroups, making them a key treatment option for HFpEF patients without contraindications. Early initiation of heart failure guideline-directed therapy (GDMT) improves long--term adherence. Studies like SOLOIST-WHF demonstrated that sotagliflozin (not FDA-approved) significantly reduced cardiovascular deaths and heart failure-related hospitalizations in recently hospitalized T2DM patients across all ejection fraction ranges. Similarly, the EMPULSE trial found empagliflozin safe and effective in acutely decompensated heart failure patients, improving decongestion and clinical outcomes, with benefits seen across different ejection fraction groups.

Diuretics for symptom relief (Class I recommendation)

Diuretics play a key role in the symptomatic treatment of HFpEF, particularly in reducing fluid retention and alleviating congestion. Loop diuretics, such as furosemide, bumetanide, and torasemide, are the most commonly used and the most potent diuretics. They act by inhibiting sodium and chloride reabsorption in the loop of Henle, leading to intense diuresis. Torasemide has better bioavailability and a longer duration of action compared to furosemide, which may result in better symptom control and fewer hospitalizations. In some cases, thiazide diuretics (bendroflumethiazide, chlorthalidone, hydrochlorothiazide, indapamide, or metolazone) are used in patients with diuretic resistance. Thiazide diuretics act on the distal tubule, increasing sodium excretion and enhancing the effect of loop diuretics. Additionally, mineralocorticoid receptor antagonists (MRAs), such as spironolactone or eplerenone, may be used, especially in patients with elevated natriuretic peptides, significant fluid retention, or coexisting hypertension. MRAs not only help regulate fluid volume but also reduce fibrosis and inflammation, which play a crucial role in the pathophysiology of HFpEF.

Other pharmacological options (Class IIb recommendations)

- MRAs: drugs such as spironolactone or eplerenone may benefit selected patients, particularly those with elevated natriuretic peptides or evidence of significant fluid overload
- ARNIs: in patients with HFpEF, especially those with LVEF below 55–60%, ARNI agents like sacubitril/valsartan may be beneficial; their use is associated with improved hemodynamics and a reduced risk of heart failure hospitalizations
- angiotensin receptor blockers (ARBs): for patients unable to tolerate ARNIs due to intolerance or high cost, ARBs such as valsartan or losartan can be used as an alternative; these are particularly useful for optimizing blood pressure and alleviating symptoms of fluid overload
- angiotensin-converting enzyme inhibitors **(**ACEIs): in the treatment of HFpEF, the use of ACEIs, including perindopril, ramipril, and enalapril, can be considered; however, they are mainly used in the presence of coexisting hypertension.

On the flowchart (Figure 2), a simplified scheme for pharmacological treatment of HFpEF is presented.

The European Society of Cardiology (ESC) provides evidence-based recommendations to optimize treatment, focusing on symptom relief, hemodynamic stabilization, and reducing the risk of hospitalization and cardiovascular mortality. Table III provides a summary of the key pharmacological interventions recommended by the ESC for the management of HFpEF, along with their respective classes of recommendation and levels of evidence.

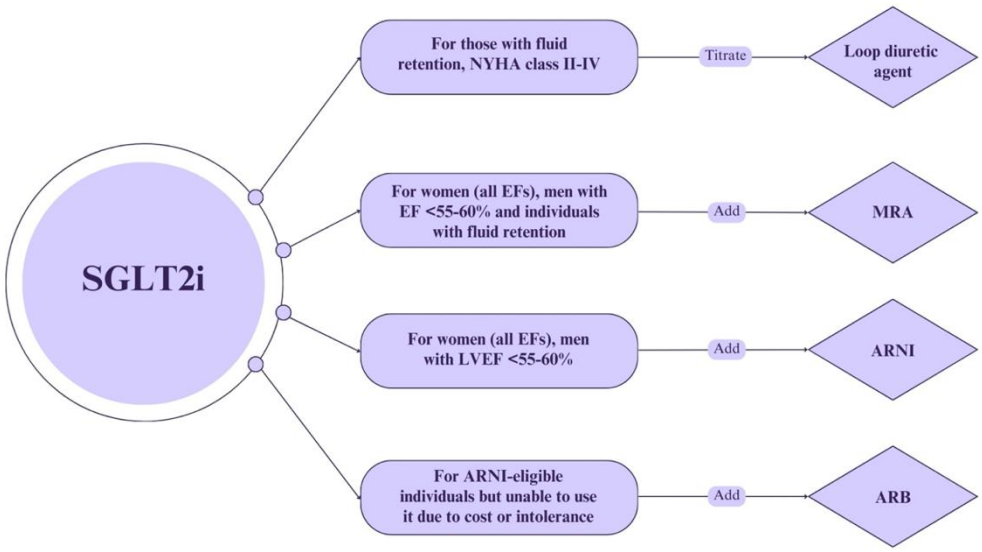

Fig. 2. Heart failure with preserved ejection fraction treatment according to the American College of Cardiology guidelines (based on [33]). SGLT2i – sodium--glucose cotransporter-2 inhibitors; NYHA – New York Heart Association (classification); EF – ejection fraction; MRA – mineralocorticoid receptor antagonist; LVEF – left ventricular ejection fraction; ARNI – angiotensin receptor-neprilysin inhibitor; ARB – angiotensin receptor blocker.

Table III. European Society of Cardiology heart failure with preserved ejection fraction treatment recommendations

Drug class	Recommendation class	Primary benefits
Sodium-glucose cotransporter-2 inhibitors	Class I	Reduces HF hospitalizations and CV mortality, beneficial in patients with and without diabetes.
Diuretics	Class I	Relieves congestion and fluid overload symptoms.
Mineralocorticoid receptor antagonists	Class IIb	May reduce HF hospitalizations in selected patients with elevated natriuretic peptides.
Angiotensin receptor-neprilysin inhibitors	Class IIb	May improve outcomes in HFpEF patients with LVEF below 55–60%.
Angiotensin receptor blockers	Class IIb	Alternative for patients who cannot tolerate ARNI.
Angiotensin-converting enzyme inhibitors	Class IIb	Used in patients with HFpEF and hypertension, though benefits in HFpEF remain uncertain.

HF – heart failure; CV – cardiovascular; HFpEF – heart failure with preserved ejection fraction; LVEF – left ventricular ejection fraction; ARNI – angiotensin receptor-neprilysin inhibitor.

In addition to optimizing blood pressure control, treating comorbidities is essential in HFpEF, as they significantly influence disease progression and patient outcomes. The main comorbidities and their targeted treatments include:

Hypertension

The treatment of hypertension in HFpEF aims to maintain blood pressure within recommended targets, similar to HFrEF. The goal is < 140/90 mmHg, with a preferred systolic range of 120–130 mmHg in patients with left ventricular hypertrophy (LVH). ACEIs, ARBs, calcium channel blockers (CCBs), diuretics, and MRAs are commonly used antihypertensive agents.

Comparative studies, such as ALLHAT, have demonstrated that ACEIs, including perindopril, offer superior long-term cardiovascular protection compared to other antihypertensive classes, reducing the risk of myocardial infarction, stroke, and heart failure hospitalizations, particularly in high-risk populations with diabetes and obesity [46,47,48,49,50,51,52]. Perindopril has also been shown to reduce vascular resistance and myocardial stiffness, improving hemodynamics and alleviating symptoms such as dyspnea, fatigue, and edema.

The ACCOMPLISH trial highlighted the benefits of combining perindopril with amlodipine, showing greater cardiovascular protection than diuretic-based regimens. Similarly, studies like ASCOT and Brisighella Heart Study confirmed that this combination is more effective than beta-blockers or thiazide diuretics in stabilizing blood pressure and improving lipid profiles.

Patients with obesity or difficult-to-control hypertension may particularly benefit from perindopril plus indapamide, as demonstrated in the FORSAGE study, where over 70% of patients achieved target blood pressure (BP) within three months. Additionally,

single-pill combinations (SPC) improve adherence and long-term cardiovascular outcomes, as observed in recent trials [46,47,48,49,50,51,52].
ACEIs, including perindopril, are generally well tolerated, with fewer metabolic side effects than beta--blockers or thiazide diuretics. Although some patients experience cough or hyperkalemia, these are usually mild, making ACEIs a preferred choice for long-term hypertension management in HFpEF.

Diabetes

Diabetes is one of the most common comorbidities in patients with HFpEF, significantly contributing to disease progression and poor cardiovascular outcomes. The EMPEROR-Preserved trial evaluated the efficacy of empagliflozin, an SGLT2 inhibitor, in treating HFpEF in patients with and without diabetes. The results demonstrated a significant reduction in heart failure hospitalizations and improved cardiovascular outcomes, establishing empagliflozin as a key therapy in HFpEF management [1,53,54].

Obesity

Obesity is a major risk factor for the development and progression of HFpEF, contributing to increased left ventricular stiffness, systemic inflammation, and elevated filling pressures. For patients with obesity, preferred treatments include glucagon-like peptide 1 (GLP-1) receptor agonists and lifestyle modifications [55].

Atrial fibrillation

Key strategies include rhythm or rate control and anticoagulation to reduce the risk of stroke and improve hemodynamics. The COMMANDER HF study evaluates the effectiveness of anticoagulants in reducing thrombosis risk. Additionally, some studies suggest that statins may reduce the incidence of atrial fibrillation in HFpEF, consistent with the inflammatory response theory [1,55,56,57,58,59].

Pulmonary hypertension

Pulmonary hypertension is a frequent complication in HFpEF, mainly due to increased left atrial pressure and pulmonary vascular remodeling. Treatment focuses on optimizing volume status, improving left ventricular diastolic function, and managing left heart disease.

Chronic kidney disease

Chronic kidney disease is commonly seen in HFpEF and is associated with worse clinical outcomes. Post-hoc analysis of the TOPCAT trial suggests spironolactone may reduce cardiac deaths and hospitalizations, especially in patients with LVEF > 45% [1,55].

Obstructive sleep apnea

Obstructive sleep apnea is a highly prevalent but often underdiagnosed condition in HFpEF patients. Recurrent nocturnal hypoxia and sympathetic activation contribute to hypertension, increased left ventricular filling pressures, and systemic inflammation, all of which exacerbate HFpEF progression. Patients with sleep-disordered breathing may benefit from continuous positive airway pressure (CPAP) therapy.

Anemia

Anemia and iron deficiency are common in HFpEF and are associated with increased morbidity and reduced exercise tolerance. Impaired oxygen delivery to tissues worsens fatigue and dyspnea, significantly impacting quality of life. Patients with anemia or iron deficiency may require intravenous iron supplementation.

Non-pharmacological treatment

Non-pharmacological management plays a crucial role in improving outcomes in HFpEF patients. Lifestyle modifications and targeted interventions can alleviate symptoms, reduce disease progression, and enhance overall cardiovascular health. These approaches are particularly important in patients with multiple comorbidities, where pharmacotherapy alone may not be sufficient.

Lifestyle modifications

Regular physical activity (e.g. aerobic exercise) improves exercise capacity and quality of life. Dietary recommendations, including a low-sodium diet and caloric restriction, also play a crucial role [60].

Management of comorbidities

This includes targeted therapy for obstructive sleep apnea, anemia, thyroid disorders, and electrolyte imbalances.

Patient education

Regular follow-up visits are essential for tailoring treatment plans and monitoring disease progression.
Managing HFpEF requires a comprehensive approach addressing the underlying disease mechanisms, symptoms, and comorbidities. Evidence-based pharmacological therapies, such as SGLT2 inhibitors, and lifestyle modifications play a central role in improving patient outcomes. Ongoing research continues to refine therapeutic strategies, offering hope

for more effective management of this complex condition [33].

Prognosis

The prognosis for HFpEF is usually variable and depends on many factors, such as the stage of the disease, the presence of comorbidities, the effectiveness of treatment, and the patient's lifestyle. Overall, HFpEF is a complex condition, and the prognosis may vary from patient to patient.

The stage of heart failure is one of the main prognostic factors. Patients with HFpEF are often classified according to the New York Heart Association (NYHA) functional category, with stage I indicating mild symptoms and stage IV representing severe heart failure [61]. The presence of other diseases, such as hypertension, diabetes, chronic kidney disease, or cardiovascular disease, may influence the prognosis. Control of these comorbidities is crucial [62]. The response to treatment, including pharmacotherapy, control of risk factors, and possible interventional procedures, affects the prognosis. Regular assessment and adaptation of the treatment plan are essential. The PARAGON-HF study confirms that patients with HFpEF treated with sacubitril/valsartan had a lower risk of cardiovascular events, which may improve prognosis [63]. The PARAMOUNT study, which examined the treatment of patients with HFpEF with irbesartan, showed that this therapy reduces the risk of hospitalization due to heart failure [64]. The TOPCAT study assessed the effectiveness of spironolactone in patients with HFpEF. The results suggest that spironolactone may reduce the risk of hospitalization due to heart failure, which impacts prognosis [65].

The prognosis of HFpEF is generally poor, with a 5-year mortality rate of 75.3%, according to the Get With The Guidelines (GWTG) registry. Additionally, HFpEF patients have a 30-day all-cause readmission rate of 21%, which underscores the disease's high burden and risk of recurrent hospitalizations. Compared to HFrEF, HFpEF incidence and prevalence are steadily rising, with an increasing proportion of HF cases being attributed to HFpEF rather than HFrEF. Over time, both incidence and prevalence continue to increase, driven largely by an aging population and the growing prevalence of comorbid conditions such as obesity and diabetes.

Sex differences also play a role in HFpEF prognosis. While HFpEF is more prevalent in women, clinical outcomes tend to be worse in men, who exhibit higher cardiovascular mortality. However, survival remains poor in both sexes. Compared to HFrEF, HFpEF patients have similarly poor survival rates, though cardiovascular mortality appears slightly lower in HFpEF than in HFrEF.

Patient age is another element influencing prognosis, as older patients often face additional treatment challenges and slower recovery. Potential complications, such as pulmonary embolism, cardiac arrhythmias, or thrombosis, may further impact patient outcomes. Each patient may vary in their individual response to therapy. Therefore, it is essential to monitor and adjust treatment based on the patient's response [66].

Since HFpEF remains an area of intense research, the prognosis may improve as scientific knowledge advances and new therapies emerge. Ensuring that patients with HFpEF receive specialized care tailored to their individual needs is crucial. Regular check-ups and close control of risk factors remain key to optimizing the care of HFpEF patients.

Assessment of prognosis in HFpEF includes a wide range of factors that are taken into account. Various questionnaires can help in collecting data and evaluating different aspects that affect a patient's prognosis. Some useful tools include the Kansas City Cardiomyopathy Questionnaire (KCCQ) for quality of life assessment, the NYHA classification for functional status, and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score, which integrates multiple risk factors to estimate mortality in heart failure patients.

Conclusions

HFpEF is becoming the predominant form of heart failure, particularly among older individuals and women, highlighting the need for intensified research into its pathogenesis, diagnosis, and treatment. This condition has a multifactorial etiology, involving diastolic dysfunction, myocardial fibrosis, hypertension, obesity, and chronic inflammation. The coexistence of multiple comorbidities, such as diabetes, chronic kidney disease, and atrial fibrillation, further complicates its course and prognosis.

Until recently, HFpEF treatment primarily focused on symptom management and the treatment of comorbid conditions. However, new drug classes are now playing an increasingly significant role. SGLT2 inhibitors, such as empagliflozin and dapagliflozin, have demonstrated benefits in reducing heart failure hospitalizations and cardiovascular mortality, even in patients without diabetes. Diuretics remain essential for symptom control in congestion, while MRAs, including spironolactone and the newer agent finerenone, show promise in reducing fibrosis and inflammation. ARNIs, particularly sacubitril/valsartan, have been shown to lower hospitalization rates. Beta--blockers, ACEIs, and ARBs are used in selected patients, especially those with coexisting hypertension or ischemic heart disease. Additionally, emerging therapies targeting systemic inflammation and

myocardial remodeling, such as novel anti-fibrotic agents, are being explored. These advances are reshaping the landscape of HFpEF management and offering new hope for improved patient outcomes.

Blood pressure control remains a key component of therapy. Comparative studies have provided evidence that ACEIs, including perindopril, offer superior long--term cardiovascular protection compared to other classes of antihypertensive drugs. ACEI-based therapies have been more effective in reducing the risk of cardiovascular events, such as myocardial infarction and stroke, particularly in high-risk populations, including patients with diabetes, hypertension, and other comorbidities.

Non-pharmacological approaches to HFpEF management include lifestyle modifications, regular physical activity, and a low-sodium diet, all of which can significantly improve patients' quality of life. The prognosis in HFpEF varies and depends on multiple factors, including disease severity, the presence of comorbidities, treatment efficacy, and adherence to lifestyle recommendations. Survival rates in HFpEF are comparable to those observed in HFrEF, although some studies suggest slightly better outcomes in HFpEF. Recent clinical trials, such as PARAGON-HF, EMPEROR-Preserved, and TOPCAT, have demonstrated benefits from new pharmacological treatments, including ARNI, SGLT2 inhibitors, and spironolactone, offering hope for improved patient outcomes.

The introduction of diagnostic tools such as the HFA-PEFF algorithm and the H_2FPEF score allows for a more precise identification of HFpEF patients and the implementation of optimal treatment strategies. Since HFpEF remains an area of intensive research, the future of its therapy appears promising, and further advancements in understanding the disease mechanisms may contribute to better quality of life and prolonged survival for affected patients.

Authors' contribution

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Data collection – M. Niemiec, J. Niemiec, D. Piłat, K. Bednarz, N. Dyrek, B. Basiaga
Manuscript preparation – M. Niemiec, N. Dyrek, B. Gruchlik, M. Podolski, B. Basiaga
Literature research – M. Niemiec, B. Gruchlik, N. Dyrek, K. Czepczor, K. Bednarz, K. Mizia-Stec
Final approval of the version to be published – K. Mizia-Stec

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PRACA POGLĄDOWA
REVIEW

The role of virtual reality-based relaxation therapy in the treatment of mental disorders – a narrative review

Rola terapii relaksacyjnej z wykorzystaniem wirtualnej rzeczywistości w terapii zaburzeń psychicznych – przegląd narracyjny

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ABSTRACT

In recent years, there has been rapid development in technologies utilizing virtual reality (VR), leading to their increasingly frequent application in medicine, including psychiatry. Relaxation therapy using VR techniques may offer an innovative solution to support the treatment of mental disorders. This narrative review discusses the potential applications of VR in relaxation therapy, focusing on its effectiveness in treating depression, anxiety disorders, schizophrenia, and bipolar disorder. VR technology has been shown to offer significant advantages over traditional relaxation methods. Numerous studies confirm its effectiveness in reducing psychiatric symptoms, while also highlighting the need to consider potential side effects, such as nausea or "cybersickness". VR therapy combines the benefits of technology and psychotherapy, making it a promising method for supporting the treatment of mental disorders.

KEYWORDS

depression, anxiety disorders, virtual reality

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STRESZCZENIE

W ostatnich latach nastąpił gwałtowny rozwój technologii wykorzystujących wirtualną rzeczywistość (*virtual reality* – VR), co doprowadziło do coraz częstszego stosowania ich w medycynie, w tym w psychiatrii. Terapia relaksacyjna z wykorzystaniem technik VR może stanowić innowacyjne rozwiązanie wspomagające leczenie zaburzeń psychicznych. W niniejszym przeglądzie narracyjnym omówiono możliwości zastosowania VR w terapii relaksacyjnej, skupiając się na jej skuteczności w leczeniu depresji, zaburzeń lękowych, schizofrenii oraz choroby afektywnej dwubiegunowej. Wykazano, że technologia VR oferuje istotne korzyści w porównaniu z tradycyjnymi metodami relaksacyjnymi. Liczne badania potwierdzają jej skuteczność w łagodzeniu objawów psychicznych, jednocześnie wskazując na konieczność uwzględnienia potencjalnych skutków ubocznych, takich jak nudności czy tzw. cyberchoroba. Terapia VR łączy zalety technologii i psychoterapii, co czyni ją obiecującą metodą wspomagającą leczenie zaburzeń psychicznych.

SŁOWA KLUCZOWE

depresja, zaburzenia lękowe, wirtualna rzeczywistość

Introduction

Mental disorders are becoming increasingly prevalent, both globally and in Poland. According to the 2011 EZOP I study, 3% of the Polish population suffered from depression, while various forms of anxiety disorders affected 1.1% of individuals [1]. Moreover, the EZOP II study, which was conducted seven years later, revealed that 3.85% of people struggled with depressive disorders and 7% with anxiety disorders. These results indicate a significant increase compared to the earlier study [2]. Another study, more localized, investigated the prevalence of depression and anxiety in the Żywiec district in 2022 [3]. The findings showed that anxiety disorders affected 11.2% of the population, while depression affected 14.4% of the study population, which counted 1659 people. This study also identified factors associated with increased and decreased risk of developing depressive and anxiety disorders. Factors that increase the risk of depression include: female gender, age over 60, unemployment, low education level, mental work, lack of physical activity, intensive sports practice, smoking, the presence of chronic somatic diseases, and the use of over-the-counter sleeping and sedative medications. On the other hand, factors reducing the risk include: male gender, age between 40 and 59, higher education level, stable employment, and physical work [4]. Risk factors for anxiety disorders included: unemployment, self-employment or retirement, lack of physical activity, daily alcohol consumption, complete alcohol abstinence, smoking, use of psychostimulants, the presence of somatic diseases, and use of sedatives and sleeping pills, both over-the-counter and prescribed. Protective factors included stable employment and occasional alcohol consumption [4]. A systematic review investigating factors contributing to the development of depression in individuals aged 65 and older, based on articles from 2000–2020, found that the presence of chronic diseases and sleep difficulties correlate with an increased risk of depression [5].

Given the growing number of cases of these disorders, scientists are exploring new treatment methods. So far, one of the most popular and effective treatments is pharmacotherapy. Analyzing existing research, it is important to note that first-line antidepressant therapy leads to symptomatic remission in 25–35% of patients. In the STAR-D project, only one-third of patients achieved a therapeutic response after the first antidepressant. Even after a year of treatment with four different antidepressants, each used for 12 weeks, remission was achieved in only two-thirds of patients [6]. In the treatment of generalized anxiety disorder, psychiatrists most often use escitalopram, sertraline, pregabalin, and paroxetine [7]. For depression, drugs from two main groups are primarily used: selective serotonin reuptake inhibitors (SSRIs), which include fluoxetine, fluvoxamine, citalopram, escitalopram, sertraline, and paroxetine, as well as serotonin and norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine [8]. Among the known non-pharmacological treatments for anxiety-depressive disorders are various psychotherapeutic approaches, biological interventions such as transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), transcutaneous vagus nerve stimulation (taVNS), deep brain stimulation (DBS), and naturopathic interventions including herbal medicine, dietary supplements, acupuncture, and light therapy [9,10]. Meta-analyses show that remission rates for anxiety disorders treated with cognitive-behavioral therapy range from 13% to 53% [11]. Studies on tDCS indicate moderate effectiveness in treating acute depressive disorders, though data on treatment-resistant depression are limited. tDCS is considered a safe therapeutic method with minor side effects such as itching, tingling, and burning sensations [12]. TMS has been most extensively studied in patients with depressive disorders, and its effectiveness in treating other mental disorders is also being researched. The best results are observed after 26–28 sessions, while a lack of efficacy is noted with unsatisfactory therapeutic effects after 20 sessions [13]. The effectiveness of ECT in treating depression is estimated to be between 80% and 90%. According to the STAR-D study, ECT's effectiveness in treatment-resistant depression is around 50%, still higher than

that of the previously mentioned pharmacological therapies [14]. The possibility of using transcutaneous vagus nerve stimulation (taVNS) in treatment-resistant depression has also been explored, in a pilot study, with promising results. In a group of five individuals with severe depression, two patients showed improvement, while failure in the other three was due to difficulties with operating the device [15]. While DBS is a proven method for treating bipolar disorder, its effectiveness in treating depression, despite many reports of positive effects on mood, the ability to experience pleasure, and anxiety reduction, raises ethical concerns about obtaining consent for such an invasive method and the potential loss of opportunity for patients to benefit from other treatments [16,17]. The positive impact of naturopathic therapies was examined in a comprehensive systematic review of the literature from 1996–2016 on the use of single-component herbal preparations in cancer patients, aimed at reducing drug burden and improving mental health. Among the 38 plants analyzed, those that showed potential in alleviating anxiety and depression included cohosh, chamomile, chaste tree, lavender, passionflower, and saffron [18]. A study on the effectiveness of acupuncture demonstrated that this method significantly alleviates accompanying symptoms of depression and anxiety in patients with tension headaches [19]. The effectiveness of light therapy has been confirmed by numerous clinical studies. Based on these studies, it was established that exposure to light with an intensity of 10,000 lux for 30 minutes daily is optimal for treating seasonal depression. The response to light therapy usually appears within 2–4 days, and the effects may last for varying periods, typically for several weeks after treatment, which lasts about 14 days [20].

Also helpful in the treatment of mental disorders are relaxation sessions of which the most common are those proposed by Schultz and Jacobson in the 1960s [21]. The effectiveness of autogenic training, developed by Johannes Schultz in 1932, has been confirmed by numerous studies. A meta-analysis of 60 studies (including 35 randomized trials) showed improvements in the health of individuals suffering from anxiety disorders, mild to moderate depression, and functional sleep disorders [22]. Analyzing the quantitative and qualitative effects of relaxation techniques on sleep quality in patients with insomnia caused by anxiety and depressive disorders, based on the Insomnia Severity Index (ISI), revealed a statistically significant reduction in insomnia severity from moderate to mild. Patients reported subjective improvements in sleep quality, experiencing fewer disruptions in daily tasks and fewer inconveniences related to sleep disturbances. Additionally, improvements in mood, self-esteem, and self-control were observed [23]. The effectiveness of both relaxation techniques in reducing anxiety was confirmed in a meta-analysis based on studies from 1997–2007 [24]. Research on the effects of progressive muscle relaxation, developed by Jacobson, demonstrated positive outcomes in reducing anxiety and increasing happiness levels [25]. This technique also proved effective in improving sleep quality in cancer patients [26].

Over the next decade, experts predict a rise in the popularity of online therapy, psychosomatic state monitoring methods, and virtual reality (VR) technologies. Their opinions on long-term changes are divided–ranging from futuristic concepts (such as mind-reading) to a return to traditional therapeutic methods [27]. In practice, more and more centers are attempting to utilize contemporary technology in psychiatry. An example of such a device is VR glasses, which provide high-quality relaxation with simultaneous elimination of distracting and stressful influences of the environment, potentially reducing depressive symptoms, anxiety, and stress, improving quality of life, and reducing the risk of suicide [28]. The aim of this narrative review is to analyze the functioning and potential application of VR techniques in mental disorders.

Virtual reality – historical review

VR is a three-dimensional, digital world created using computer systems, display devices, and interfaces that provide the user with immersion in an interactive environment. VR engages the user's senses, particularly sight and sound, while also allowing for the creation of tactile sensations [29]. The term "virtual reality" comes from Jaron Lanier, who coined it in the 1980s, and his company, VPL, became one of the first to commercially sell VR systems [30].

The origins of VR technology date back to 1957, when filmmaker Morton Heilig proposed that audiences could be more effectively immersed in stories if all of their senses were stimulated. Three years later, he built a device that included a display, fans, scent emitters, a sound system, and a moving chair that simulated motion. This system only allowed for sensory experiences but did not enable interaction with the material being presented. The first head-mounted display (HMD), called the Headsight, was developed in 1961. This device featured a video screen and a motion-tracking system linked to a camera. It was primarily used in hazardous environments, allowing users to remotely observe real-world settings. The equipment was utilized in military training operations and by helicopter pilots [31].

The concept of VR began to evolve in the mid-1960s. At the time, Ivan Sutherland was working on interactive computer systems using displays mounted on the user's head. The researcher's idea was to create

a computer that could simulate the real world, allowing the operator to interact with it [32].

In 1970, Sutherland and his team of researchers developed the first operational interactive head-mounted display system [33]. From that time, similar systems began to develop in several different directions, leading to the rapid growth of VR technology by the late 1980s [32]. However, this technology was primarily used for training military personnel, pilots, and astronauts, remaining largely inaccessible to the general public [31].

The first applications of VR in medicine occurred in the 1990s, in simulations of colonoscopy and upper gastrointestinal endoscopy [31].

In 2012, Palmer Luckey presented a prototype of the first Oculus, a VR headset intended for commercial use. In 2014, Facebook acquired Oculus, leading to a significant increase in the popularity of VR devices for home use. Since then, VR has gained widespread popularity and has become more accessible to the average consumer, with more VR headsets on the market, such as the HTC Vive, Samsung VR, Oculus and Google Cardboard [34].

Initially, VR technology was primarily developed within the gaming industry. However, it is now used in many other fields, including education, medicine, and engineering [34]. In medicine, VR has a wide range of applications, including in education, diagnostics, treatment, counselling, and rehabilitation [31].

In medical education, VR is used for learning anatomy, surgical procedures, and skills such as cardiopulmonary resuscitation. The equipment is also used to develop soft skills, such as teaching empathy and communication with patients through simulations involving virtual patients [35].

Research is underway on the use of VR technology in radiological diagnosis [36] and in the diagnosis of anxiety disorders. This technology can be helpful in assessing the severity of anxiety [37].

Research is being conducted on the use of VR technology in radiological diagnostics [36] and in the diagnosis of anxiety disorders. VR technology can assist in assessing the severity of anxiety [37]. Additionally, VR devices are used in the treatment of various conditions, particularly in cognitive-behavioral therapy for anxiety disorders. They are also used to reduce pain and anxiety experienced by patients during medical procedures [38,39,40], as well as in rehabilitation following strokes, in Parkinson's disease, chronic pain, and other neurological and orthopedic conditions. Studies have demonstrated the effectiveness of VR in improving both motor and cognitive functions [41,42,43,44].

Equipment and software

VR content can be presented in two main ways: through HMD (Head-Mounted Display) systems and CAVE (Cave Automatic Virtual Environment) systems. Some authors also identify a third method of presenting VR content via a computer monitor [45].

HMDs are created using special goggles and headphones. The goggles, which contain a display, present images for each eye, creating a stereoscopic scene. Each image is calculated and rendered separately, taking into account the proper perspective from the position of each eye relative to the mathematical description of the three-dimensional virtual scene. The HMD continuously tracks the position of the user's head, and therefore their gaze direction. When users turn or move their heads to look around, the computer updates the images, allowing them to see a surrounding three-dimensional scene that can change dynamically [46]. These systems are easily accessible, portable, and often affordable, making them commonly used in research and widely available for public use [47]. Examples of devices based on this system include the HTC Vive, Oculus, and Samsung VR.

The CAVE system, much less frequently used, involves a small, square room where images are projected onto the walls. The three-dimensional effect is achieved through the use of 3D glasses [48,49].

The main difference between the two systems is that HMD systems cause full immersion in the virtual environment, the sense of one's own body can be createdby producing a virtual body in the form of avatar. In contrast, the CAVE system allows the participant to see their own body, which leads to more natural task execution [45].

However, the CAVE system is expensive, occupies a large space, and is not mobile, making it impractical and rarely used in research, with limited potential for widespread use.

Immersion, sense of presence, and interaction

There are three key aspects of VR: immersion, sense of presence, and interaction. Immersion refers to the sensory context of the experienced reality, providing stimuli that give the impression of being in that world. It is achieved by minimizing stimuli from real life and replacing them with elements from the virtual environment. The quality of immersion largely depends on the technology: image resolution, refresh rate, and spatial sound. The more high-quality sensory stimuli the system can provide, the better it replicates reality. With maximum immersion, the human brain would not

be able to distinguish between the real world and the computer-generated one [50]. Immersion is one of the features of VR, which can be described as the sensory context of reality, evoking the impression of being in it. It is achieved by eliminating real stimuli and replacing them with virtual sensations. Immersion is influenced by various factors, such as the quality of the hardware, image resolution, refresh rate and spatialization of sound [50].

The concept of presence is closely related to immersion, which is why authors often do not separate the two terms. Some researchers view immersion as an objective indicator of engagement in the virtual world, while presence is seen as a subjective experience of that environment [51]. Presence can be defined as perceiving the virtual environment as if it were real [52]. The level of immersion is indicated by how realistically people in a virtual environment respond to presented stimuli, whether physiologically, emotionally, or behaviorally [53]. Presence includes two elements: the illusion of place, which involves feeling like one is physically in the depicted environment, and the illusion of plausibility, the belief that the situation being experienced is genuine [54]. Furthermore, user engagement and the intensity of emotions evoked by virtual environment stimuli are critical to experiencing presence [50].

Another key aspect of VR is interaction, which allows for detecting the user's actions and responding to them in real-time. This enables adjustments, such as changes in the landscape or execution of user commands, based on the current situation. Interaction is closely linked to the sense of presence [50].

Research clearly indicates the connection between presence, immersion, and emotional responses of users, highlighting that the effectiveness of relaxation techniques in VR environments is inextricably tied to these concepts [51]. It is worth noting, however, that strong negative emotions are much more dependent on immersion and presence than the milder positive emotions we aim to achieve when using relaxation techniques in a virtual environment [50].

Relaxation therapy in virtual reality

The effectiveness of VR techniques in relaxation therapy has been confirmed by numerous studies [55]. For example, a study conducted by Veling et al. [56] involved 49 participants suffering from bipolar disorder, anxiety, depression, psychosis, or mixed states. Of this group, 24 individuals engaged in traditional relaxation exercises (serving as the control group), while 25 used VR headsets (forming the experimental group). In both cases, the relaxation therapy lasted for 10 days. Before and after the therapy, participants used a visual analog scale to rate their well-being, which included levels of relaxation, calmness, joy, satisfaction, overall positive feelings, confusion, anxiety, depression, irritability, and overall negative feelings. After ten days, participants reported an improvement in well-being regardless of the therapy method, but those using VR headsets experienced greater improvement, except in the area of calmness, where traditional relaxation exercises were more effective. The study also found that the most preferred VR scenario was a beach with interactive virtual exercises, a beach without such exercises, and a deep-sea setting with dolphins.

A study, similar to the one described above, was also conducted among patients suffering from depression and anxiety disorders, in which some subjects were treated with 3 sessions of relaxation therapy using VR techniques. Scenery played during the sessions included forest and marine landscapes. The control sample for this study consisted of depression patients to whom classical relaxation techniques were applied. The condition of the patients before and after the study was compared using the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Patient Health Questionnaire 9-Item Version (PHQ-9), among other scales, which showed that patients using VR techniques achieved statistically significant greater benefits compared to the control group, including a reduction in the severity of depressive and anxiety symptoms [57].

Schizophrenia is another mental disorder where VR-assisted relaxation therapy has shown potential benefits, as demonstrated by a study by Freeman et al. [58]. This study included 41 participants suffering from schizophrenia or similar disorders, who underwent four 30-minute VR therapy sessions over four weeks. Their symptoms were assessed before therapy, four weeks after the start, and again 24 weeks after. Tools such as the Psychotic Symptoms Rating Scale (PSYRATS) and the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) were used. The study observed a significant reduction in psychotic symptoms in the VR therapy group compared to the control group. The study also compared the effectiveness of VR relaxation therapy with VR cognitive therapy and found both to be equally effective, though cognitive VR therapy is not the focus of this paper.

There is also a pilot study [59] on the use of relaxation therapy with VR techniques in the treatment of schizophrenia. In this study, a group of 13 participants reported reduced anxiety levels, measured using a visual analogue scale for anxiety in schizophrenia. This assessment was made after the first and fifth VR sessions and was compared to the patients' baseline levels before the therapy.

As previously mentioned, VR-assisted relaxation therapy can also be effective in treating bipolar disorder. A study by Ilioudi et al. [60] supports this, in which 18 participants with bipolar disorder were shown desert and forest scenes in VR. They then participated

in semi-structured interviews, which were analyzed using qualitative methods based on inductive theory. The results indicated that participants felt calmer after the VR sessions and reported an overall improvement in their well-being.

Safety of therapy

Studies on the safety of VR therapy are relatively consistent. Participants generally report no side effects or experience them at low intensity [56,61]. The most common side effects include nausea, headaches, dizziness, vision disturbances, and eye discomfort, such as dryness, redness, or irritation [56,62,63]. A relatively common side effect is "cybersickness", likely resulting from a mismatch between the sense of movement in the virtual environment and physical immobility in the real world [64]. This condition manifests in three symptom areas: disorientation (dizziness), nausea, and oculomotor symptoms (eye strain, difficulty focusing eyesight, blurred vision, and headaches) [50]. The frequency and severity of side effects depend on the device, the type of tasks performed (e.g. walking or driving), and individual predispositions of those using VR goggles [63].

Manufacturers of VR headsets warn of the potential for seizures during use. Another risk is the transmission of conjunctivitis between users of the same device, which can be mitigated by disinfecting VR goggles after each use. The user manuals also mention the possibility of skin irritation, redness, itching, and swelling on the face.

Contraindications and recommendations for VR headset use vary by manufacturer, and there are no standardized guidelines on this issue. Common temporary contraindications include fatigue, colds, flu, headaches, migraines, and earaches. Manufacturers also recommend medical consultation for pregnant women, the elderly, those with binocular vision disorders, epilepsy, schizophrenia, post-cataract surgery patients, individuals with pacemakers, or those with other serious health conditions.

Recommendations for safe VR use include operating the devices in a safe environment, ensuring proper positioning, making sure the headset is level and securely fastened, starting with short sessions, taking frequent breaks during longer use, especially when discomfort occurs [65,66,67].

Conclusions

Mental disorders such as depression are a growing problem in the 21st century. The scale of this issue necessitates active exploration of innovative solutions that could help reduce it. One of these solutions is relaxation therapy using VR techniques. This method uniquely combines the traditional method of psychotherapy, which has been known since the second half of the last century, and equally old (but developing intensively only in the 21st century) digital technology. This combination allows for immersion, a sense of presence, and patient interaction, which enhances the therapy's effectiveness and offers an advantage over traditional relaxation therapy.

The effectiveness of relaxation therapy using VR techniques has been proven by numerous studies. These included the use of this method in supporting the treatment of depression and anxiety, bipolar disorder, as well as schizophrenia and psychotic disorders. Researchers agree that this method is a valuable complement to other therapeutic approaches.

The application of VR in therapy requires consideration of potential side effects, such as nausea, headaches, and cybersickness. Adjusting session length and ensuring VR is used in a safe environment are recommended. Additionally, the development of standardized safety guidelines for VR use appears necessary.

Authors' contribution

Study design – M. Stencel, B. Pilarski, B. Bula
Data collection – S. Florek, M. Stencel, B. Pilarski, B. Bula
Manuscript preparation – R. Pudlo, M. Stencel, B. Pilarski
Literature research – S. Florek, M. Stencel, B. Pilarski
Final approval of the version to be published – S. Florek, R. Pudlo

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OPIS PRZYPADKU
CASE REPORT

Cystic lymphangioma of the greater omentum coexisting with groin hernia in 2-year-old girl, mimicking intra-abdominal fluid with Nuck's canal hydrocele

Torbiel sieci większej współistniejąca z przepukliną pachwinową u 2-letniej dziewczynki, imitujące wolny płyn wewnątrzotrzewnowy z wodniakiem kanału Nucka

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ABSTRACT

INTRODUCTION: Lymphatic cysts are congenital malformations that predominantly occur in the head and neck region. Intra-abdominal lesions are rare and may be present in the mesentery, retroperitoneal space, and greater omentum. When a cyst in the abdominal cavity is suspected, ultrasonography is the diagnostic procedure of choice. Radical resection, if feasible, is the preferred treatment, as incomplete excision can lead to recurrence. However, for lesions located in the mesentery and retroperitoneal space, aspiration with the administration of obliterating agents may be a better approach than surgical treatment. In recent years, laparoscopy has become a favorable alternative to laparotomy.
CASE REPORT: A 2-year-old girl was referred for surgery due to the presence of fluid in the abdominal cavity along with a coexisting right-sided hydrocele of the canal of Nuck. During the surgical procedure, a large multilocular lesion originating from the greater omentum and extending into the hernia sac of a right inguinal hernia was identified. The cyst was resected laparoscopically, and the inguinal hernia was repaired. Histopathological examination confirmed a lymphatic cyst.
CONCLUSIONS: Laparoscopic resection is a safe method for treating a large lymphatic cyst of the greater omentum.

KEYWORDS

cystic lymphangioma, greater omentum, Nuck's canal hydrocele, children

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STRESZCZENIE

WSTĘP: Torbiele chłonne są wrodzonymi malformacjami, występującymi głównie w obrębie szyi i głowy. Zmiany wewnątrzbrzuszne są rzadkie i mogą być obecne w krezce jelit, przestrzeni zaotrzewnowej i sieci większej. W przypadku podejrzenia torbieli w jamie brzusznej ultrasonografia jest procedurą diagnostyczną z wyboru. Preferowanym leczeniem, jeśli to możliwe, jest radykalna resekcja, podczas gdy niecałkowite wycięcie może prowadzić do nawrotu. Jednak w przypadku zmian zlokalizowanych w krezce jelita i przestrzeni zaotrzewnowej aspiracja z podażą środków obliterujących może być lepszą metodą niż leczenie operacyjne. W ostatnich latach laparoskopia stała się korzystną alternatywą dla laparotomii.

OPIS PRZYPADKU: 2-letnia dziewczynka została zakwalifikowana do operacji z powodu obecności płynu w jamie brzusznej oraz współistniejącego prawostronnego wodniaka kanału Nucka. W trakcie zabiegu stwierdzono dużą wielotorbielowatą zmianę, wychodzącą z sieci większej i wnikającą do worka przepuklinowego prawostronnej przepukliny pachwinowej. Torbiel usunięto laparoskopowo, a przepuklinę pachwinową zaopatrzono. Na podstawie badania histopatologicznego stwierdzono torbiel chłonną.

WNIOSKI: Wycięcie laparoskopowe jest bezpieczną metodą leczenia dużej torbieli chłonnej sieci większej.

SŁOWA KLUCZOWE

torbiel chłonna, sieć większa, wodniak kanału Nucka, dzieci

INTRODUCTION

Lymphangiomas are benign congenital malformations, primarily occurring in the neck and head regions [1,2]. Intra-abdominal changes can be found in the mesentery, retroperitoneal area, and the greater omentum, accounting for approximately 1% of all lymphangiomas [3]. Frequently, these changes remain asymptomatic and pose no immediate harm, often being discovered incidentally [4]. However, in certain cases, they can become symptomatic due to factors such as hemorrhage, rupture, infection, or exerting pressure on adjacent anatomical structures, potentially leading to life-threatening situations [4,5]. Diagnosis typically involves the use of ultrasound, computed tomography (CT) scans, and magnetic resonance imaging (MRI) examinations, with over 80% of cases being identified by the age of five [3]. The preferred treatment, if possible, is complete resection, which offers an excellent prognosis [1,4]. In cases of incomplete resection, there is a heightened risk of recurrence [1].

CASE REPORT

A 2-year-old girl was referred from another center to our department after an ultrasound examination at the referring center revealed fluid in the peritoneal cavity and right inguinal canal (diagnosed as a hydrocele of the canal of Nuck). Over a six-month observation period, the fluid volume gradually increased, prompting surgical intervention.

There were no comorbidities, prior hospitalizations, or surgeries in her medical history. She did not experience any pain. On physical examination, only a slight, painless swelling of the inguinal canal was noted, which decreased upon compression.

In the ultrasound examination repeated upon admission to our hospital, fluid was noted in the mid and lower abdomen, with a separation ranging from 2 to 4.2 cm. A single hyperechogenic septum was observed in the right lower abdomen. A widened right canal of Nuck containing a small amount of fluid was also identified. The ovaries and uterus were unchanged, and no other abnormalities were observed.

The patient was qualified for laparoscopy. Three ports were used in a standard triangular configuration: a 10-mm port below the umbilicus for the laparoscope and two 5-mm trocars in the lower abdomen. The cyst's size necessitated a 10-mm port for its extraction. During the procedure, a large, thin-walled, multicystic formation was found, originating from the greater omentum (Figure 1) and extending from the right epigastrium along the right flank to the lower abdomen (Figure 2).

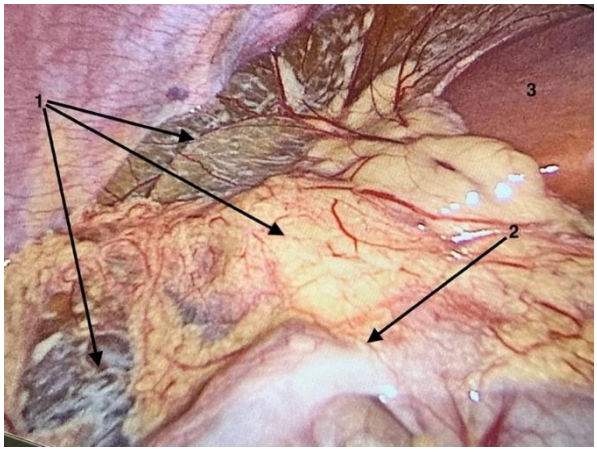

Fig. 1. Greater omentum with cyst. 1 – The arrows indicate greater omentum with large cystic lymphangioma. 2 – The arrow indicates transverse colon with attachment of greater omentum. 3 – The liver.

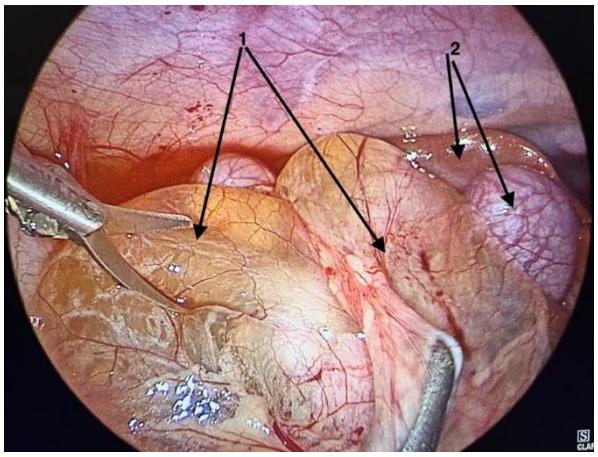

Fig. 2. The multicystic lymphangioma before opening with scissors in order to drain the fluid. 1 – The arrows indicate the cystic lymphangioma. 2 – The arrows indicate the liver with gallbladder.

The cyst extended into the right inguinal canal, mimicking a hydrocele of the canal of Nuck. Once the cyst (hernia content) was pulled from the inguinal canal, the open inguinal ring became visible (Figure 3).

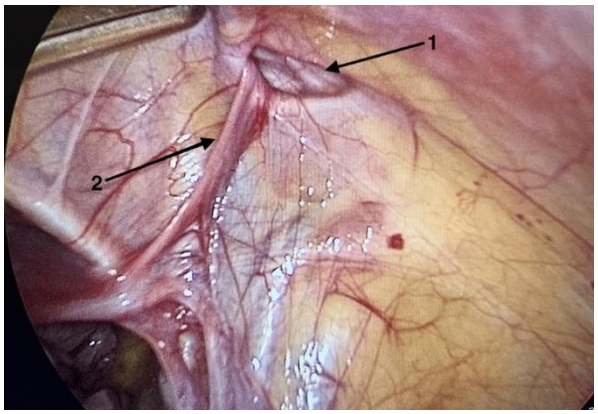

Fig. 3. Open right deep inguinal ring leading into hernial sac. 1 – The arrow indicates right deep inguinal ring. 2 – The arrow indicates teres ligament.

In the pelvis, it pushed the uterus towards the bladder. The ovaries remained unchanged and were located on the iliac vessels at the entrance to the pelvis. The omental multicystic formation was resected along with the greater omentum using the LigaSure device (Figure 4) after the larger cystic parts were opened to reduce its volume (Figure 2).

The material was extracted via a trocar in a medical bag (Figure 5).

An unchanged appendix, located fully retrocecally, was removed in the standard manner due to its unfavorable position. The right inguinal hernia was repaired in a standard manner, as laparoscopic insertion of the entire hernia sac retrogradely into the peritoneal cavity and subsequent ligation was not feasible due to the hernia's size.

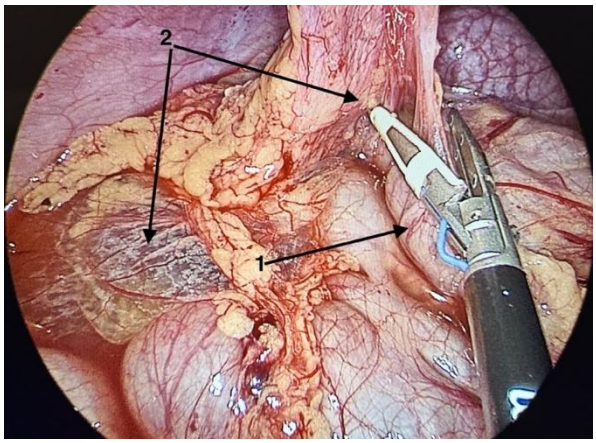

Fig. 4. Resection of multicyst with LigaSure device. 1 – The arrow indicates tranverse colon. 2 – The arrows indicate multicystic lymphangioma.

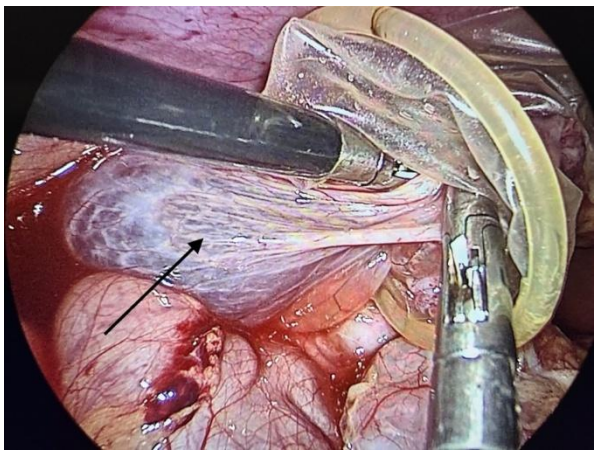

Fig. 5. Resected cyst inserted into endobag. The arrow indicates the cyst inserted to endobag.

The postoperative period was uneventful, and she was discharged on the third postoperative day.

On histopathological examination, a cyst measuring 11 × 7 × 0.6 cm was identified in the greater omentum and diagnosed as a lymphangioma (immunohistochemical stains: CD34 positive, calretinin negative, SMA negative).

The patient was referred back to the surgeon who had originally referred her for surgery, and the follow-up period–which includes both physical examinations and ultrasound evaluations–now exceeds 30 months. No complications or recurrences have been observed during this time.

DISCUSSION

Lymphangiomas are congenital lesions originating from lymphatic channels that make up 5% of all benign lesions in children, primarily found in the neck and axilla [1,3,6]. They can also occur in other locations,

such as the mouth, arm, mediastinum, lung, and, though less commonly, in the abdomen [6]. Intra-abdominal changes may manifest in retroperitoneal locations, the mesentery, and the omentum [3]. Notably, 68% of omental cysts are detected in children under the age of 10 and 40% of those cysts are discovered incidentally [7]. These cysts may grow asymptomatically, reaching sizes of up to 3 liters. However, as they enlarge, they can adversely impact neighboring organs, potentially causing disorders in the urinary or respiratory system, along with symptoms resulting from compression of the portal vein [7]. What's more, in 11–19%, bleeding, volvulus, or rupture of the cyst lead to an acute abdomen [7].

In our case, the ultrasound examination established the diagnosis, as ultrasonography is the diagnostic procedure of choice for suspected abdominal cysts, which typically appear as thin-walled, well-circumscribed structures, often exhibiting septa [3,6]. A CT scan might be valuable for assessing the size and origin of the cyst and distinguishing lymphangiomas from other abdominal cysts [3,6]. On the other hand, MRI is better in providing a classification of the content within the cyst [2,4]. The differential diagnosis mainly includes intra-abdominal abscesses, pancreatic tumors, retroperitoneal tumors, lipomas, as well as large ovarian cysts, duplications of the digestive tract and lymphomas [2,4].

In our case, we performed a complete resection of the cyst, as complete surgical excision is the treatment of choice (when feasible) and provides an excellent prognosis, whereas incomplete resection may lead to recurrence [1,4,6]. Some authors advocate resection even in asymptomatic patients, due to the risk of complications (as well as the exceedingly rare transformation of omental cysts into sarcoma or adenocarcinoma) [7,8]. Conversely, others recommend monitoring asymptomatic patients through repeated imaging, while a third group suggests considering the use of sclerosing agents–particularly for retroperitoneal or mesenteric lymphangiomas that pose a high risk of incomplete resection or may lead to short bowel syndrome if a long segment of bowel and its mesentery must be removed [5,9]. Moreover, some experts remain skeptical about these approaches because they often yield poor results, with recurrence rates of up to 100% [2,4,9]. In the review by Tsopozidi et al. [10], it is noteworthy that no recurrence occurred in cases involving omental lymphangiomas, which is consistent with our own observation.

Laparotomy has long been the traditional surgical approach for abdominal interventions. However, with the advancement of technology, laparoscopy has emerged as an appealing and viable alternative [4]. Laparoscopy offers several advantages over laparotomy, including reduced pain, a more favorable cosmetic outcome, and a quicker postoperative recovery. While laparoscopy generally provides a superior view of the abdominal cavity, it is important to note that in the presence of large cysts, visibility can be compromised, and there is an elevated risk of potential trauma to adjacent organs [4]. As a result, some authors have suggested that for large cysts, an additional incision may be necessary [7,10].

In our case, laparoscopy was initially used as a diagnostic tool, given the preoperative suspicion of intra-abdominal fluid and a hydrocele of the canal of Nuck. During the procedure, an omental cyst was found extending into the open inguinal canal–an observation that underscored the advantage of laparoscopy over laparotomy by providing a precise diagnosis. A complete resection of the cyst was then performed without requiring any additional incision.

Regarding the groin hernia, an open repair was chosen because this approach is considered the gold standard for pediatric inguinal hernias, even though minimally invasive methods are becoming increasingly popular. As previously noted, laparoscopic reduction and ligation of the entire hernia sac retrogradely into the peritoneal cavity was not feasible due to the hernia's size. Moreover, although the percutaneous internal ring suturing (PIRS) technique is recognized worldwide, it has a higher rate of hernia recurrence [11,12] and contradicts the fundamental principles of excising the hernia sac, performing a high ligation, and repairing the inguinal canal. Consequently, a method with a lower risk of recurrence was selected.

Ultimately, the core surgical approach involved abdominal surgery performed laparoscopically–first as a diagnostic measure, then as definitive treatment for the lymphangioma once the diagnosis was confirmed.

CONCLUSIONS

Congenital omental cysts are rare, and their consideration should always be part of the differential diagnosis for abdominal cystic lesions and intraabdominal fluid. Optimal management involves complete resection, offering the most favorable prognosis. Laparoscopy presents a viable alternative to laparotomy. In our case, laparoscopic excision has proven to be a safe and practical method for effectively managing a sizable omental lymphangioma in a young girl.

Authors' contribution

Study design – M. Mikulski, M. Pasierbek, W. Korlacki
Manuscript preparation – M. Pasierbek
Literature research – M. Pasierbek
Final approval of the version to be published – W. Korlacki

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PRACA ORYGINALNA
ORIGINAL PAPER

Comparative cytotoxicity of perphenazine on different human glioblastoma cells

Wpływ perfenazyny na przeżywalność różnych linii komórkowych glejaków

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ABSTRACT

INTRODUCTION: Despite medical advances glioblastoma multiforme (GBM) is still the most common malignant primary brain tumor. Additionally, the gold standard treatment possesses poor (only 12–15 months) survival median. Thus, drug repurposing may be a helpful strategy for discovering more effective GBM chemotherapeutic drugs. Interestingly, phenothiazine derivatives have been considered a promising candidate for drug repurposing for cancer therapy, since they possess several biological activities, such as anticancer, antibacterial, antifungal, and antiviral effects.
MATERIAL AND METHODS: We investigated the impact of perphenazine on the viability of several human glioblastoma (U-87 MG, A172, and T98G) cell lines after 24-, 48-, and 72-hour incubation using WST-1 assay.
RESULTS: Data showed that the tested phenothiazine derivative decrease glioblastoma viability in a time- and concentration-dependent manner.
CONCLUSIONS: Based on EC_{50} values, perphenazine is the most efficient against A172 human glioblastoma in all of the tested treatment time periods compared to T98G and U-87 MG cells. Based on previous research, which revealed that perphenazine does not affect normal human astrocytes, this drug is a promising candidate for glioblastoma treatment. Further studies are required to unravel the complete antitumor mechanism of these phenothiazine derivatives in GBM.

KEYWORDS

antitumor activity, cell viability, glioblastoma multiforme, perphenazine, DMSO, WST-1

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STRESZCZENIE

WSTĘP: Mimo postępu medycyny glejak wielopostaciowy (*glioblastoma multiforme* – GBM) jest nadal najczęstszym złośliwym pierwotnym guzem mózgu. Ponadto złoty standard leczenia charakteryzuje się niską (tylko 12–15 miesięcy) medianą przeżycia. Zatem ponowne wykorzystanie istniejących leków (*repurposing*) może być pomocną strategią w odkrywaniu skuteczniejszych leków chemioterapeutycznych w terapii GBM. Co ciekawe, pochodne fenotiazyny zostały uznane za obiecującego kandydata do ponownego wykorzystania leku w terapii nowotworowej, gdyż posiadają wiele istotnych aktywności biologicznych, takich jak działanie przeciwnowotworowe, przeciwbakteryjne, przeciwgrzybicze i przeciwwirusowe.

MATERIAŁ I METODY: Wpływ perfenazyny na przeżywalność różnych linii komórkowych ludzkiego glejaka wielopostaciowego (U-87 MG, A172 i T98G) po 24-, 48- i 72-godzinnej inkubacji zbadano z użyciem testu WST-1.

WYNIKI: wykazano, że testowana pochodna fenotiazyny zmniejsza żywotność glejaka wielopostaciowego w sposób zależny od czasu i stężenia.

WNIOSKI: Na podstawie uzyskanych wartości EC_{50} stwierdzono, że perfenazyna jest najskuteczniejsza przeciwko ludzkiemu glejakowi wielopostaciowemu A172 w porównaniu z komórkami T98G i U-87 MG. Na podstawie poprzednich badań, które wykazały, że perfenazyna nie wpływa na normalne ludzkie astrocyty, można stwierdzić, że lek ten jest obiecującym kandydatem w leczeniu glejaka wielopostaciowego. Konieczne są dalsze badania w celu odkrycia pełnego mechanizmu aktywności przeciwnowotworowej pochodnych fenotiazyny w terapii GBM.

SŁOWA KLUCZOWE

aktywność przeciwnowotworowa, przeżywalność, glejaki, perfenazyna, DMSO, WST-1

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor [1]. The National Brain Tumor Society reported that GBM accounts for about 50.1% of all primary malignant brain tumors [2]. In 2024 in the USA, estimated new brain and other nervous system cancer cases and deaths are 25,400 and 18,760, respectively [3]. According to the data of Cancer Global Observatory, in 2022 in Europe, 67,559 cases of brain and other nervous system cancer incidents and 54,001 mortality cases were noticed. Noteworthy, the data from around the world were 321,731 incidents and 248,500 mortality cases in 2022 [4]. Despite the medical advances, the standard in GBM treatment is still "surgical resection followed by radiotherapy plus concomitant and adjuvant chemotherapy with temozolomide" with a poor survival median (only 12 to 15 months) [1]. Therefore, the search for new and more effective GBM treatment methods is crucial.

Interestingly, in past years, phenothiazine derivatives have been of particular interest and are considered as potential drug repurposing for cancer therapy [5]. Perphenazine is piperazinyl phenothiazine [6] used to treat psychotic disorders (schizophrenia, mania in bipolar disorder, and psychosis), migraines, nausea, and vomiting [6,7]. Additionally, phenothiazine derivatives possess novel biological activities, such as antibacterial [8], antifungal [8], antiviral [8,9], and anticancer effect [8,10], even in multidrug resistance models of cancer [11].

Thus, in the present study, we evaluated the effects of perphenazine on the viability of human glioblastoma (U-87 MG, A172, and T98G) cell lines.

MATERIAL AND METHODS

Materials

Perphenazine, cell proliferation reagent WST-1, and human glioblastoma cell lines (U-87 MG, A172, and T98G) were purchased from Merck Life Science (Poland). The dimethyl sulfoxide (DMSO) analytical grade was purchased from Chempur (Poland). DMEM medium without sodium pyruvate, with 4.5 g/l glucose, L-glutamine, and 3.7 g/l $NaHCO_3$, fetal bovine serum (FBS), amphotericin B 250 µg/ml, penicillin/streptomycin solution, and trypsin/EDTA solution 0.25%/0.02% in PBS were obtained from PAN Biotech (Germany).

Cell treatment

The human glioblastoma cell lines were cultured in T-75 bottles in a growth medium DMEM medium supplemented with FBS (50 ml/500 ml of basal medium), amphotericin B (5 ml/500 ml of basal medium), and penicillin/streptomycin solution (5 ml/500 ml of basal medium) at 37°C in 5% CO_2.

Cell viability

Cell viability was measured using cell proliferation reagent WST-1 [12] with slight modification. U-87 MG, A172, or T98G were seeded 2500 cells/well and incubated with the supplemented growth medium for 24 hours. After 24 h incubation, the growth medium was changed into 150 µl medium containing perphenazine (0.5, 1.0, 5.0, 10.0, 25.0, and 50.0 µM), DMSO 1%, and the supplemented growth medium without DMSO. The concentration of DMSO in the analyzed samples of perphenazine was 1%. Cells were

incubated for 24, 48, and 72 hours at 37°C. Three hours before the end of incubation, 15 µl/well of WST-1 was added. The absorbance at 450 nm with a reference wavelength of 620 nm was measured by the microplate reader TRIAD LT microplate reader (Dynex Technologies, Chantilly, VA, USA). The results were expressed as the percentage of the control.

Statistical analysis

In the viability assay, mean values of at least three independent experiments (n = 3) performed in seven repetitions ± standard deviation (SD) were calculated. Statistical analysis was performed with one-way ANOVA with Dunnett's multiple comparison test and two-way ANOVA (the influence of incubation time and drug concentration), followed by the Tukey post--hoc test using GraphPad Prism 8 software. One-way ANOVA was also used to compare obtained EC_{50} values. The significance level was established at the value of $p < 0.05$ (*) or $p < 0.01$ (**).

RESULTS

The effect of DMSO on the human glioblastoma cell lines viability

First, we determined the effect of DMSO (1%) on the assay, since it was used as vehicle for phenothiazine derivatives. The results obtained after 24-, 48-, and 72-hour treatment with 1% DMSO for A172, T98G, and U-87 MG cells are presented in Figure 1 (A–C). As control, we used cells incubated in the supplemented growth medium but without DMSO (1%). No statistically significant differences were observed, excluding the possibility of the vehicle exhibit cytotoxicity at this concentration. Thus, DMSO was used as vehicle for the drugs in the assay.

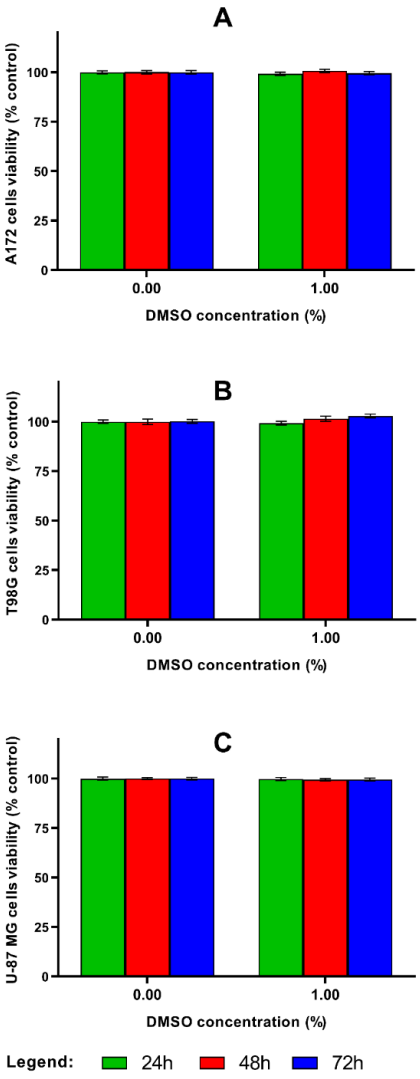

Fig. 1. Impact of DMSO (1%) after 24-, 48-, and 72-hour treatment on the viability of A172 (A), T98G (B), and U-87 MG (C). The cell proliferation reagent WST-1 was used to perform a viability assay. Mean values ± SD from three independent experiments (n = 3) performed in four repetitions are presented.

The effect of perphenazine on A172, T98G, and U-87 MG cells viability

Perphenazine in the concentration range from 0.5 to 50 μM decreased the viability of A172 cells concentration-dependently (Figure 2A). As a control, we used cells incubated in the supplemented growth medium without DMSO (1%). After 24-hour incubation of A172 cells perphenazine, we observed a significant decrease in viability by 9.6, 17.3, 28.3, 32.5, 72.7, and 90.7%, respectively, compared to the control. After 48-hour incubation of A172 cells perphenazine, we observed a significant decrease in viability by 19.1, 27.3, 50.5, 64.9, 94.5, and 95.1%, respectively, compared to the control. After 72-hour incubation of A172 cells perphenazine, we observed a significant decrease in viability by 18.2, 24.4, 44.3, 78.5, 97.4, and 96.8%, respectively, compared to the control. Moreover, we observed statistically significant differences between 24- and 72-hour and 24- and 48-hour perphenazine (0.5 to 25 μM) treatment. The statistically significant difference between 48- and 72-hour treatment was observed only after perphenazine (10 μM) treatment. Thus, we did not notice a time-dependent decrease in the viability of A172 cells caused by perphenazine (Figure 2A).

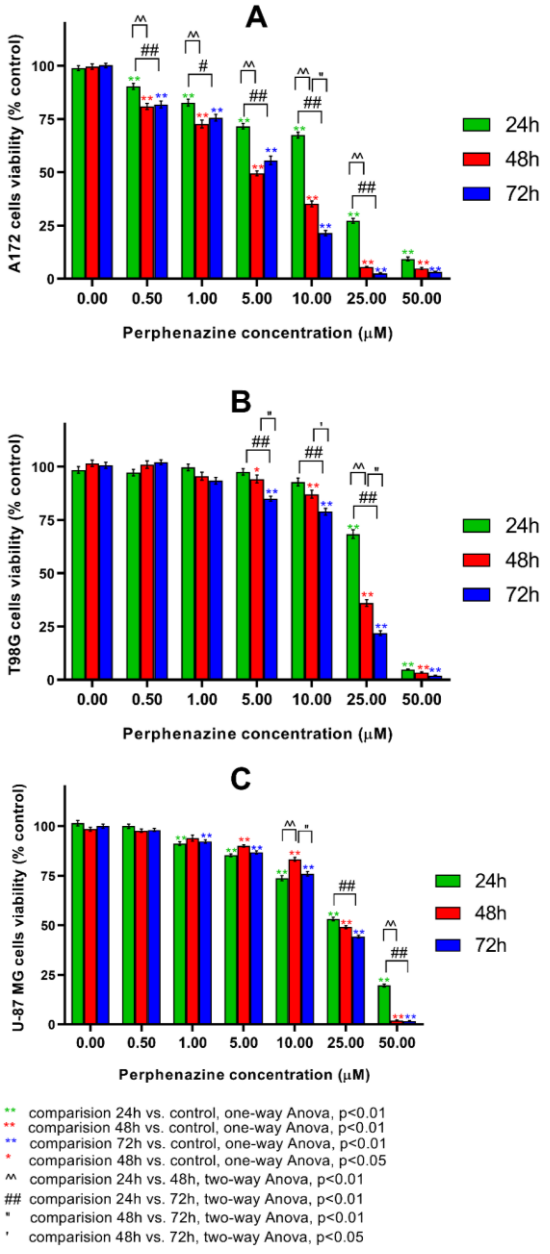

Fig. 2. Impact of perphenazine (0.5, 1.0, 5.0, 10.0, 25.0, and 50.0 μM) after 24-, 48-, and 72-hour treatment on the viability of A172 (A), T98G (B), and U-87 MG (C). The cell proliferation reagent WST-1 was used to perform a viability assay. Mean values ± SD from three independent experiments (n = 3) performed in four repetitions are presented. The values $p < 0.05$ and $p < 0.01$ were established as statistically significant.

In the case of T98G cell line, perphenazine in the concentration range from 5 to 50 μM caused a dose--dependently decrease in the viability (Figure 2B). As a control, we used cells incubated in the supplemented growth medium without DMSO (1%). 24-hour incubation of T98G cells with perphenazine (25 and 50 μM) decreased viability by 31.6 and 95.3% compared to the control. In the case of 48-hour incubation, perphenazine (5 to 50 μM) decreased viability by 5.7, 12.8, 63.9, and 96.5%, respectively, compared to the control. 72-hour incubation of T98G cells with perphenazine (5 to 50 μM) decreased viability by 15.0, 21.1, 78.0, and 98.0%, respectively, compared to control. Moreover, we observed statistically significant differences between 24- and 72-hour and 48- and 72-hour perphenazine (5 to 25 μM) treatment. A statistically significant difference between 24- and 48-hour treatment was observed after perphenazine (25 μM) treatment. Thus, we did not notice a time-dependent decrease in the viability of A172 cells caused by perphenazine (Figure 2B).

Perphenazine in the concentration range from 1.0 to 50 μM dose-dependently decreases the viability of U-87 MG cells (Figure 2C). As a control, we used cells incubated in the supplemented growth medium without DMSO (1%). After 24-hour incubation of U-87 MG cells perphenazine (1 to 50 μM), we observed a significant decrease in viability by 8.8, 14.7, 26.2, 46.9, and 80.3%, respectively, compared to the control. After 48-hour incubation of U-87 MG cells perphenazine (5 to 50 μM), we observed a significant decrease in viability by 9.9, 16.7, 50.9, and 98.0%, respectively, compared to the control. After 72-hour incubation of U-87 MG cells perphenazine (1 to 50 μM), we observed a significant decrease in viability by 7.7, 13.2, 23.9, 55.7, and 98.3%, respectively, compared to the control. Moreover, we observed statistically significant differences between 24- and 72-hour perphenazine (25 and 50 μM) and 24- and 48-hour perphenazine (10 and 50 μM) treatment. The statistically significant difference between 48- and 72-hour treatment was observed only after perphenazine (10 μM) treatment. Thus, we did not notice a time-dependent decrease in the viability of U-87 MG cells caused by perphenazine (Figure 2C).

The calculated EC_{50} values of perphenazine for tested cell lines after 24, 48, and 72 hour treatment are shown in Table I.

Table I. EC_{50} values were calculated for human glioblastoma incubated with perphenazine for 24, 48, and 72 hours

Cell line	Time of incubation with perphenazine (h)	EC_{50} ± SD (μM)
A172	24	12.28 ± 1.29
	48	4.46 ± 1.43
	72	3.94 ± 1.56
T98G	24	28.21 ± 2.26
	48	20.02 ± 2.44
	72	15.43 ± 1.03
U-87 MG	24	29.88 ± 4.95
	48	25.10 ± 1.44
	72	21.99 ± 1.48

DISCUSSION

In the presented manuscript, we evaluated the viability of human glioblastoma cell lines (A172, T98G, and U-87 MG) after 24, 48, and 72 hour treatment with perphenazine. First, we observed that DMSO could be utilized in the assays we performed since there were no statistically significant differences between the supplemented growth medium with DMSO (1%) and without DMSO (1%).

Gil-Ad et al. [13] analyzed the impact of perphenazine on the viability of rat glioma (C6) and human neuroblastoma (SHSY-5Y) after 24-hour exposure using neutral red and alamar blue staining. Perphenazine was dissolved in lactic acid (1%). The authors observed a dose-dependent decrease in viability in the 10 to 24 μM concentration range. The calculated IC_{50} were 15 ± 1.7 and 14 ± 1.9 μM for rat and human glioblastoma, respectively. Tzadok et al. [14] measured the viability of perphenazine dissolved in lactic acid (1%) on the viability of human glioblastoma U-87 MG using sulphorhodamine B staining. 1×10^4/ml cells were seeded on a 24-well plate. A dose-dependent decrease in U-87 MG cells viability was noticed after seven days of perphenazine (2 to 10 μM) treatment. The obtained LC_{50} value was 6.8 μM. Cheng et al. [15] tested the impact of perphenazine on human glioblastoma GBM8401 cells using MTT and clonogenic assay. For the MTT assay, 1500 cells/well in a 96-well plate were added, while 1000 cells/well in a 6-well plate were added for the

clonogenic assay. The study showed that the obtained IC_{50} differs depending on the method used. The obtained MTT IC_{50} were from 5 to 10 μM, while the clonogenic IC_{50} value was < 10 μM. Otręba and Buszman [16] measured the viability of U-87 MG cells after 24-hour treatment with perphenazine. Phenothiazines were solved in phosphate buffer pH 6.8. 2500 cells/well in a 96-well plate were seeded. The authors observed a dose-dependent decrease in viability after perphenazine (0.1 to 10 μM) treatment. The calculated IC_{50} value was 0.98 μM. Jacob et al. [17] analyzed the viability of human glioblastoma (U-87 MG, T98G, and LN18) cells, patient-derived human glioblastoma (OSU2, OSU61, ACPK1, ACPK4, and ACPK8), and normal human astrocytes after 24-hour perphenazine (5 to 25 μM) treatment using MTS viability assay. The authors noticed a dose--dependent decrease in patient-derived glioblastoma and commercially available human glioblastoma viability. In the case of normal human astrocytes, no changes in viability were observed up to 25 μM. Interestingly, all GBM cells showed sensitivity at a concentration range from 5 to 15 μM. A 50% decrease in viability was observed after perphenazine treatment (about 12 and 15 μM) for U-87 MG and T98G cells. The above assays align with our present results, showing that perphenazine can decrease the viability of human glioblastoma cells. It also suggests that the viability results depend not only on the cell line but also on the solvent, the method of analysis used, the equipment, and the cell number. Thus, it may explain the differences observed between calculated EC_{50} values in Otręba and Buszman [16] and the present study. Noteworthy, our previous study exploring the viability of normal human astrocytes after perphenazine treatment showed that perphenazine (0.1 to 10 μM) does not significantly decrease the viability of human astrocytes [18]. It is in line with Jacob et al. [17], showing no impact of perphenazine on normal human astrocyte viability after 24-hour treatment up to 25 μM.

Based on a statistical analysis of the obtained EC_{50} values (Table I) from the present study, we claimed that perphenazine is the most effective ($p < 0.01$) against A172 human glioblastoma after 24-, 48-, and 72-hour treatment compared to T98G and U-87 MG cells. No statistically significant differences were observed between T98G and U-87 MG cells, suggesting that anti-glioblastoma activity of perphenazine is present as follows:

$$A172 > T98G \sim U\text{-}87\ MG$$

Furthermore, the obtained EC_{50} value for A172 cells after 24-hour perphenazine treatment was 12.28 ± 1.29 μM. Thus, considering Jacob et al. [17], results about normal human astrocytes suggest that perphenazine may be potentially used in A172 human glioblastoma treatment since it does not decrease normal human astrocytes up to 25 μM.

CONCLUSIONS

The present study showed that perphenazine decreases glioblastoma viability dose-dependently. Based on EC_{50} values, the tested drug is the most effective against A172 human glioblastoma in all of the tested treatment time periods compared to T98G and U-87 MG cells. Based on our previous research, which revealed that perphenazine does not affect normal human astrocytes, this drug is a promising candidate to be used in the glioblastoma treatment. Of course, more studies are essential to explain the complete mechanism of phenothiazine's anti-glioblastoma activity. Thus, in further studies, we want to focus on the type of cell death (autophagy, necroptosis, and apoptosis) caused by perphenazine in human glioblastoma cells.

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Studies involving human and/or animals

Not applicable

Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Authors' contribution

Study design – M. Otręba
Data collection – M. Otręba
Data interpretation – M. Otręba, A. Rzepecka-Stojko, T. Rodrigues
Statistical analysis – M. Otręba
Manuscript preparation – M. Otręba, A. Rzepecka-Stojko, T. Rodrigues, J. Stojko
Literature research – M. Otręba

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PRACA ORYGINALNA
ORIGINAL PAPER

Collaboration or a systemic gap? Relations between oncology coordinators and representatives of patient support institutions

Współpraca czy luka systemowa? Relacje koordynatorów onkologicznych z przedstawicielami instytucji wspierających pacjenta

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ABSTRACT

INTRODUCTION: Despite the reforms being implemented in the Polish health system, the situation of oncology patients remains difficult. The health system is unable to meet the challenges on its own, which generates the potential for cooperation with other sectors. Coordinators can serve as a link between hospitals and other patient-oriented institutions.
MATERIAL AND METHODS: The aim of the article is to assess the degree of cooperation between coordinators and representatives of social, rehabilitation, palliative care and non-governmental organizations (NGOs). The article is based on selected results of the project: "Oncological patient coordinators. Profile, experiences and opinions of persons performing the functions of coordinators in Polish hospitals", the results of which will be described in the emerging dissertation of the author of the article. The survey was conducted in 2023. It involved 149 coordinators from Polish hospitals implementing rapid oncology therapy (*szybka terapia onkologiczna* – STO). The study used a survey questionnaire and individual in-depth interviews (IDI). The program IBM SPSS Statistics (29.0.0.0) was used as the main statistical analysis tool.
RESULTS: The results indicate that cooperation between coordinators and representatives of the above-mentioned institutions is marginal; 77.9% of coordinators had never cooperated with NGOs and 62.4% had no contact with social assistance. Only 12.1% frequently collaborate with palliative care, and 7.4% with rehabilitation specialists. The review also took into account oncology Unit structures used in hospitals and participation in the pilot project of the National Cancer Network (NCN; Krajowa Sieć Onkologiczna – KSO). The lack of differences in inter-institutional cooperation suggests that even in more organized models, mechanisms for coordinators to cooperate with representatives of social welfare, rehabilitation, palliative care and NGOs have not been put in place.

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CONCLUSIONS: There is a lack of systemic action and cooperation between coordinators and representatives of institutions that can support oncology patients. Strengthening intersectoral relationships can benefit patients and ease the burden on medical staff by implementing shared care.

KEYWORDS

organization of oncological care, oncological patient coordinators, lack of cooperation, cooperation with representatives of NGOs, cooperation with social welfare representatives

STRESZCZENIE

WSTĘP: Pomimo reform wdrażanych w polskim systemie ochrony zdrowia sytuacja pacjentów onkologicznych pozostaje trudna. System zdrowotny nie jest w stanie samodzielnie sprostać tym wyzwaniom, co stwarza możliwość współpracy z innymi sektorami. Funkcję łącznika pomiędzy szpitalami i innymi instytucjami zorientowanymi na pacjentów mogą pełnić koordynatorzy.
MATERIAŁ I METODY: Celem artykułu jest ocena stopnia współpracy koordynatorów onkologicznych z przedstawicielami opieki społecznej, rehabilitacyjnej, paliatywnej i organizacji pozarządowych (*non-governmental organizations* – NGOs). Artykuł bazuje na wybranych wynikach projektu: „Koordynatorzy pacjentów onkologicznych. Profil, doświadczenia i opinie osób pełniących funkcje koordynatorów w polskich szpitalach", którego wyniki zostaną opisane w dysertacji doktorskiej autorki artykułu. Badanie przeprowadzono w 2023 r. Uczestniczyło w nim 149 koordynatorów z polskich szpitali, realizujących szybką terapię onkologiczną (STO). W badaniu zastosowano kwestionariusz ankiety oraz indywidualne wywiady pogłębione (*in-depth interview* – IDI). Jako główne narzędzie do analizy statystycznej wykorzystano program IBM SPSS Statistics (29.0.0.0).
WYNIKI: Wyniki wskazują, że współpraca koordynatorów z przedstawicielami wspomnianych instytucji jest marginalna; 77,9% nigdy nie współpracowało z NGOs, a 62,4% nie miało kontaktu z opieką społeczną. Tylko 12,1% regularnie współpracuje z placówkami opieki paliatywnej, a 7,4% ze specjalistami rehabilitacji. Podczas przeglądu uwzględniono również występujące w szpitalach rozwiązania typu Unit (tzw. centra narządowe) oraz udział w pilotażu Krajowej Sieci Onkologicznej (KSO). Brak różnic w zakresie kooperacji międzyinstytucjonalnej sugeruje, że nawet w bardziej zorganizowanych modelach nie wprowadzono mechanizmów współpracy koordynatorów z przedstawicielami opieki społecznej, rehabilitacyjnej, paliatywnej i NGOs.
WNIOSKI: Brak systemowych działań oraz współpracy między koordynatorami i przedstawicielami instytucji mogących wspierać chorych onkologicznie. Wzmacnianie relacji międzysektorowych może przynieść korzyści pacjentom i odciążyć personel medyczny poprzez wdrożenie opieki współdzielonej.

SŁOWA KLUCZOWE

organizacja opieki onkologicznej, koordynatorzy pacjentów onkologicznych, brak współpracy, współpraca z przedstawicielami NGOs, współpraca z przedstawicielami opieki społecznej

INTRODUCTION

For more than a decade, changes in the organization of oncology care in Poland have focused mainly on improving diagnosis and treatment. Areas related to comprehensive patient support have remained largely unchanged. Strengthening these activities is sought primarily by patient organizations [1]. Institutions such as non-governmental organizations (NGOs) and social welfare entities can play an important role in meeting non-medical needs of patients. Currently, however, they are rarely invited to collaborate by hospitals [2]. In many countries, their participation in oncology care is much greater [3]. Polish regulations allow hospitals to formally cooperate with patient organizations and social welfare institutions. An example is the regulation enabling representatives of these entities to participate in meeting of the oncology medical team (*konsylium*) in hospitals implementing Comprehensive Oncological Care (Kompleksowa Opieka Onkologiczna – KON) centres[1] [4]. The special requirements for these facilities indicate that the conferences may be attended by people other than the staff, for example social care workers or representatives of patient organizations [5]. In practice, however, hospitals rarely use this option. One of the few solutions that integrate the health and social welfare system is the function of the social nurse. Her task is to organize support for patients in difficult life situations [6]. These nurses mainly take care of

[1] Oncology centres in Poland offering Comprehensive Oncological Care (KON) are specialized facilities that must meet strictly defined meet high requirements. Unlike traditional oncology centres, they provide comprehensive care at all stages of the disease. They also offer the latest treatment methods. KON are dedicated to specific cancers, e.g. breast or colon. It is profitable for the hospital to treat at KON. The procedures are better priced.

chronically ill and dependent people. However, their activities are ad hoc and are not part of a long-term strategy of intersectoral cooperation. The Polish social welfare system lacks programs dedicated to oncology patients. Assistance is provided on the basis of general criteria, such as degree of disability or material situation. This limits the possibility of targeted support, especially after treatment ends [7]. In the context of these challenges, it is worth understanding the role of oncology patient coordinators employed in Polish hospitals implementing rapid oncology therapy (*szybka terapia onkologiczna* – STO)[2] [8]. In Poland, the oncology coordinator function was introduced in 2015 with the Oncology Package. Currently, it is implemented in various models – within the framework of the STO, Unit structures or the National Cancer Network (NCN)[3] [9]. Care coordination is a key element in the organization of services for patients with chronic diseases, especially in oncology. The role of coordinators is to provide continuous, planned and tailored support to the patient – from diagnosis, through treatment, to the aftercare stage. This includes, among other things, keeping the patient informed, organizing services, monitoring the pathway and fostering communication between members of medical teams. They are the only professional group in the healthcare system whose responsibilities include broad-based organizational and informational support for patients. Assessing the extent of their cooperation with representatives of institutions that can support hospitals in key areas can provide valuable information on possible changes in the support system for cancer patients.

MATERIAL AND METHODS

The study, a fragment of which is presented in this article, was conducted in 2023. The results presented in this article are based on selected results of a broader research project: "Oncological Patient Coordinators. Profile, experiences and opinions of persons performing the functions of coordinators in Polish hospitals". The full results of this study will be presented in the author's upcoming doctoral dissertation. The aim of the study was to assess the position, characteristics and scope of activities of oncological coordinators. In the context of this study, the focus was on identifying medical and non-medical entities that cooperate with coordinators. The study involved 149 coordinators employed in hospitals implementing STO.

The respondents came from all provinces and had diverse education and professional experience. The triangulation method was used, combining quantitative and qualitative approaches in order to increase the reliability of the results. Data were collected using a survey and individual in-depth interviews (IDIs). Triangulation allowed for the analysis of the problem from different perspectives and reduced measurement errors. The survey consisted of 54 closed and open-ended questions. The entire survey generated 16 research questions, two of which were relevant to this study: 1) What medical and non-medical entities do coordinators work with? 2) Are there networks of intersectoral relationships supporting cancer patients? In the quantitative analysis, a set of crosstabulations was developed and the chi-square test and Fisher's exact test were used to assess the statistical significance of differences between groups. In the qualitative part, 12 IDI interviews were conducted, and their content was subjected to thematic analysis. The aim of the article is to assess the degree of cooperation between coordinators and rehabilitation and palliative care facilities, and to identify coordinators' relationships with NGOs and social services. The assessment also takes into account the impact of implementing certain organizational solutions in hospitals. A comparison was made between the level of cooperation in facilities that have implemented models such as Cancer Unit (e.g. Breast Cancer Unit) [10] and KON (e.g. KON-Breast)[4] [4] or participated in the pilot of the NCN, and those that have not. It was hypothesized that facilities using higher organizational standards may be characterized by greater integration with external institutions, fostering better collaboration with NGOs, social care, rehabilitation and palliative care. After collecting the data in a spreadsheet, they were imported into IBM SPSS Statistics (version 29.0.0.0), which served as the primary tool for statistical analysis. Additionally, Microsoft Excel 2021 (MSO) was used to support data processing.

[2] Rapid oncology therapy (STO) is an organizational solution aimed at efficiently and quickly guiding the patient through the next stages of oncological diagnostics and treatment. STO is intended for all patients in whom doctors suspect or confirm the occurrence of malignant tumors. STO was introduced to Polish hospitals in 2015. This was the first major oncological reform in Poland. It had not existed in Poland before. In the same year, oncological patient coordinators were also introduced to hospitals. Not every hospital implementing STO employed a coordinator.

[3] National Cancer Network (NCN) is currently being introduced to Polish hospitals. Only specific facilities are included in the NCN, and only they can treat cancer patients. These hospitals must cooperate with each other. These facilities must meet high requirements and have different levels. The first level has only the surgical ward. The second level has the surgical ward and radiotherapy. The third, highest level has the surgical ward, radiotherapy and systemic treatment.

[4] Some hospitals in Poland treat according to the procedures in force in Units and KON. These are more highly specialized units. They are considered higher level hospitals and specialize in the treatment of e.g. breast cancer, colon cancer and lung cancer.

RESULTS

To better understand the context of the analyses, the presentation of the results began by determining the frequency of cooperation between oncology coordinators and representatives of various entities, both medical and non-medical (Figure 1).

The data show that oncology coordinators most often cooperate with other hospitals. Frequent contacts with these facilities are reported by 57.7% of respondents. IDIs show that the cooperation is mainly related to cancer diagnosis and treatment card (*karta diagnostyki i leczenia onkologicznego – karta* DiLO)[5] and patient transfer. It is much less common for coordinators to cooperate with primary health care (PHC)[6]. Not even half of the respondents (38.3%) consider this cooperation to be limited, and 20.8% say it does not occur at all. Statements from the interviews confirm these results. The coordinators emphasized that their contacts with PHC are mainly limited to matters related to *karta* DiLO (*K6: It's mainly about closing or improving these cards, if at all possible*). Some coordinators admitted that they do not send *karta* DiLO back to PHCs, despite current regulations. The survey results indicate a lack of real cooperation between these sectors. Coordinators' contacts with outpatient specialty clinics and diagnostic laboratories outside their hospitals are also not common. Frequent contacts with such facilities are reported by 40.9% of respondents. Qualitative interviews revealed that a structured network of cooperation between outpatient specialist care (OSC)[7] and cancer hospitals is lacking (*K10: I, in my professional work, have not encountered something like this, that a coordinator from OSC called me (...). And in my opinion, outpatient clinics that diagnose breast cancer in the OSC should have coordinators responsible for contacting administrative and substantive coordinators, if I remember their names correctly*). The least developed is cooperation between representatives of NGOs and employees of social welfare institutions. As many as 77.9% of oncology patient coordinators have never worked with foundations and associations, and 62.4% have had no contact with social welfare institutions. In interviews, coordinators stressed that patients rarely ask if they can contact NGOs. In their opinion, this reduces the need to establish cooperation with this sector (*K1: Foundations? In general, patients don't ask about foundations. I'll be honest, at least not us, and so I don't have any contact with foundations*). Some coordinators also pointed to a lack of procedures to integrate NGOs into the oncology system and a reluctance towards such organizations (*K6: No, we don't cooperate. Hardly, for example, amazons – when the boss sees them or hears about them, he is sick. Patients don't ask on their own either*). Similarly, cooperation between oncology coordinators and palliative care representatives and rehabilitation staff is limited. Only 12.1% of coordinators report frequent contact with palliative care staff and 7.4% with rehabilitation staff. Oncology patient coordinators emphasized that patients are mainly referred to hospices and rehabilitation centres by family doctors or specialists. Their own role in this regard is marginal (*K10: Most of the time it's like palliative care, the patient goes to a family doctor or a specialist makes a referral to a home or inpatient hospice. And it's totally out of the coordinator already*). Table I presents data on the impact of implementing the Unit/KON models on the level of cooperation between oncology patient coordinators and representatives of external entities.

[5] Cancer diagnosis and treatment card (*karta* DiLO) is a key document in Poland. Patients suspected of having cancer receive this *karta* DiLO Card. The card facilitates their access to rapid diagnostics and then treatment. And the rapid deadlines specified in the regulations must be maintained here. Everyone who has a *karta* DiLO receives their own coordinator. This document was implemented in Poland as part of the STO reform in 2015.

[6] Primary health care (PHC) is understood in Poland as the care of a general practitioner. The advice of a PHC doctor is paid for by the state, not the patient. The PHC doctor is the primary physician who (if necessary) refers the patient to a specialist.

[7] Outpatient specialist care (OSC) is a group of specialist doctors.

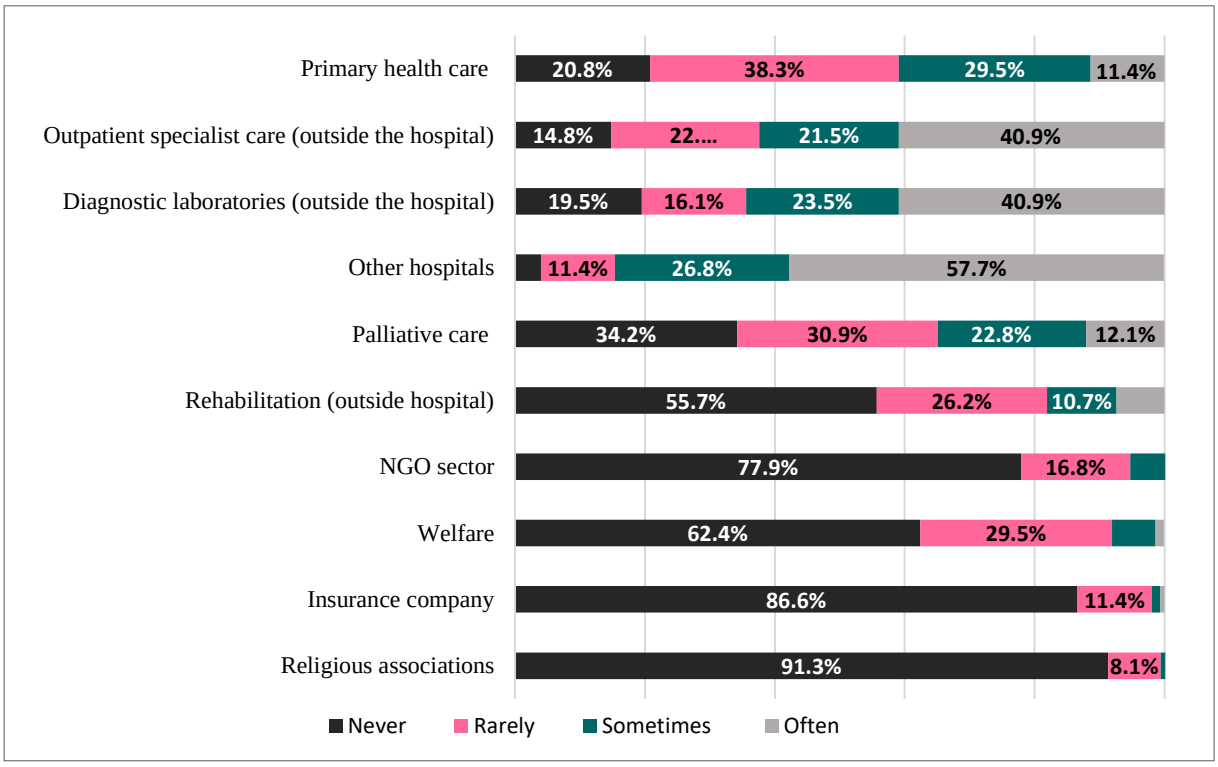

Fig. 1. Cooperation of oncology coordinators with representatives of external institutions supporting oncology patients (N = 149; author's own study); NGO – non-governmental organization.

Table I. Collaboration of oncology coordinators with representatives of other institutions, with a division of facilities with Units/KON vs facilities without Units/KON (N = 149)

Inter-institutional cooperation	Implementation of Unit/KON organizational solutions in the hospital (%)		Statistical significance tests
	implemented	not implemented	Fisher's test
Cooperation with palliative care/hospices			
Never	35.20%	33.70%	
Rarely	33.30%	29.50%	
Sometimes	25.90%	21.10%	p = 0.311
Often	5.60%	15.80%	
Cooperation with rehabilitation (outside the hospital)			
Never	46.30%	61.10%	
Rarely	25.90%	26.30%	
Sometimes	18.50%	6.30%	p = 0.088
Often	9.30%	6.30%	
Cooperation with patient support organizations (NGOs)			
Never	72.20%	81.10%	
Rarely	20.40%	14.70%	
Sometimes	7.40%	4.20%	p = 0.046
Often	0.0%	0.0%	
Cooperation with social welfare			
Never	57.40%	65.30%	
Rarely	31.50%	28.40%	
Sometimes	11.10%	4.20%	p = 0.299
Often	0.0%	2.10%	

Author's own study. KON – Kompleksowa Opieka Onkologiczna (Comprehensive Oncological Care); NGOs – non-governmental organizations.

The data collected suggest that the implementation of Unit/KON models had no significant effect on coordinators' collaboration with palliative and hospice care (p = 0.311, Fisher's test). The percentage of coordinators who never collaborated with these units was similar in both groups (35.2% in facilities with Unit/KON vs 33.7% in facilities without these structures). Frequent cooperation was slightly more common in hospitals without Unit/KON (15.8% vs 5.6%). In the case of out-of-hospital rehabilitation, the data show a greater lack of cooperation in facilities that have not implemented Unit/KON. As many as 61.1% of coordinators from these units have never cooperated with employees of rehabilitation clinics, compared to 46.3% in facilities with such structures. There are also differences in occasional cooperation. Coordinators from facilities with Unit/KON were more likely to report occasional contact with specialists rehabilitation (18.5% vs 6.3%). Although Fisher's test showed no significant differences (p = 0.088), the noticeable trend may suggest that more integrated organizational models favor more frequent cooperation with representatives of rehabilitation facilities. The survey results indicate a low level of cooperation with NGOs in both groups. 72.2% of coordinators from establishments with Unit/KON and 81.1% from establishments without these structures never collaborated with NGOs. The chi-square test did not show any significant differences (p = 0.438), but the Fisher test suggests some correlation (p = 0.046). This may indicate the beginning of cooperation between oncology coordinators employed in hospitals where a Unit/KON was implemented and representatives of patient support organizations. As with NGOs, cooperation with social welfare institutions remains low. There are no significant differences between groups (p = 0.299, Fisher's test). More than half of the coordinators reported no cooperation with this sector (57.4% in facilities with Unit/KON vs 65.3% in facilities without these structures). However, facilities with Unit/KON were more likely to have occasional contacts with social welfare institutions. The percentage of coordinators declaring occasional cooperation was 11.1% vs 4.2% in the other units. The review of the data included in Table I indicates that the implementation of Unit/KON did not significantly affect coordinators' cooperation with palliative care, rehabilitation, NGOs and social welfare institutions. However, some trends suggest a slightly higher (though still low) involvement of coordinators from facilities with comprehensive care models, especially in the areas of rehabilitation and NGOs. It is worth analyzing whether and to what extent the participation of facilities in the pilot of the NCN has affected the level of cooperation between coordinators and other institutions. NCN is a new model for organizing oncology care. It is important to examine whether coordinators from facilities participating in the pilot cooperate more often with representatives of medical and non-medical entities than those who did not participate in the pilot. Detailed data are presented in Table II.

Table II. Collaboration of oncology coordinators with representatives of other institutions, and participation of hospital in pilot program of NCN vs no participation of hospital in pilot (N = 149)

Inter-institutional cooperation	Hospital participation in pilot of NCN (%)		Statistical significance tests
	participated	not participated	Fisher's test
Cooperation with palliative care/hospices			
Never	38.30%	32.40%	p = 0.554
Rarely	23.40%	34.30%	
Sometimes	23.40%	22.50%	
Often	14.90%	10.80%	
Cooperation with rehabilitation (outside the hospital)			
Never	63.80%	52.00%	p = 0.325
Rarely	17.00%	30.40%	
Sometimes	12.80%	9.80%	
Often	6.40%	7.80%	
Cooperation with patient support organizations (NGOs)			
Never	78.70%	77.50%	p = 0.845
Rarely	14.90%	17.60%	
Sometimes	6.40%	4.90%	
Often	0.0%	0.0%	

cd. tab. II

Cooperation with social welfare			
Never	57.40%	64.70%	p = 0.634
Rarely	31.90%	28.40%	
Sometimes	8.50%	5.90%	
Often	2.10%	1.00%	

Author's own study. NCN – National Cancer Network (Krajowa Sieć Onkologiczna); NGOs – non-governmental organizations.

In the facilities participating in the NCN pilot, cooperation with palliative and hospice care was slightly more frequent (14.9% vs 10.8%). At the same time, coordinators from these units more often declared a complete lack of cooperation with this sector (38.3% vs 32.4%). The results indicate that the participation of the hospital in the NCN pilot had no significant effect on the cooperation of oncology patient coordinators with palliative and hospice care representatives (p = 0.554, Fisher's test). The lack of cooperation with rehabilitation facilities outside the oncology centre was declared by 63.8% of coordinators from NCN pilot facilities and 52.0% from non-pilot units. Occasional cooperation ("sometimes") and frequent cooperation ("often") in both groups was at similar level. In piloted units it was 12.8% and 6.4%, respectively, and in non-piloted units 9.8% and 7.8%. Fisher's test did not show any significant differences (p = 0.325). These data indicate that the cooperation of coordinators with representatives of rehabilitation workers remains marginal, regardless of participation in the NCN pilot. A similar relationship was observed in the case of NGOs. The lack of cooperation with NGOs was declared by 78.7% of coordinators from facilities participating in the pilot and 77.5% from other units. Fisher's test did not show any significant differences (p = 0.845), which may suggest that participation in the pilot did not influence the development of this cooperation. Cooperation between coordinators and social welfare institutions also remains low. More than half of coordinators reported its complete lack (57.4% in facilities participating in the NCN pilot vs 64.7% in non-pilot units). These differences were not statistically significant (p = 0.634, Fisher's test). In summary, the review of results did not reveal significant differences in the extent to which oncology coordinators cooperate with medical and non-medical institutions depending on the participation of the institution in the NCN pilot. The lack of statistical differences suggests that implementation of the NCN model will not intensify intersectoral cooperation.

DISCUSSION

The results of the study indicate that the implementation of the Unit/KON organizational models and participation in the NCN pilot did not have a significant impact on the cooperation of oncology patient coordinators with representatives of external entities. Although some positive trends were observed in the case of coordinators' contact with NGOs and rehabilitation facilities, among coordinators employed in facilities using comprehensive care models (Unit-type), these differences were not significant. Cooperation of coordinators with representatives of palliative care and the social care sector remains at an equally low level, regardless of the implemented organizational solutions. Of particular concern is the almost complete lack of cooperation between coordinators and the social care sector and NGOs. The data show that eight out of ten oncology coordinators have never had contact with employees of NGOs, and an equally low level of cooperation applies to social care workers. Coordinators indicate a lack of tools for identifying non-medical needs of patients, and hospitals lack mechanisms for regulating intersectoral cooperation. Foreign studies of coordinated care emphasize the importance of the concept of "shared care", in which different sectors work together for comprehensive patient support [11]. It is crucial to include representatives of non-medical professions in the coordination process. In many coordinated care systems, the role of coordinators is played not only by nurses, but also by representatives of other professions [12]. Experts stress that effective care requires the involvement of multiple institutions, which should be aware of the challenges patients face during treatment. It is also important to have a better understanding of the roles and responsibilities of all parties involved and to support patients in making informed use of the available resources of the health and social welfare system [11]. In some countries, coordinated care systems involve close integration of hospitals with other entities. In many foreign models, up to 90% of coordinators maintain contact with patients after treatment, helping to organize follow-ups and long-term care [13]. Meanwhile, in Poland, the role of coordinators mainly focuses on the diagnostic stage, organizing consiliums, and often ends when treatment begins. Further interventions are usually initiated by patients. The limited role of coordinators means that their potential is not fully realized. Patient support could also include areas beyond the scope of the *karta* DiLO. Oncology rehabilitation, which, despite its

important role, is rarely treated as a standard component of comprehensive care, remains a particular challenge. Expert reports indicate unequal access to rehabilitation facilities [14]. Although oncological coordinators play a key role in organizing the diagnostic and therapeutic path, their involvement in referring patients to rehabilitation centres outside their home hospitals is very limited. More than half of the surveyed oncological patient coordinators have never cooperated with rehabilitation facilities outside their centre. The involvement of coordinators in referring patients to palliative and hospice care units is similar – more than one third of the oncological coordinators participating in the study claim that they have not had contact with this sector, and another third report only occasional cooperation.

Foreign reports indicate that coordinators' activities should include not only optimization of the diagnostic and therapeutic pathway, but also psychological, social and professional support, which significantly affects the quality of life after treatment [15]. In Poland, coordination usually ends with the therapeutic process. As a result, patients are often left without formal support during the period of recovery and return to daily functioning. In many countries, it is noted that effective coordination should include integration with the social security system and training of medical personnel in cooperation with social organizations [11]. In Poland, such integration is still marginal, and intersectoral cooperation is neither structured nor widespread. Although training for oncology coordinators includes elements on cooperation with NGOs, systemic solutions that would realistically strengthen such cooperation are lacking. The introduction of such mechanisms could significantly improve the quality of life of oncology patients by minimizing barriers to accessing support both during and after treatment.

CONCLUSIONS

1. It cannot be stated that the implementation of organizational models such as Unit/KON and participation in the pilot of the NCN contributed to the strengthening of cooperation between oncological coordinators and representatives of external institutions. The lack of significant differences in inter-institutional and inter-sectoral cooperation suggests that even in more organized Unit-type models, effective mechanisms for integrating the healthcare system – oncological patient coordinators with the non-governmental sector, social care, palliative or rehabilitation – have not emerged.
2. There are grounds to believe that the Polish oncological care system has still not reached a level at which the need for close inter-sectoral cooperation is widely recognized and implemented. The lack of integration of activities of the healthcare sector, social care and NGOs is one of the key systemic challenges. The lack of such cooperation may negatively affect both patients and healthcare facilities that do not use the potential of other entities.
3. Coordination of oncology care in Poland is still mainly focused on the diagnostic and treatment stages. It is necessary to introduce mechanisms to enable earlier and more effective integration of patients into rehabilitation programs and to ensure a smooth transition to palliative care when necessary.
4. Organizational reform measures are worth supplementing with mechanisms that integrate the health care system, especially oncology coordinators with broader social support. Only then will it be possible to provide oncology patients with comprehensive and holistic care.

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Manual tracing and artificial intelligence tracing of lateral cephalograms: A critical comparative assessment of performance

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ABSTRACT

INTRODUCTION: Cephalometric analysis, a cornerstone of orthodontics and craniofacial surgery, traditionally involves manual radiograph tracing, a time-consuming and potentially variable process. Artificial intelligence (AI) offers a potential alternative for faster, more consistent analysis. This study compared AI-driven and manual cephalometric methods to assess agreement and identify discrepancies.

MATERIAL AND METHODS: This quantitative, comparative cross-sectional study was conducted in a private practice in Peshawar, Pakistan (August–November 2024), including 29 orthodontic patients who met specific criteria (good-quality cephalograms and absence of facial clefts/intra-oral appliances). Cephalometric radiographs were analyzed by two experienced dentists using manual tracing and by AI software (Audaxceph 6.0.50.3887). Five key angular measurements (SNA, SNB, ANB, FMA, and SN-Mp), used in Steiner's and Tweed's analyses, were compared. Inter-rater reliability for the manual tracings was assessed using intraclass correlation coefficients (ICCs).

RESULTS: Excellent inter-rater reliability was observed for manual tracings (ICCs > 0.90). Paired t-tests revealed no significant differences between manual and AI methods for SNA, SNB, ANB, and FMA. However, a statistically significant difference ($p = 0.006$) was found for SN-Mp.

CONCLUSIONS: This study, comparing manual and AI-driven cephalometric analysis, found strong agreement for most key measurements (SNA, SNB, ANB, and FMA), suggesting AI's potential to enhance clinical efficiency. The significant difference in SN-Mp, however, emphasizes the need for continued clinical oversight. A combined approach, integrating AI with clinical expertise, is recommended for optimal diagnostic accuracy and treatment planning.

KEYWORDS

artificial intelligence, AI, cephalography, cephalogram, tracing

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INTRODUCTION

Cephalometric analysis has a rich history dating back to the late 1800s, when radiographs were first employed to study the head and neck. In the 1930s, Holly Broadbent, a professor of orthodontics at the University of Michigan, analyzed the correlation between the teeth and the skull. This pioneering work involved measuring various angles and distances on radiographic images, establishing the foundations of cephalometric analysis [1]. Cephalometric analysis was initially coined to describe manually locating landmarks on acetate overlays over a light table and measuring the linear and angular values with a protractor, which is tedious, time-consuming, and subjective [2]. Cephalometric skeletal analysis plays a pivotal role in orthodontics and craniofacial surgery, serving as a critical diagnostic tool for understanding craniofacial structure and function. This method is essential for diagnosing skeletal discrepancies, evaluating growth patterns, and planning treatment strategies for individuals with orthodontic and craniofacial conditions [3]. Traditionally, this process has relied on manual techniques, demanding a high level of expertise and attention to detail from clinicians. However, recent advancements in artificial intelligence (AI) have introduced a new dimension to cephalometric analysis, challenging the dominance of manual methods. AI is concerned with developing programs and computers that can gather data, apply reason to it, and then translate it into intelligent actions. AI is a broad area that includes reasoning, typical linguistic dispensation, machine learning, and planning. The manual approach to cephalometric skeletal analysis involves identifying and marking anatomical landmarks on radiographs, followed by precise measurements to assess craniofacial relationships. While this approach has been the standard for decades, it is not without its challenges [4]. The proces is time-consuming, labor-intensive, and prone to variability, as the accuracy of the results often depends on the skill and experience of the practitioner [5,6]. Inter- and intra-observer inconsistencies can lead to discrepancies in measurements, affecting both diagnosis and treatment outcomes [7]. Convolutional neural networks, a type of deep learning model, have various applications, including image classification and segmentation, natural language processing, facial landmark detection, and lane detection [8].

AI-driven tools can analyze cephalometric images with remarkable speed and precision, minimizing human error and variability. AI-based methods of cephalometric analysis can be semi-automatic or fully automatic. The fully automatic method uses AI to trace, identify landmarks, and calculate the cephalometric measurements, whereas the semi-automatic method involves a combination of manual selection of landmarks followed by automated calculation of values [9,10].

These systems are trained on large datasets, enabling them to recognize complex patterns and deliver consistent results across different cases [11]. As such, AI holds the promise of revolutionizing cephalometric skeletal analysis by enhancing accuracy, efficiency, and accessibility. Some studies have found statistically significant differences between manual and AI-based methods. Hwang et al. [12] reported AI to be more accurate than a manual method for 14 out of the 46 landmarks measured in their study, while another 14 variables were found to be more accurately measured by the manual method as compared to the AI-based method, and similar results were obtained by Agrawal et al. [13].

The aim of this study was to comprehensively compare AI-driven and manual methods for cephalometric skeletal analysis. By examining the strengths, limitations, and practical applications of both approaches, this research can provide a nuanced understanding of their respective roles in clinical practice. Key aspects will be explored – such as accuracy, reliability, and efficiency – along with the implications of integrating AI into orthodontic and craniofacial workflows. The introduction of AI into cephalometric skeletal analysis marks a significant step forward in the evolution of diagnostic methodologies. As the field continues to evolve, understanding the interplay between traditional expertise and technological innovation becomes increasingly important. By critically analyzing these two approaches, this research sheds light on their potential to complement each other and drive advancements in patient care and clinical outcomes.

MATERIAL AND METHODS

This is a quantitative, comparative cross-sectional study, conducted at a private practice in Peshawar, Khyber Pakhtunkhwa, Pakistan between August 2024 and November 2024. Prior to its commencement, proper informed consent was taken from the patients. Initially, the study involved 55 patients; after applying the inclusion and exclusion criteria, 29 patients were enrolled in the study. The inclusion criteria consisted of subjects seeking orthodontic treatment whose records included cephalometric X-rays. The exclusion criteria were a lack of consent, poor quality cephalograms, cephalograms showing artifacts, any history of facial clefts, and use of intra-oral appliances. No restrictions were placed on the gender, age, or ethnicity of the patients.

All the measurements were based on the American Board of Orthodontics Analysis and included the

angles SNA and SNB, as well as ANB, which is SNA minus SNB. The AI tracing was done with the help of Audaxceph version 6.0.50.3887. The manual tracing and evaluation of the cephalograms were conducted by two proficient dentists. For this study, five specific readings from the traced cephalograms were included, focusing on the angles SNA, SNB, SN-Mp, and FMA as per Steiner's and Tweed's skeletal analysis. Descriptive statistics such as mean, median, and standard deviation were obtained for age and percentages for gender. For intergroup comparisons, a sample paired t-test was used. All the data are described in tables and charts.

RESULTS

The frequencies of male and female patients participating in this study were in a ratio of 31.03% to 68.96%, respectively (9 females and 20 males). The mean age of the sample was 18.10 years with standard deviation of 5.690 and a median of 16.0, as shown in Table I.

Table I. Statistics with regard to the participants' age

Age (years)		
N	valid	29
	missing	0
Mean		18.10
Median		16.00
Std. deviation		5.690
Minimum		7
Maximum		30

The paired sample t-test showed no significant differences between the values for SNA, SNB, ANB, and FMA that were traced manually versus those traced with the help of AI, although a p-value of 0.006 was obtained for SNMP, as shown in Table II.

Table II. Paired sample t-test

Paired differences									
Pairs		Mean	Std. deviation	Std. error mean	95% confidence interval of the difference		t	df	Sig. (2-tailed)
					lower	upper			
Pair 1	Angle SNA Manual – Angle SNA Ai	-.9724	3.7192	.6906	-2.3871	.4423	-1.408	28	.170
Pair 2	Angle SNB Manual – Angle SNB Ai	-.0966	2.7197	.5050	-1.1311	.9380	-.191	28	.850
Pair 3	ANB Values Manual – ANB Values Ai	-.8724	3.5360	.6566	-2.2174	.4726	-1.329	28	.195
Pair 4	SN-MP Angle Manual – SN-MP Angle Ai	-2.6552	4.8426	.8992	-4.4972	-.8132	-2.953	28	.006
Pair 5	FMA Angle Manual – FMA Angle Ai	-1.1793	6.3147	1.1726	-3.5813	1.2227	-1.006	28	.323

Manual cephalometric tracings were performed independently by two experienced dentists. Inter-rater reliability was assessed using intraclass correlation coefficients (ICCs). High levels of agreement were observed for all measurements (ICCs > 0.90 for all variables), indicating excellent inter-rater reliability.

DISCUSSION

This study presents a detailed analysis comparing five key cephalometric parameters measured manually by two experienced dentists and using AI-driven software. The excellent inter-rater reliability observed for the manual tracings (ICCs > 0.90 for all variables) confirms the consistency and accuracy of the manual method and provides a strong baseline for comparison with the AI-based approach. This high level of agreement between the dentists (manual raters) strengthens the validity of the study's findings.

The core finding of this research is the general agreement between AI-driven and manual cephalometric analysis. For the majority of the parameters assessed (SNA, SNB, ANB, and FMA), no statistically significant differences were found between the two methods. This suggests that AI-based tools and applications can provide comparable results to traditional manual tracing, offering a faster and more efficient alternative in clinical practice. The efficiency gained by using AI is a significant advantage, particularly in busy clinical settings where time constraints are a major issue. AI can process images and generate measurements much faster than manual methods, freeing up clinicians' time for other essential tasks, such as interacting with patients and planning treatments.

However, a statistically significant difference was observed for SNMP ($p = 0.006$), indicating a potential discrepancy between the manual and AI tracing methodologies specific to this measurement. This finding is crucial and requires further investigation and research. It suggests that the AI algorithm may have difficulty accurately identifying the specific landmarks or performing the calculations involved in determining SNMP angle. This discrepancy could be due to several factors, including the complexity of the anatomical structures involved in SNMP measurement, variations in image quality, or limitations in the AI's training data. Further research is needed to pinpoint the exact cause of this difference and to explore potential solutions, such as refining the AI algorithm or improving image acquisition protocols.

This finding aligns with the research published by Mercier et al. in 2024 [11], which suggests that current AI technology has not yet reached a level of 100% accuracy in landmark detection. While AI has made significant improvement in image analysis, challenges remain in accurately identifying complex anatomical landmarks in all cases. This highlights the importance of continued research and development in AI-driven cephalometric analysis to improve its accuracy and reliability. It also emphasizes the need for clinicians to take great caution when interpreting AI-generated results, particularly for parameters where discrepancies have been identified.

The implications of these findings for clinical practice are significant. While AI offers the potential for more efficiency and less variability in cephalometric analysis, it is not yet a perfect replacement for manual methods. Clinicians should be aware of the potential limitations of AI-based tools, particularly for parameters like SNMP. A hybrid approach that combines AI-driven analysis with clinical expertise and judgment may be the most effective strategy for the foreseeable future. This approach would leverage the speed and efficiency of AI while ensuring accurate, reliable results through a careful review and interpretation by experienced clinicians.

Authors' contribution

Study design – Q.J. Hayat, B.R. Khan
Data collection – B.R. Khan, M. Kashif
Data interpretation – Q.J. Hayat, Z. Khan
Statistical analysis – Q.J. Hayat, M. Kashif
Manuscript preparation – Q.J. Hayat, Z. Khan, M.A. Zuhair
Literature research – Q.J. Hayat, B.R. Khan

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Role of salivary immunoglobulins in oral health: Investigating levels of IgA and IgG in saliva and their impact on periodontal disease among patients in Peshawar, Pakistan

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ABSTRACT

INTRODUCTION: Salivary immunoglobulins, IgA and IgG, play a crucial role in the oral immune system, influencing oral health. Given the high prevalence of periodontal disease in Pakistan and the influence of socio-cultural factors on oral health practices, this study aims to assess the levels of salivary immunoglobulins to periodontal health.
MATERIAL AND METHODS: A cross-sectional study was conducted involving 99 participants aged 18 to 65, grouped by periodontal health and smoking status: healthy non-smokers, smokers with gingivitis, and smokers with periodontitis. Patients having other comorbidities such as diabetes mellitus, cardiovascular diseases, neurological diseases and severe periodontitis were excluded. The participants were recruited from dental clinics in Peshawar. Salivary samples were collected, and immunoglobulin levels were measured using an enzyme-linked immunosorbent assay (ELISA). Clinical parameters, including bleeding on probing (BOP), the probing pocket depth (PPD), and plaque index (PI), were also recorded. Statistical analysis was performed using SPSS version 25, with the Pearson correlation coefficient to assess relationships between the immunoglobulin levels and clinical parameters.
RESULTS: The study found that salivary immunoglobulins levels were significantly higher in the groups of participants being smokers (66%) having gingivitis (IgA: 1.5 mg/mL, IgG: 1.1 mg/mL) and periodontitis (IgA: 2.5 mg/mL, IgG: 2.0 mg/mL) compared to healthy non-smoking (33%) individuals (IgA: 0.4 mg/mL, IgG: 0.3 mg/mL). Additionally, the BOP and PPD values were the lowest in the healthy non-smoking participants and increased significantly in the smoking group with periodontal disease.
CONCLUSIONS: Elevated levels of salivary immunoglobulins correlate with periodontal disease and smoking, indicating their potential as biomarkers for diagnosis and monitoring treatment.

KEYWORDS

salivary immunoglobulins, IgA, IgG, periodontal disease, smoking, biomarkers, socioeconomic status, oral health, Pakistan

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INTRODUCTION

Salivary immunoglobulins, particularly immunoglobulin A (IgA) and immunoglobulin G (IgG), are important components of the oral immune system, playing a significant role in maintaining oral health and preventing periodontal diseases. IgA, the most abundant immunoglobulin in saliva, acts as the first line of defence by neutralizing pathogens and inhibiting their adherence to oral surfaces, thereby preventing infections [1,2]. In contrast, IgG mainly mediates systemic immunity, providing protection against bacterial infections and contributing to inflammatory responses associated with periodontal disease [3,4]. Periodontal disease, characterized by inflammation and the destruction of tooth-supporting structures, poses a significant public health challenge globally, with a high prevalence reported in Pakistan [5,6]. Research indicates that altered levels of salivary immunoglobulins correlate with the severity of periodontal disease, suggesting their potential as biomarkers for diagnosis and treatment monitoring [7,8]. Furthermore, the influence of socio-cultural factors on oral health practices in specific populations underscores the need for localized research [9,10]. This study aims to investigate the levels of salivary IgA and IgG among individuals in Peshawar and their correlation with clinical parameters of periodontal disease, providing insights into the immunological aspects of oral health in this region [11,12]. Understanding these relationships can guide preventive and therapeutic strategies, contributing to improved oral health outcomes in the community [13,14,15].

MATERIAL AND METHODS

This cross-sectional study was conducted in Peshawar, Pakistan, involving participants from various demographic backgrounds to assess the levels of salivary immunoglobulins (IgA and IgG) in relation to periodontal health. A total of 100 participants was recruited for this study, aged between 18 and 65, 33.33% individuals being non-smokers and 66.67% individuals being smokers. The sample included individuals with varying periodontal health statuses, classified as healthy and non-smokers with no other comorbidities (diabetes, cardiovascular diseases, neurological disorders, etc.) and smokers with gingivitis and periodontitis having no other comorbidities (diabetes, cardiovascular diseases, neurological disorders, etc.). Individuals with only mild to moderate gingivitis and periodontitis were included. Participants were included if they were adults aged 18–65, willing to provide informed consent, and had not used antibiotics within the last 3 months. Individuals with oral cancers or significant oral lesions, those undergoing periodontal treatment within the last 6 months, individuals with severe gingivitis and periodontitis, pregnant or lactating women were excluded from the study. Similarly, individuals with comorbidities such as diabetes mellitus, cardiovascular disease, neurological disease, etc. were also excluded. The participants were recruited from dental clinics and community health centres in Peshawar, with informed consent obtained prior to enrolment. A thorough clinical examination was performed to assess the periodontal status using the plaque index (PI), gingival index (GI), probing pocket depth (PPD) measurements, and the clinical attachment level (CAL). Salivary samples were collected by instructing the participants to avoid food and drink for at least 1 hour prior to collection. Unstimulated saliva was gathered by having the participants spit into a sterile container, with samples immediately frozen at -20°C for later analysis. The salivary IgA and IgG levels were quantified using Ray Biotech enzyme-linked immunosorbent assay (ELISA) kits pre-coated with capture antibodies specific to IgA or IgG, following the manufacturer's instructions, and all the assays were performed in duplicate to ensure accuracy.

The data were analysed by means of statistical software SPSS version 25. Descriptive statistics were calculated for the demographic characteristics and immunoglobulin levels. The correlation between the salivary immunoglobulin levels and periodontal parameters were assessed utilizing the Pearson correlation coefficient, with a p-value of < 0.05 considered statistically significant. All the participants were provided with written informed consent.

RESULTS

A total of 99 participants were included in the study, categorized by their oral health status: healthy and non-smoking individuals (33%), individuals with gingivitis who smoke (33%) and individuals with periodontitis being smokers (33%). The demographic characteristics of the participants, including their age, gender, and oral health status, are summarized in Table I.

Table I. Participant demographics

Demographic variable	Healthy (no gingivitis, periodontitis) and non-smokers (n = 100) (33%)	Gingivitis (mild to moderate) and smokers (n = 100) (33%)	Periodontitis (mild to moderate) and smokers (n = 100) (33%)
Age (years)	25.4 ± 5.1	26.8 ± 6.2	28.5 ± 7.1
Gender (male/female)	equal	equal	equal
Socioeconomic status	low: 30%, medium: 50%, high: 20%	low: 35%, medium: 45%, high: 20%	low: 40%, medium: 40%, high: 20%

The mean levels of salivary immunoglobulins IgA and IgG varied significantly among the three groups. The healthy non-smoker group having no other comorbidities had a mean IgA level of 0.4 mg/mL (± 0.2) and an IgG level of 0.3 mg/mL (± 0.1). In contrast, the participants with gingivitis being smokers had higher mean levels of IgA (1.5 mg/mL ± 0.6) and IgG (1.1 mg/mL ± 0.5). The periodontitis group being smokers exhibited the highest mean levels, with IgA at 2.5 mg/mL (± 0.8) and IgG at 2.0 mg/mL ± 0.7 (Table II).

Table II. Salivary immunoglobulin levels

Group	IgA (mg/mL)	IgG (mg/mL)
Healthy and non-smokers (33%)	0.4	0.3
Gingivitis and smokers (33%)	1.5	1.1
Periodontitis and smokers (33%)	2.5	2.0

Bleeding on probing (BOP), PPD, PI, and the functional dentition index (FDI) scores were also significantly different across the groups. The mean BOP was lowest in the healthy non-smoker group (1.0 ± 0.5), increased in the gingivitis smokers' group (5.0 ± 1.5), and was highest in the periodontitis smokers group (7.0 ± 1.8; Table III). Similarly, the mean PPD was 0.0 mm (healthy), 2.0 mm (gingivitis), and 5.5 mm (periodontitis). The PI was higher in the individuals with periodontal disease, averaging 6.5 (periodontitis) compared to 14.0 (healthy).

Also, as the socioeconomical status decreases (more individuals in low socioeconomic status – SES categories), the levels of salivary immunoglobulins (IgA and IgG) tend to increase, indicating a potential relationship between socioeconomic factors and periodontal disease severity. These findings suggest that interventions aimed at improving oral health in lower SES populations could help mitigate the severity of periodontal disease and its immunological consequences (Table IV). The Pearson correlation analysis revealed significant positive correlations between the levels of immunoglobulins (IgA and IgG) and the severity of periodontal disease ($p < 0.01$; Table V). Additionally, a negative correlation was observed between the immunoglobulin levels and clinical parameters such as BOP and PPD.

Table III. Clinical parameters

Group	BOP (%)	PPD (mm)
Healthy and non-smokers (33%)	1.0	0.0
Gingivitis and smokers (33%)	5.0	2.0
Periodontitis and smokers (33%)	7.0	5.5

BOP – bleeding on probing; PPD – probing pocket depth

Table IV. Correlation between socioeconomical status (SES) and immunoglobulin levels

Parameter	Healthy non-smokers	Gingivitis smokers	Periodontitis smokers
Low SES (%)	30%	35%	40%
Medium SES (%)	50%	45%	40%
High SES (%)	20%	20%	20%
IgA level (mg/mL)	0.4	1.5	2.5
IgG level (mg/mL)	0.3	1.1	2.0

IgA – immunoglobulin A; IgG – immunoglobulin G

Table V. Correlation between salivary immunoglobulins and clinical parameters

Immunoglobulin	Clinical parameter	Correlation coefficient (r)	p-value
IgA	BOP (%)	0.75	< 0.01
IgA	PPD (mm)	0.70	< 0.01
IgG	BOP (%)	0.80	< 0.01
IgG	PPD (mm)	0.75	< 0.01

IgA – immunoglobulin A; IgG – immunoglobulin G; BOP – bleeding on probing; PPD – probing pocket depth

DISCUSSION

The findings of this study underscore the significant role that salivary immunoglobulin, particularly IgA and IgG, play in oral health, especially in relation to periodontal disease and the status of smoking and non-smoking. The altered levels of immunoglobulins in individuals with gingivitis and periodontitis highlight their potential as biomarkers for disease severity. Results indicate a clear progression in immunoglobulin levels, where the healthy non-smoking individuals exhibited baseline levels of IgA (0.4 mg/mL) and IgG

(0.3 mg/mL), which increased significantly in individuals who smoke and exhibit gingivitis (IgA: 1.5 mg/mL, IgG: 1.1 mg/mL) and periodontitis (IgA: 2.5 mg/mL, IgG: 2.0 mg/mL). These findings are consistent with previous studies indicating that salivary IgA levels are altered in periodontal disease, suggesting a compensatory immune response to the bacterial challenge in the oral cavity [16,17].

In addition to immunoglobulin levels, the clinical parameters measured in this study, such as BOP and PPD, provide insight into the relationship between the oral immune response and periodontal disease severity. Our data showed an increase in BOP and PPD corresponding to the severity of periodontal conditions, aligning with findings from Joss et al. [18] and Lang et al. [19], which confirmed that these parameters are probable indicators of periodontal health.

Interestingly, while the altered immunoglobulin levels in our smokers with gingivitis and periodontitis groups were consistent with existing literature [20,21], the overall BOP and PPD values in the healthy non--smokers and smokers with gingivitis groups were lower than typically reported. This discrepancy may suggest a regional variation in periodontal disease prevalence or differences in oral hygiene practices in the population studied [22]. Such factors should be considered when interpreting these findings as cultural and socioeconomic differences may influence oral health outcomes. Furthermore, our data showed significant positive correlations between the salivary immunoglobulin levels and the clinical parameters of periodontal disease, echoing previous findings that suggest salivary immunoglobulins could serve as reliable biomarkers for assessing periodontal health [23]. The correlation of elevated IgA with increased BOP and PPD strengthens the argument for their role in the host's immune response to periodontal pathogens. This study also reveals a notable trend: as SES decreases, the levels of salivary immunoglobulins IgA increase, suggesting a link between SES and periodontal disease severity. This aligns with previous research indicating that individuals from lower SES backgrounds often experience worse oral health outcomes [24]. The clinical implications of these findings are significant. Targeted interventions aimed at improving oral health in lower SES populations may help reduce the severity of periodontal disease and its immunological effects. Enhancing access to dental care and education about oral hygiene could play a crucial role in improving health outcomes in these communities.

CONCLUSIONS

This study emphasizes the importance of salivary immunoglobulins as potential biomarkers for periodontal disease and smoking individuals as well as highlights the need for further research in diverse populations to better understand the relationship between immune response and periodontal health. Future studies should explore the underlying mechanisms connecting salivary immunoglobulin levels with clinical outcomes to enhance the diagnostic and therapeutic approaches in periodontal disease management [25,26].

Ethical considerations

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was acquired from all the participants prior to their enrolment in the study. The participants were provided with comprehensive information regarding the purpose, procedures, potential risks, and benefits of the study. In addition, they were assured that their participation was voluntary and that they could withdraw at any time without any consequence. Ethical approval was received from Ethical Review Board.

Conflict of interest

The author states no conflict of interest.

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OPIS PRZYPADKU
CASE REPORT

High-flow nasal oxygen therapy used to facilitate bronchofiberoscopy in high-risk patients not qualified for urgent bronchofiberoscopy procedure

Wysokoprzepływowa tlenoterapia donosowa stosowana w celu ułatwienia wykonania bronchofiberoskopii u pacjentów wysokiego ryzyka niekwalifikujących się do pilnej bronchofiberoskopii

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ABSTRACT

The case series illustrates clinical challenges associated with performing fiberoptic bronchoscopy (FOB) on patients with severe respiratory and cardiovascular diseases. Standard respiratory support methods may be insufficient or may pose risks in this population. The first case involved a patient with a congenital heart defect, unstable hemodynamics, and suspected inflammatory changes in the lungs who required diagnostic FOB due to bleeding from the respiratory tract. Use of high-flow nasal oxygen therapy (HFNOT) allowed for safe performance of FOB, minimizing the risk of barotrauma-related complications. The second patient was diagnosed with Melnick-Needles syndrome, chronic respiratory failure and bronchial cartilage chondromalacia, which can be responsible for complications during standard FOB. HFNOT was also used during the procedure, which prevented complications resulting from anatomical limitations and barotrauma. These cases suggest that HFNOT is an effective alternative to traditional respiratory support methods during FOB for patients at a high risk of complications, especially those with congenital heart defector airway anomalies.

KEYWORDS

barotrauma, respiratory failure, bronchofiberoscopy, non-invasive ventilation support

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STRESZCZENIE

Seria przypadków klinicznych ilustruje wyzwania związane z wykonaniem bronchofiberoskopii (*fiberoptic bronchoscopy* – FOB) u pacjentów obciążonych kardiologicznie i pulmonologicznie. Standardowe metody wsparcia oddechowego mogą być niewystarczające u tej grupy pacjentów. Pierwszy przypadek dotyczy pacjentki z wrodzoną wadą serca, niewydolnością oddechową i podejrzeniem zmian zapalnych w płucach, wymagającej diagnostycznej FOB z powodu krwioplucia. Zastosowanie wysokoprzepływowej tlenoterapii donosowej (*high-flow nasal oxygen therapy* – HFNOT) pozwoliło na bezpieczne wykonanie FOB, minimalizując ryzyko powikłań związanych np. z barotraumą. Drugi przypadek dotyczy pacjentki ze zdiagnozowanym zespołem Melnicka i Needlesa, przewlekłą niewydolnością oddechową i chondromalacją chrząstki oskrzelowej, co mogło stanowić przyczynę powikłań podczas standardowej FOB. W trakcie zabiegu również zastosowano HFNOT, co zapobiegło powikłaniom wynikającym z ograniczeń anatomicznych i ewentualnej barotraumy. Opisane przypadki kliniczne mogą sugerować, że zastosowanie HFNOT u pacjentów z wysokim ryzykiem powikłań, zwłaszcza z wrodzoną wadą serca i anomaliami dróg oddechowych, jest skuteczną alternatywą dla tradycyjnych metod wsparcia oddechowego.

SŁOWA KLUCZOWE

barotrauma, niewydolność oddechowa, bronchofiberoskopia, nieinwazyjne metody wsparcia oddechowego

INTRODUCTION

Fiberoptic bronchoscopy (FOB) remains an important diagnostic and therapeutic method in pulmonology, but its use in patients with advanced respiratory failure and comorbidities associated with a high risk of complications requires particular caution. Choosing an appropriate method of respiratory support during the procedure, especially in patients with anatomical anomalies of the respiratory tract or circulatory system, is important for ensuring patient safety and the effectiveness of the examination. This paper presents two clinical cases – a patient with cyanotic heart disease and a patient with Melnick-Needles syndrome – in whom FOB was performed using high-flow nasal oxygen therapy (HFNOT) as an alternative to non-invasive mechanical ventilation (NIV). The case reports illustrate the complexity of management in situations where conventional treatment methods may not be possible or carry a risk of serious complications, and highlight the potential role of HFNOT in enabling safe bronchoscopy in high-risk patients.

CASE REPORTS

Case 1

A 34-year-old female patient with a cyanotic congenital heart defect was admitted to the Department of Pulmonary Diseases due to hemoptysis. For about a week, she had been expectorating about 150 ml of bloody sputum. She visited the ear, nose, and throat (ENT) emergency department twice, where inflammation or other possible sources of bleeding in the upper airway region were ruled out.

The patient's medical history indicated pulmonary atresia with ventricular septal defect (PA-VSD) coexisting with a right aortic arch. Blood was supplied to the pulmonary circulation via collateral circulation originating from the aorta. During infancy, the patient underwent a Blalock-Taussig systemic-pulmonary shunt as part of cardiac surgery treatment which was closed in the patient's first year of life.

Laboratory tests have shown signs of polycythemia, with a hemoglobin concentration of 22 g/dL, which was a decrease from previous results. Saturation measurements showed oxygen saturation of 75%. This was confirmed by blood gas analysis, which also showed signs of type 1 respiratory failure. No increase in inflammatory markers was found.

Due to hemoptysis and a cardiological history, a decision was made to perform a computed tomography (CT) angiography of the pulmonary arteries. Imaging confirmed the presence of a ventricular septal defect and a right-sided aortic arch; however, the pulmonary artery could not be visualized. Other vascular abnormalities included primary branches originating from the aortic arch and additional sources of arterial vascularization from the descending aorta, which connected to the network of pulmonary collateral vessels leading to segmental pulmonary vessels on both sides. No signs of embolism were found in any of the visualized vascular structures.

Numerous infiltrative-atelectatic changes were revealed in the lung parenchyma, with the greatest intensity in the lower lobe of the left lung. Additionally, there were 'ground glass' opacities and a *cobblestone pattern*, as well as signs of bronchial obstruction caused by secretions. The complete radiological image indicated that the changes in the lung parenchyma were inflammatory in nature.

The results of the diagnostic tests suggested a potential inflammatory cause of the hemoptysis. In the context of an uncorrected heart defect, this carried a significant risk of progression to massive hemoptysis with accompanying hemodynamic instability. For this reason, the patient was urgently referred for FOB to confirm the infection, isolate the causative agent, and control the bleeding locally.

Considering the patient's chronic respiratory failure resulting from a cyanotic heart defect and the presence of numerous anastomoses, various potential respiratory support options were considered. The presence of a left-to-right shunt disqualified the patient from the classic oxygen therapy through oxygen cannulas. Despite the use of relatively high flow rates, in the range of 6–8 l/min, peripheral blood saturation and arterial blood gas parameters did not change significantly. Other possible methods of respiratory support were HFNOT or NIV. As of today, there are no clinical studies conducted on large groups of patients directly comparing these two techniques in the specific situation of our patient. Nevertheless, there is a lot of indirect data available on various heart defects in patients after cardiac surgery due to heart defects. A direct comparison of HFNOT and NIV in pediatric patients after cardiac surgery indicates a lower risk of intubation in patients treated with HFNOT, but the choice of technique does not affect postoperative pO_2 and pCO_2 [1,2].

Similarly, in the pediatric patients who have underwent correction of a congenital heart defect, HFNOT, compared to respiratory support methods requiring the use of a mask, reduces the risk of desaturation and the need for mechanical ventilation [3]. On the other hand, NIV is the recommended treatment for patients with respiratory failure in the course of acute circulatory failure [4].

FOB did not reveal any signs of potential inflammation. Bloody secretions originating from the left main bronchus were observed in the bronchial tree. The entire mucosa from the trachea level was covered with numerous dilated vessels (Figure 1 and Figure 2). The source of the bleeding was a vessel located within the mucosa of the left main bronchus. The bleeding site was lavaged with cold saline limiting the bleeding.

The patient was transferred to a cardiology center to assess the possibility of performing vascular procedures or cardiac surgery.

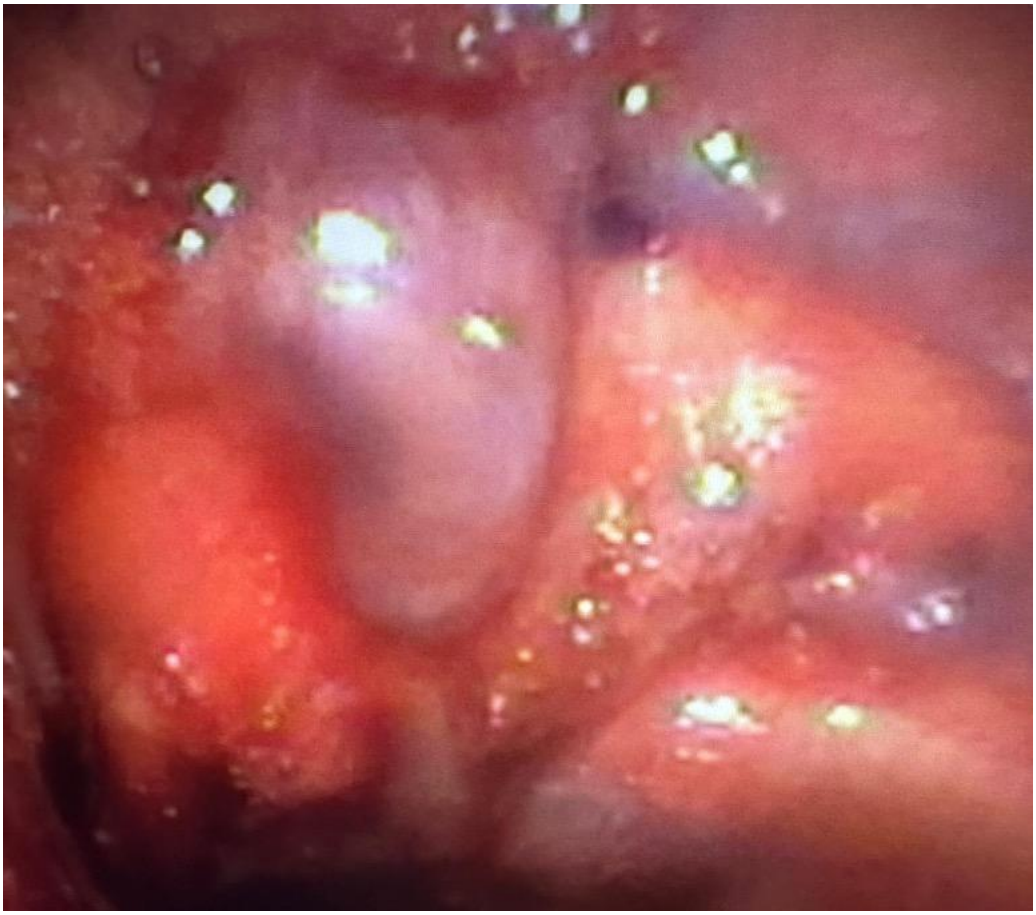

Fig. 1. Vascular malformations visible during bronchoscopy procedure.

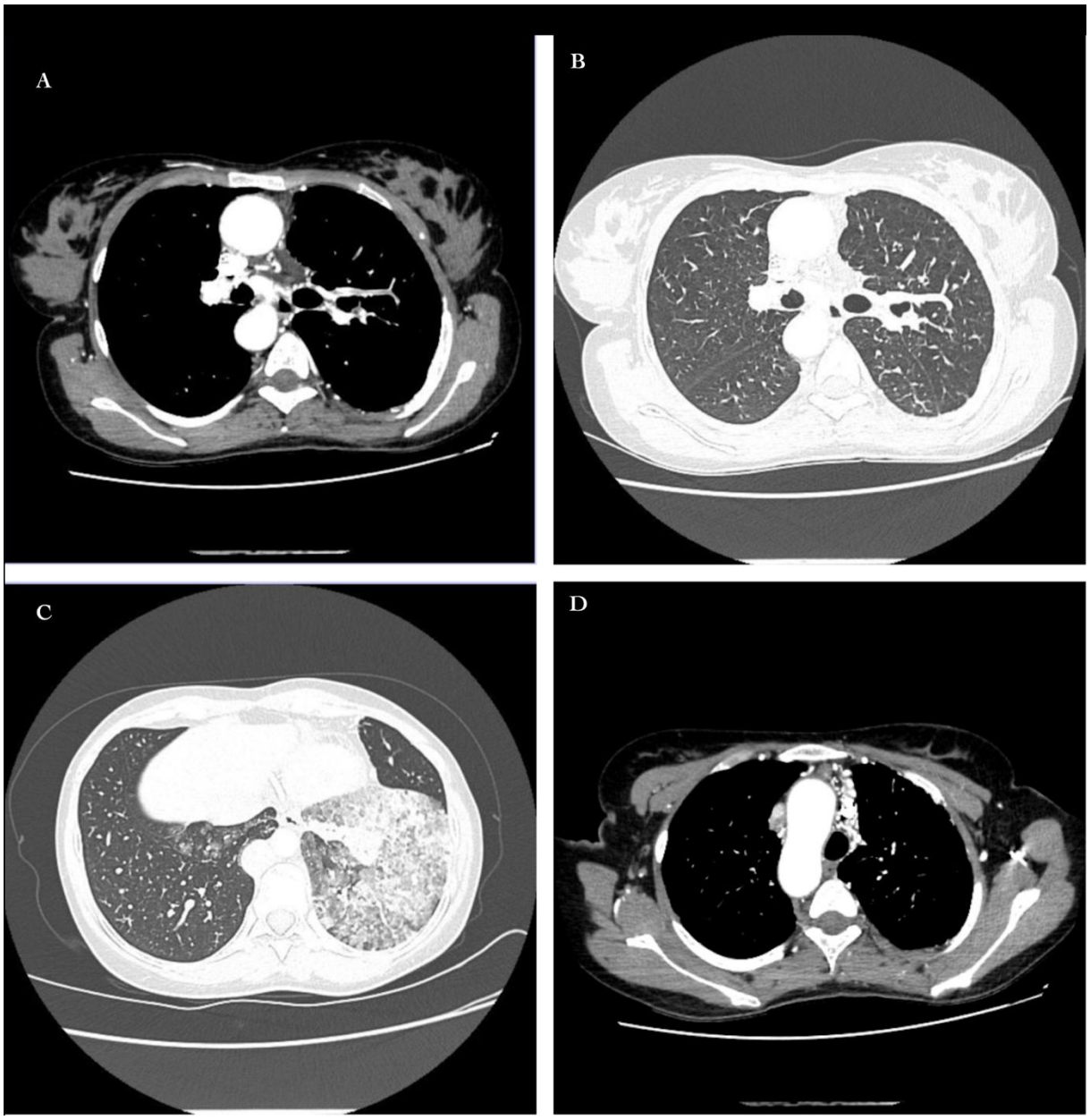

Fig. 2. A – Numerous collateral and additional pulmonary vessels – mediastinal window; B – Numerous collateral and additional pulmonary vessels – pulmonary window; C – Ground-glass opacities and infiltrations in left lower lobe; D – Web of additional vessels originating from descending aorta.

Case 2

A 21-year-old female patient with Melnick-Needles syndrome, height 1.45 m, weight 30 kg, was admitted to the Department of Pulmonary Diseases for a diagnostic and therapeutic bronchoscopy, as there was a suspicion of secretion retention due to massive bronchiectasis. Melnick-Needles syndrome is a very rare osteochondrodysplasia caused by mutations in the *FLNA* gene, which encodes filamin A. Patients with this condition typically have unusual facial features, ribs and long bones deformities and scoliosis. More severe cases are associated with respiratory failure secondary to the chest wall abnormalities [5,6].

Due to the size of the respiratory tract (diameter of the trachea estimated at 10 mm and main bronchi at 7 mm based on chest CT scan), the patient was disqualified from FOB at other tertiary care clinics.

On May 20–22, 2025, the patient was hospitalized in the Clinical Department of Internal Medicine, Pneumology and Allergology 4th Military Clinical Hospital in Wroclaw due to a reported desaturation < 80% SpO_2 during physical activity and an increasing sensation of secretion retention in the respiratory tract over the previous month. The patient has previously been treated with azithromycin and clindamycin without clinical improvement. The patient has been undergoing nasal oxygen therapy at home at a flow

rate of 1 L/min for a month. For the last five years, the patient has also been treated with NIV due to chronic respiratory failure.

The patient's medical history included medical observation for pulmonary hypertension following AH1N1 pneumonia in 2013, but no invasive diagnostic procedures were performed. The patient's medical history also includes surgical correction of the mandible due to micrognathia in 2021.

A chest CT scan on May 21, 2025, revealed skeletal abnormalities, areas of ground glass opacity and heterogeneous lung parenchyma density, as well as thoracic kyphoscoliosis and progression of peribronchial consolidations. An attempt to perform spirometry was unsuccessful.

A decision was made to perform interventional bronchoscopy using HFNOT to reduce the risk of barotrauma associated with high inspiratory pressures applied during NIV.

Bronchoscopy was performed under local anesthesia using lidocaine spray and analgo-sedation. The initial HFNOT settings were 40 L/min, FiO_2 = 40%, temperature 37°C. After inserting the bronchoscope, a reduction of SpO_2 to 86% was noted, most likely due to effect of benzodiazepine on the respiratory drive. Therefore, the HFNOT settings were adjusted to a flow rate of 60 L/min and FiO_2 of 50%. As hypoxemia persisted, the settings were further increased to flow rate of 70 L/min and FiO_2 of 100%, which enabled safe bronchoscopy without respiratory distress throughout the procedure.

During the procedure, features of chondromalacia and mucosal oedema were visible in the bronchi of the left lung. During suctioning, the bronchial lumen collapsed. Numerous fragments of deformed sub-segmental cartilages were visible in the lobar and segmental bronchi, bulging into the lumen of the respiratory tract. In the right lung bronchi, mainly in the main, lobar and segmental sections, numerous fragments of deformed bronchial cartilage were visible, bulging into the airway lumen. Material was collected for histopathological, bacteriological and mycological examination. Arterial blood gas analysis performed after bronchoscopy revealed: pH = 7.38, PO_2 84 mmHg, PCO_2 49 mmHg and saturation 98%.

Notably, a standard adult-sized bronchofiberoscope was used during the procedure, which allowed for the assessment of subsegmental bronchi openings. We conclude that the measurements of the bronchi and trachea based on CT were underestimated due to their collapse caused by cartilage defects in the course of Melnick-Needles syndrome.

DISCUSSION

Bronchoscopy is becoming an increasingly common procedure for patients with respiratory failure. In patients with severe or impending respiratory decompensation, exacerbations of respiratory failure can occur, which pose a risk to the patient's life. In cases of advanced respiratory failure, respiratory support in the form of invasive or non-invasive mechanical ventilation is necessary. When selecting a support method, it should be taken into account that airway resistance increases to the fourth power of the radius (Hagen–Poiseuille law).

Therefore, anatomical changes leading to airway stenosis may pose a risk of barotrauma or hypoventilation, which may result in respiratory acidosis and exacerbation of respiratory failure due to the generation of high positive pressure during invasive or non-invasive mechanical ventilation.

In both cases, positive airway pressure may cause complications such as bleeding or hemorrhage from the respiratory tract. In patient 1, there was also a risk of significant hypotension resulting from circulatory failure. In patient 2, the risk was caused by potential barotrauma and/or hypoventilation. Inducing turbulent flow and flushing out the anatomical dead space with HFNOT allowed the procedure to be performed safely in both cases.

However, NIV is important for patients with respiratory failure requiring bronchoscopy, and the respiratory support technique can usually be chosen based on blood gas analysis [7].

Furthermore, a meta-analysis revealed that the use of NIV after cardiac surgery in adults has no effect on the incidence of cardiac and pulmonary complications or intubation rates [8], which contrasts with the aforementioned pediatric study [3].

In special situations, the anatomical conditions of the respiratory tract, as well as conditions resulting from the size and capacity of the circulatory system – which may be disturbed by excessive chest pressure – will require the use of respiratory support methods that are not primarily based on the severity of initial respiratory failure and the required respiratory support, but on the risk of complications associated with comorbidities.

The use of HFNOT may enable safe bronchoscopy in high-risk patients, who would otherwise be disqualified from this procedure.

When using a bronchoscope, the external diameter is 5.4 mm in adults and 3 mm in children, while the biopsy

channel diameter is 3.0 mm in adults and about 1.0 mm in children, which significantly limits the working channel and diagnostic possibilities. Furthermore, introducing a larger bronchoscope into the respiratory tract during respiratory support, considering the Hagen–Poiseuille law, requires higher pressure to ensure the proper ventilation of the patient. This increases the risk of complications, such as barotrauma, particularly in patients with anatomical airway narrowing. Using HFNOT, we were able to perform the examination on patients who were initially disqualified due to the risk of exacerbating respiratory failure, thus avoiding complications such as barotrauma.

Prospective randomized studies are necessary to determine precise indications for selecting the optimal form of respiratory protection for high-risk patients requiring FOB.

Announcement

We obtained written consent from both patients for publication of the clinical case.

Conflict of interest

There was no conflict of interest.

Financial disclosure

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Authors' contribution

Study design – A. Oraczewska, M. Zieliński, S. Skoczyński, I. Zielińska-Leś
Manuscript preparation – A. Oraczewska, M. Zieliński, S. Skoczyński, M. Rycerski, P. Rzepka-Wrona, I. Zielińska-Leś
Literature research – A. Oraczewska, M. Zieliński, S. Skoczyński, M. Rycerski, P. Rzepka-Wrona,
Final approval of the version to be published – A. Oraczewska, M. Zieliński, S. Skoczyński, I. Zielińska-Leś

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PRACA ORYGINALNA
ORIGINAL PAPER

The influence of betulin and its derivatives on the expression of TNF and its receptors in RPTEC cells

Wpływ betuliny i jej pochodnych na ekspresję TNF i jego receptorów w komórkach RPTEC

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ABSTRACT

INTRODUCTION: Despite their promising anticancer properties, betulin derivatives may have serious side effects, including nephrotoxicity. Tumor necrosis factor (TNF) and its receptors may play crucial roles in renal cells' reaction to these compounds. The aim of this study was to examine the effect of the derivatives EB5 and ECH147 on renal cell expression of TNF and its receptors.

MATERIAL AND METHODS: Human renal proximal tubule epithelial cells (RPTECs) were treated with betulin, EB5, and ECH147, as well as cisplatin and 5-fluorouracil. The transcript levels of the genes *TNF*, *TNFR1*, and *TNFR2* were assessed using real-time RT-qPCR. Protein concentrations in the culture media were determined using ELISA.

RESULTS: The transcriptional activity of the gene *TNF* was induced in cells treated with 0.5 µg/mL betulin or ECH147. Similar changes in transcriptional activity were observed for *TNFR1*. Betulin and its derivatives strongly inhibited the expression of *TNFR2*. No TNF or sTNFR2 proteins were detected in the culture media. EB5 downregulated sTNFR1 release in comparison with the other compounds.

CONCLUSIONS: EB5 at low concentrations may be less harmful to renal cells. The lower toxicity of EB5 may be a result of the altered expression of TNF and its receptors.

KEYWORDS

betulin, betulin derivatives, TNF, TNFR1, TNFR2, RPTEC

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STRESZCZENIE

WSTĘP: Pomimo obiecujących właściwości przeciwnowotworowych pochodne betuliny mogą powodować poważne skutki uboczne, w tym nefrotoksyczność. Czynnik martwicy nowotworu (*tumor necrosis factor* – TNF) i jego receptory mogą odgrywać kluczową rolę w reakcji komórek nerkowych na te związki. Celem badania było określenie wpływu pochodnych EB5 i ECH147 na ekspresję TNF i jego receptorów w komórkach nerkowych.
MATERIAŁ I METODY: Ludzkie komórki nabłonkowe kanalika proksymalnego nerki (*renal proximal tubule epithelial cells* – RPTECs) poddano działaniu betuliny, EB5 i ECH147, a także cisplatyny i 5-fluorouracylu. Poziomy transkryptów genów *TNF*, *TNFR1* i *TNFR2* oceniono z użyciem RT-qPCR w czasie rzeczywistym. Stężenia rozpuszczalnych form białek w podłożu hodowlanym określono za pomocą testu ELISA.
WYNIKI: W komórkach poddanych działaniu 0,5 µg/ml betuliny lub ECH147 stwierdzono nasilenie aktywności transkrypcyjnej genu *TNF*. Podobne zmiany w aktywności transkrypcyjnej zaobserwowano dla genu *TNFR1*. Betulina i jej pochodne silnie hamowały ekspresję *TNFR2*. W pożywkach hodowlanych nie wykryto rozpuszczalnej formy białka TNF oraz sTNFR2. EB5 zmniejszyło uwalnianie sTNFR1 w porównaniu z innymi związkami.
WNIOSKI: EB5 w niskich stężeniach może być mniej szkodliwy dla komórek nerkowych. Niższa toksyczność EB5 może wynikać ze zmienionej ekspresji TNF i jego receptorów.

SŁOWA KLUCZOWE

betulina, pochodne betuliny, TNF, TNFR1, TNFR2, RPTEC

INTRODUCTION

Betulin, a lupane-type triterpenoid (lup-20(29)--en-3*β*,28-diol), is a compound obtained from birch bark and known for its anti-inflammatory, antioxidant and anticancer properties [1,2]. However, this compound is characterized by poor bioavailability, which prompts the search for derivatives with better pharmacokinetic properties and greater activity. A large pool of candidates is betulin derivatives, with anticancer activity against various cell lines of breast cancer, lung cancer, prostate cancer, colon cancer, and human and murine leukemia cells [3,4,5,6,7]. Structurally, these derivatives indicate that the preferred modification of the betulin structure is to introduce substituents containing a carbon–carbon triple bond [8,9,10]. Numerous studies have confirmed that introducing this type of moiety into the C-28 position of betulin produces compounds with desirable pharmacological parameters. Examples of alkynyl betulin derivatives with promising anticancer activity are the compounds EB5 (a 28-propynoyl derivative) and ECH147 (a 29-diethylphosphonate analog) [11,12,13,14,15]. However, betulin derivatives, like most anticancer drugs, may have side effects due to negative impacts on normal tissues that can lead to disorders such as nephrotoxicity [16].
Depending on the drug, the particular mechanism of nephrotoxicity may be crystal precipitation and drug accumulation in renal tubules, increased oxidative stress, induction of tubular injury, or proximal tubule dysfunction [16]. A recent study showed that the derivatives EB5 and ECH147 influence the viability of human renal proximal tubule epithelial cells (RPTECs) and change their antioxidant status through different mechanisms than those that drive betulin or cisplatin responses [17]. This difference is promising and provides hope for the development of safe anticancer drugs. However, the toxicity of these derivatives may result from other molecular changes, including altered expression of cytokines such as tumor necrosis factor (TNF).
TNF is a pleiotropic cytokine that is involved in the activation of many intracellular pathways through two receptors: TNFR1 and TNFR2 [18]. It may induce cell proliferation or cell death or may activate genes involved in processes such as inflammatory response. The influence of TNF on a particular cell type depends on receptor expression and signal transduction in that cell; these features may differ between cell types. TNF and its receptors are expressed by many cells, though the expression and activation of TNFR2 are restricted to specific cell types [18]. Previous research has shown that genes encoding TNF and its receptors are active in human RPTECs [19] and that an amphotericin B–copper II ion complex (AmB–Cu^{2+}) influences the expression of TNF and its receptors in a different way than amphotericin alone. In RPTECs, the complex was less toxic than amphotericin and promoted different expressions of genes involved in intracellular signaling. In the current study, we examined whether betulin derivatives have different effects than betulin itself regarding the expression of TNF and its receptors. To date, the effects of these compounds on the genes encoding TNF, TNFR1, and TNFR2 in kidney cells have not been investigated.

MATERIAL AND METHODS

Synthesis of EB5 and ECH147

The betulin derivatives EB5 (a 28-propynoyl derivative) and ECH147 (a 29-diethylphosphonate

analog) were synthesized at the Department of Organic Chemistry of the Faculty of Pharmaceutical Sciences in Sosnowiec (SUM), according to previously described procedures. The compound ECH147 was obtained through a several-stage modification of the betulin molecule: it was transformed into a 3,28-diacetyl derivative, then a bromine atom was introduced in the C-30 (allyl) position, and then replaced with a diethylphosphonate group in the Michaelis–Arbuzov reaction. Deacetylation (C-3 and C-28 positions) combined with isomerization to the vinyl system (C-29) resulted in 29-diethoxyphosphorylbetulin [14]. The ECH147 and EB5 used in the research were created in a reaction with propiolic acid (29-diethoxyphosphorylbetulin and betulin, respectively) [11,15]. The synthesis was carried out using the Steglich method, which is suitable for esterifying substrates which are sensitive to strongly acidic environments [20].

The target compounds were purified by column chromatography. Their identity and purity were assessed by determining their melting points and analyzing their ^{1}H and ^{13}C NMR spectra; for the ECH147, its ^{31}P NMR spectrum was also analyzed. The results corresponded to literature data [11,15].

Conditions of cell culturing

Normal human RPTECs (CC-2553) were cultured with the use of a REGM Bullet Kit CC-3190 (renal epithelial basal medium [REBM]), supplements, and growth factors (SingleQuots) at 37°C in a 5% CO_2 incubator (Direct Heat CO_2; Thermo Fisher Scientific). The RPTECs were seeded 5×10^5 per well on 6-well plates (Greiner Bio-One GmbH) and left overnight. Following previous research, the cells were treated for 24 h with two concentrations of each tested compound: 0.1 and 0.5 μg/mL [17]. Each experiment variant was performed in triplicate.

Total RNA extraction

Total cellular RNA was extracted using TRIzol reagent (Invitrogen Life Technologies), according to the manufacturer's instructions. The RNA extracts were purified and subjected to qualitative and quantitative analysis.

Real-time RT-qPCR

The transcripts' levels were assessed with the following oligonucleotide Taq-Man® Assays (Thermo Fisher Scientific): TNFA (Assay ID: Hs00174128_m1), TNFRSF1A (Assay ID: Hs01042313_m1), and TNFRSF1B (Assay ID: Hs00961750_m1). The real-time RT-qPCR analysis was carried out using a GoTaq® Probe 1-Step RT-qPCR System (Promega Corporation) and a LightCycler® 480 Instrument II (Roche). The mRNA copy numbers were recalculated per 1 μg of total RNA.

Concentration of proteins

The concentrations of TNF, sTNFR1, and sTNFR2 proteins in the culture medium were determined with the use of immunoenzymatic tests (R&DSystems Inc.) according to the supplied protocols: a Human TNF-alpha Quantikine ELISA Kit, a Human TNF RI/TNFRSF1A Quantikine ELISA Kit, and a Human TNF RII/TNFRSF1B Quantikine ELISA Kit. The concentrations were calculated from optical density readings at 450 nm with a BioTek Epoch Microplate Spectrophotometer (BioTek Instruments, Agilent Technologies).

Statistical analysis

The statistical analysis was performed using Statistica v. 13.3 software (TIBCO Software Inc.). The normality of the distribution was assessed by the Shapiro–Wilk test. The Kruskal–Wallis test (ANOVA) followed by the Mann–Whitney U test were used to evaluate differences between the groups of cells in the level of mRNA and the protein concentrations of TNF, TNFR1, and TNFR2. All results are expressed as median and quartile range (significance was set at $p < 0.05$).

RESULTS

TNF mRNA

Treatment with 0.5 μg/mL of ECH147 or betulin increased the expression of the gene *TNF* compared to 0.5 μg/mL of 5-FU ($p = 0.0027$ and $p = 0.0024$, respectively), cisplatin ($p = 0.0081$ and $p = 0.0033$, respectively), or EB5 ($p = 0.0171$ and $p = 0.0108$, respectively), as well as the control cells ($p = 0.0036$ and $p = 0.0033$, respectively; Figure 1). Cisplatin at 0.1 μg/mL downregulated *TNF* expression compared to the untreated control cells ($p < 0.001$) and compared to 0.1 μg/mL of betulin ($p = 0.0004$), ECH147 ($p = 0.0006$), EB5 ($p = 0.0062$), or 5-FU ($p = 0.0004$). Both betulin and cisplatin showed dose-dependent responses, in which higher concentrations induced greater *TNF* gene expression ($p = 0.0108$ and $p = 0.0272$, respectively).

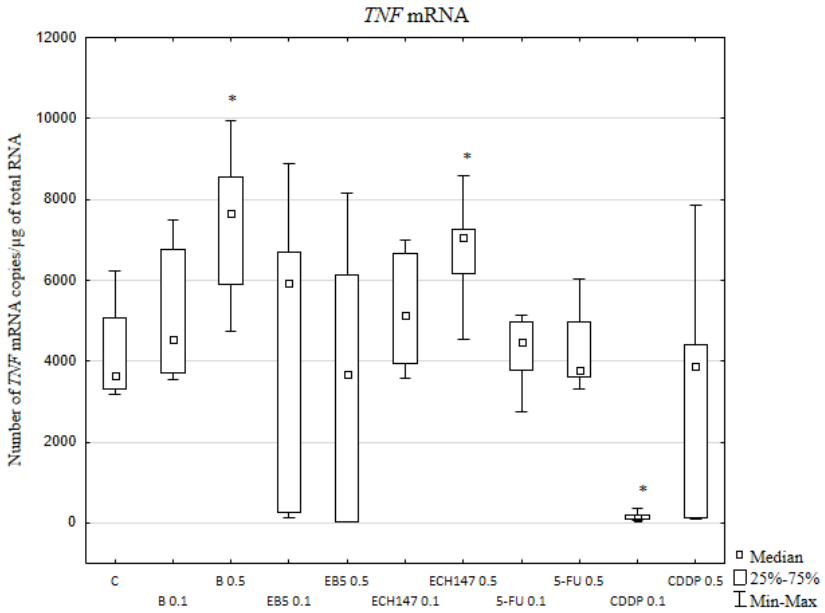

Fig. 1. Number of *TNF* mRNA copies (per 1 µg of total RNA) in the RPTECs after treatment with the tested compounds. C – control (untreated cells); B 0.1 – betulin at 0.1 µg/mL conc.; B 0.5 – betulin at 0.5 µg/mL conc.; EB5 0.1 – EB5 at 0.1 µg/mL conc.; EB5 0.5 – EB5 at 0.5 µg/mL conc.; ECH147 0.1 – ECH147 at 0.1 µg/mL conc.; ECH147 0.5 – ECH147 at 0.5 µg/mL conc.; 5FU 0.1 – 5-fluorouracil at 0.1 µg/mL conc.; 5FU 0.5 – 5-fluorouracil at 0.5 µg/mL conc.; CDDP 0.1 – cisplatin at 0.1 µg/mL conc.; CDDP 0.5 – cisplatin at 0.5 µg/mL conc.; *statistical significance ($p < 0.05$) in comparison to the controls; data represents medians and quartile ranges.

TNFR1 mRNA

The changes observed in the transcriptional activity of *TNFR1* in the RPTECs were similar to those observed for *TNF* (Figure 2). Compared to control cells, treatment with betulin at 0.5 µg/mL or ECH147 at 0.5 µg/mL or 0.1 µg/mL induced the expression of *TNFR1* ($p = 0.0062$, $p = 0.0045$, and $p = 0.0485$, respectively). This expression was downregulated after treatment with 0.1 µg/mL of cisplatin ($p = 0.0004$) or 0.5 µg/mL of EB5 ($p = 0.0171$).

Both betulin and cisplatin showed dose-dependent responses, where higher concentrations induced greater expression of *TNFR1* ($p = 0.0062$ and $p = 0.0104$, respectively). Conversely, the higher concentration of 5-FU (0.5 µg/mL) downregulated *TNFR1* gene expression ($p = 0.0006$).

As in the case of *TNF*, treatment with 0.5 µg/mL of betulin increased the number of mRNA copies of *TNFR1* compared to cells treated with 0.5 µg/mL of EB5 ($p = 0.0004$), 5-FU ($p = 0.0004$), or cisplatin ($p = 0.0047$). Treatment with 0.1 µg/mL of betulin or 5-FU decreased *TNFR1* expression compared to cells treated with 0.1 µg/mL of cisplatin ($p = 0.0004$). ECH147 at 0.1 or 0.5 µg/mL increased the *TNFR1* mRNA level compared to cells treated with 5-FU ($p = 0.0006$ and $p = 0.0006$, respectively) or cisplatin ($p = 0.0006$ and $p = 0.0045$, respectively). Treatment with 0.1 µg/mL of ECH147 increased *TNFR1* expression compared to cells treated with EB5 ($p = 0.0006$).

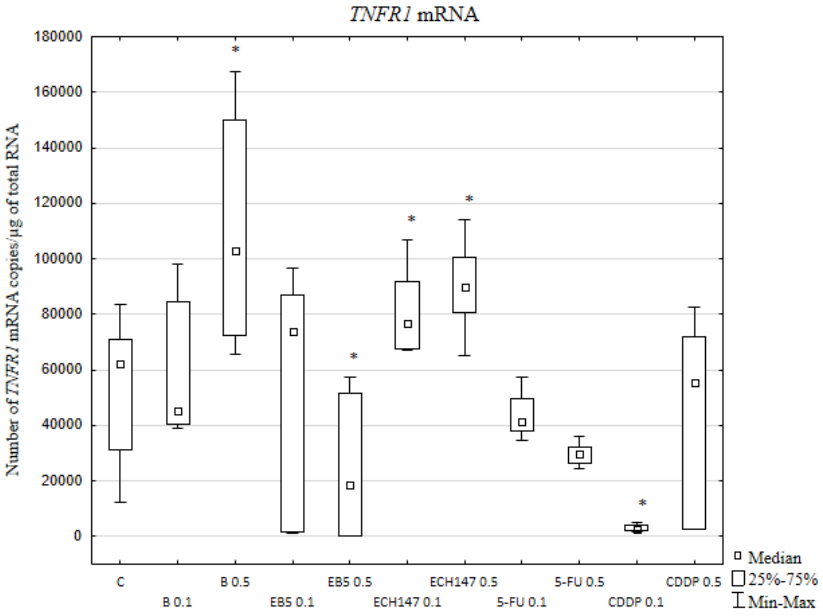

Fig. 2. Number of *TNFR1* mRNA copies (per 1 µg of total RNA) in the RPTECs after treatment with the tested compounds. C – control (untreated cells); B 0.1 – betulin at 0.1 µg/ml conc.; B 0.5 – betulin at 0.5 µg/ml conc.; EB5 0.1 – EB5 at 0.1 µg/ml conc.; EB5 0.5 – EB5 at 0.5 µg/ml conc.; ECH147 0.1 – ECH147 at 0.1 µg/ml conc.; ECH147 0.5 – ECH147 at 0.5 µg/ml conc.; 5FU 0.1 – 5-fluorouracil at 0.1 µg/ml conc.; 5FU 0.5 – 5-fluorouracil at 0.5 µg/ml conc.; CDDP 0.1 – cisplatin at 0.1 µg/ml conc.; CDDP 0.5 – cisplatin at 0.5 µg/ml conc.; *statistical significance ($p < 0.05$) in comparison to the controls; data represents medians and quartile ranges.

TNFR2 mRNA

Treating the RPTECs with betulin or its derivatives, regardless of the concentration, strongly inhibited the expression of the gene *TNFR2* (Figure 3). This inhibition was statistically significant compared to the expression in the control cells, for both concentrations of 5-FU and for cisplatin at 0.5 µg/mL ($p < 0.001$). *TNFR2* gene expression was higher in the cells treated with 0.1 µg/mL of 5-FU than in those treated with 0.1 µg/mL of CDDP ($p = 0.0181$).

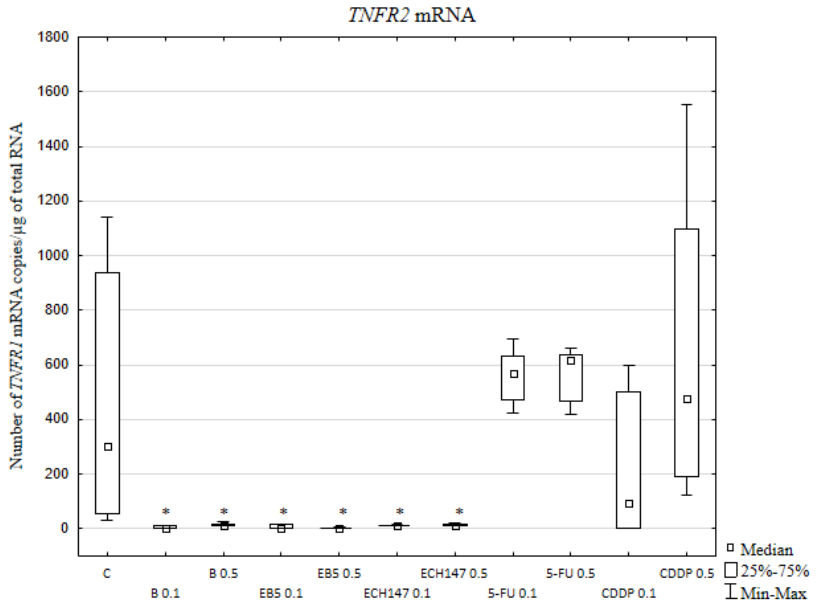

Fig. 3. Number of *TNFR2* mRNA copies (per 1 µg of total RNA) in the RPTECs after treatment with the tested compounds. C – control (untreated cells); B 0.1 – betulin at 0.1 µg/ml conc.; B 0.5 – betulin at 0.5 µg/ml conc.; EB5 0.1 – EB5 at 0.1 µg/ml conc.; EB5 0.5 – EB5 at 0.5 µg/ml conc.; ECH147 0.1 – ECH147 at 0.1 µg/ml conc.; ECH147 0.5 – ECH147 at 0.5 µg/ml conc.; 5FU 0.1 – 5-fluorouracil at 0.1 µg/ml conc.; 5FU 0.5 – 5-fluorouracil at 0.5 µg/ml conc.; CDDP 0.1 – cisplatin at 0.1 µg/ml conc.; CDDP 0.5 – cisplatin at 0.5 µg/ml conc.; *statistical significance ($p < 0.05$) in comparison to the controls; data represents medians and quartile ranges.

Protein concentrations in culture media

Neither TNF nor sTNFR2 was detected in the culture media. The concentration of sTNFR1 was higher in the medium from cells treated with cisplatin at either concentration ($p < 0.006$), those treated with ECH147 ($p < 0.006$), 0.1 µg/mL of 5-FU ($p = 0.0051$), 0.1 µg/mL of betulin ($p = 0.005$), or 0.5 µg/mL of EB5 ($p = 0.0082$), compared to the untreated control cells (Figure 4). Treatment with 0.1 µg/mL of EB5 downregulated sTNFR1 release compared to treatment with 0.1 µg/mL of ECH147, betulin, 5-FU, or cisplatin ($p < 0.006$). Treatment with 0.1 µg/mL of betulin upregulated sTNFR1 compared to treatment with ECH147 and cisplatin ($p < 0.007$). Treatment with 0.5 µg/mL of ECH147 increased sTNFR1 release compared to treatment with EB5 or 5-FU ($p < 0.006$). A dose-dependent effect was noted only for 5-FU, where the lower concentration caused a higher level of sTNFR1 in the culture medium ($p = 0.005$).

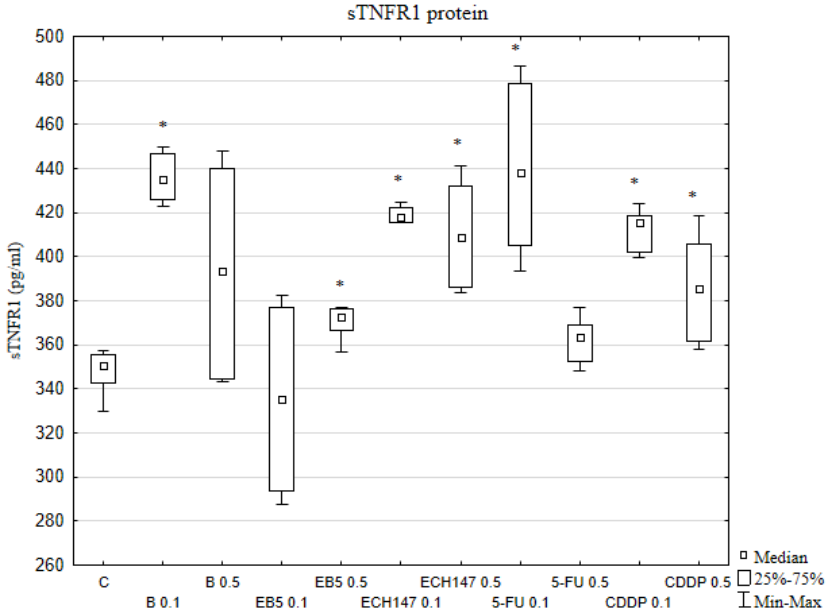

Fig. 4. Concentration of sTNFR1 in the RPTECs' culture media after treatment with the tested compounds. C – control (untreated cells); B 0.1 – betulin at 0.1 µg/ml conc.; B 0.5 – betulin at 0.5 µg/ml conc.; EB5 0.1 – EB5 at 0.1 µg/ml conc.; EB5 0.5 – EB5 at 0.5 µg/ml conc.; ECH147 0.1 – ECH147 at 0.1 µg/ml conc.; ECH147 0.5 – ECH147 at 0.5 µg/ml conc.; 5FU 0.1 – 5-fluorouracil at 0.1 µg/ml conc.; 5FU 0.5 – 5-fluorouracil at 0.5 µg/ml conc.; CDDP 0.1 – cisplatin at 0.1 µg/ml conc.; CDDP 0.5 – cisplatin at 0.5 µg/ml conc.; *statistical significance ($p < 0.05$) in comparison to the controls; data represents medians and quartile ranges.

DISCUSSION

Despite significant progress in the development of new anticancer drugs, cancer treatment remains a major challenge. The problem is not only the effectiveness of treatment, but also several adverse side effects that anticancer compounds have on normal cells. The most common issues are cardiotoxicity, hepatotoxicity, and nephrotoxicity [16]. The nephrotoxicity caused by anticancer drugs has been the subject of numerous studies and some of the mechanisms of its development are now known. For example, 5-FU increases apoptosis of mesangial cells and necrosis of tubular cells [21], while cisplatin, ifosfamide, and pemetrexed cause proximal tubulopathy [22]. Cisplatin has also been shown to induce oxidative stress in tubular cells and to increase the expression of several pro-inflammatory factors, including TNF, which plays an important role in the cisplatin-induced apoptosis of tubular cells [23]. However, the mechanisms of the nephrotoxicity induced by many drugs remain unclear. Therefore, molecular studies aimed at identifying potential mechanisms of nephrotoxicity of new compounds with anticancer activity are essential when assessing their potential use as treatments.

In the current study, for the first time, we evaluated the influence of the betulin derivatives EB5 and ECH147 on the expression of genes encoding TNF and its receptors in human RPTECs at the mRNA and protein levels (soluble forms in culture media). The involvement of TNF in renal damage has been proven in many studies [24]. For example, this cytokine causes apoptosis of renal cells (including tubular cells) while stimulating the expression of proinflammatory factors and the production of reactive oxygen species (ROS) [24]. Our previous research assessing the oxidative status of RPTECs showed that EB5 and ECH147 may be less harmful than betulin itself, which has similar effects on RPTEC antioxidant systems to those of cisplatin [17]. However, treatment with betulin and its derivatives caused significantly higher concentrations

of malondialdehyde (MDA) compared to the untreated control cells or those treated with 5-FU or cisplatin [17]. MDA forms adducts with proteins, resulting in modified intracellular signaling. MDA-acetaldehyde--protein activates protein kinase C, leading to the activation of NFκB [25]. It also activates intercellular adhesion molecule 1 and vascular adhesion molecule factors, which consequently leads to increased TNF expression [26]. In a previous study conducted on an animal model, Liu et al. [27] showed that cisplatin treatment induced the generation of ROS and MDA in the kidneys, while also activating the NFκB pathway and consequent expression of inflammatory cytokines, such as TNF, IL-6, and IL1β. This report prompted us to assess whether betulin and its derivatives are able to influence the expression of genes encoding TNF and its receptors, as these genes play crucial roles in the activation of pro-inflammatory pathways.

Our previous research showed that EB5 and ECH147 stimulated the expression of genes encoding antioxidant enzymes, suggesting an influence of these derivatives on molecular processes within the cell [17]. Interestingly, these compounds significantly increased the expression of each of these genes compared to control cells. In the current study, the expression of TNF and its receptors was higher or lower, depending on the compound and its concentration. It should also be stated that the expression of these genes was significantly lower than for those encoding antioxidant enzymes. In another study, we showed that betulin and its derivatives downregulated *TGFB1*, *BMP2*, and *GDF15* in RPTECs at the mRNA level [28]. Also, mRNA levels were significantly lower than those observed for genes encoding antioxidant enzymes. These results confirm that betulin and its derivatives may adversely influence gene transcription or may influence mRNA stability. However, other mechanisms responsible for changes in gene expression should also be taken into account. In addition, it is possible that for TNF and its receptors, as well as TGF-beta family members, fewer protein molecules are needed to obtain a cell response than in the case of antioxidant enzymes. In the current study, betulin and ECH147 caused a concentration-dependent stimulation of the expression of *TNF* and *TNFR1* at the transcriptional level (as indicated by the statistically significant differences compared to the untreated control cells), with 0.5 μg/mL of betulin having the strongest effect. Interestingly, the lower concentration of cisplatin tested here strongly downregulated the expression of these two genes. Both betulin and cisplatin showed a dose-dependent influence on *TNF* and *TNFR1* gene expression; however, the expression profile of *TNFR2* was totally unlike that of *TNF* and *TNFR1*. Betulin and its derivatives strongly downregulated the level of *TNFR2* mRNA at both concentrations. This downregulation effect was statistically significant when compared with the expression in the control cells, but also when compared to cells treated with 5-FU (either 0.1 or 0.5 μg/mL) and 0.5 μg/mL of cisplatin. We observed a similar effect in our previous study, where there was lower gene expression, especially of *BMP2* and *GDF15*, in cells treated with betulin and its derivatives.

Little is known about the expression of *TNFR2* in tubular cells exposed to cisplatin or 5-FU. In colorectal cancer cells, the TNFR2/NF-κB pathway plays an important role in the development of resistance to 5-FU [29]. Zhang et al. [30] showed that 5-FU induces *TNFR2* expression in RKO cells, which are sensitive to this drug. In our research, 5-FU treatment of RPTECs increased *TNFR2* gene transcription, as indicated by its higher mRNA level, suggesting that this gene has a protective role in the response of renal cells to this drug. However, Ramesh and Reeves [31], in studies conducted in a mouse model (C57BL/6), revealed that a lack of the gene *TNFR2* caused only minor renal dysfunction after treatment with cisplatin when compared to *TNFR1*-deficient and wild-type mice. They observed reduced apoptosis and necrosis of renal epithelial cells, as well as a diminished inflammatory response in the kidneys. These previous findings may suggest that both cisplatin and 5-FU can induce TNFR2-mediated apoptosis or necrosis of RPTECs. In our research, betulin and its derivatives strongly inhibited the expression of *TNFR2*, indicating that their impact on renal cells is not mediated by this receptor. However, the molecular mechanism of this effect needs further investigation, including analysis of the signaling pathways involved in gene regulation and *TNFR2* mRNA stability.

We also measured the amounts of the proteins TNF, sTNFR1, and sTNFR2 released into the culture media. Interestingly, TNF and sTNFR2 were not detectable in the culture media from cells treated with any of the test compounds or the controls. This is consistent with our previous research, in which we showed that neither unstimulated nor AmB-treated RPTECs released soluble forms of these proteins [19]. TNF receptors are responsible for mediating several functions of TNF, including the activation of cell death; however, they can also activate the MAP kinase and NFκB pathways, which promote cell survival, proliferation, and inflammation [18]. Overall, the result of TNF-induced signaling depends on the balance between TNFR1 and TNFR2 surface molecules and the recruitment of the proteins involved in forming intracellular signaling complexes [18]. TNFR2 is mostly involved in the promotion of cell survival and proliferation [18]; however, it can also indirectly induce cell death mediated by TNFR1. The sequestration of TRAF2 (TNF receptor associated factor) by TNFR2 may influence the formation of signaling complexes of activated TNFR1 [18]. TRAF2 is crucial for the

recruitment of the cellular inhibitors of the apoptosis proteins cIAP 1 and cIAP2, which are key factors in the activation of cell survival signaling via the NFκB, JNK, and p38 pathways [32].

The functions of TNF receptors also depend on the TNF form. Membrane-bound TNF (mTNF) may interact with soluble forms of TNF receptors to mediate reverse signaling, including activation of the pro-survival NFκB pathway [33]. Moreover, mTNF may interact with both soluble and transmembrane forms of TNFR2, leading to opposite effects [34]. Our studies cannot rule out the possibility that RPTECs retained mTNF and TNFR2 on their surfaces and that the cleavage of TNFR1 receptor molecules was crucial for their survival when exposed to the compounds tested in the present study. Nevertheless, a high level of sTNFR1 in the serum is a predictive factor in renal diseases [35,36,37]. In our study, a higher sTNFR1 concentration was observed in the culture media from RPTECs treated with ECH147 or cisplatin. By contrast, the effect of treatment with betulin, EB5, or 5-FU depended on the concentration. EB5 at 0.1 μg/mL downregulated the shedding of sTNFR1 when compared to the effects of ECH147, betulin, 5-FU, and cisplatin. This may indicate that EB5 may be less harmful to renal cells than ECH147 or betulin. However, we evaluated only the soluble forms of proteins released into the culture media; thus, a key limitation of our study is that it did not assess the transmembrane forms of TNF, TNFR1, and TNFR2. Moreover, without analyzing the activation of particular signaling pathways, we cannot conclude that EB5 is not harmful to renal cells. Negative effects may take longer to become apparent. This aspect needs further research that considers different doses and incubation times, because changes in intracellular signaling may depend on them. A further limitation is that we conducted our studies only on renal tubular epithelial cells, whereas the nephrotoxic effect of drugs may result from damage to other types of renal cells (e.g., mesangial cells) [21]. Additionally, conducting research on in vitro models precludes the study of critical interactions and changes occurring in intact kidney tissues, including the infiltration of immune cells, which can completely change these interactions. Therefore, our research is preliminary and these results should be treated with caution. However, our study shows for the first time the influence of betulin and EB5 and ECH147, its derivatives, on the expression of TNF and its receptors in RPTECs. Due to the essential and pleiotropic role of this cytokine in the regulation of many biological processes, the results may help to direct further studies.

CONCLUSIONS

This preliminary research suggests that the betulin derivative EB5, when supplied at a low concentration, may be less harmful to human RPTECs than betulin itself, indicating the possibility of its future use in therapy. The possible mechanism that provides this lower toxicity may result, at least in part, from altered expression of TNF and its receptors. However, the safety of EB5 use requires further research.

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Conflict of interest

The authors declare that they have no conflict of interest.

Authors' contribution

Study design – J.M. Gola, E. Bębenek, E. Chrobak
Data collection – C. Kruszniewska-Rajs, J. Adamska, J. Szota-Czyż
Data interpretation – J.M. Gola, C. Kruszniewska-Rajs, B. Strzałka-Mrozik
Statistical analysis – J.M. Gola
Manuscript preparation – J.M. Gola, E. Bębenek, E. Chrobak
Literature research – J.M. Gola, B. Strzałka-Mrozik

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PRACA ORYGINALNA
ORIGINAL PAPER

Assessment of the frequency of eating disorders among adolescents aged 13–19 residing in the Silesian Voivodeship

Ocena częstości występowania zaburzeń odżywiania u nastolatków w wieku 13–19 lat zamieszkujących województwo śląskie

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ABSTRACT

INTRODUCTION: Today's food products undergo continual technological progress in their production and processing. The development of knowledge about food – which should be healthy, varied, and able to be prepared quickly – it can be constantly improved upon and developed. However, this development also brings about eating disorders (EDs). One's social environment can also lead to the occurrence of EDs and the perception of one's figure. One of the greatest impacts comes from social media and the so-called influencers who shape people's body image. The aim of the study was to assess the frequency of EDs and knowledge about the type of EDs among adolescents aged 13–19 living in the Silesian Voivodeship. The research hypotheses were that the frequency of EDs is low and knowledge about them is high.
MATERIAL AND METHODS: A study of the frequency of EDs and knowledge about EDs among the 13–19-year-old population living in the Silesian Voivodeship was conducted between May and June 2023 on a representative group of 400 people. The sample included both males and females. The study used an original online survey.
RESULTS: Among the respondents who declared having knowledge of EDs, the highest number reported familiarity with anorexia. Only 4% stated that they were currently experiencing an ED for the first time, while 16% had struggled with an ED for the second time. Among individuals with EDs, as many as 79% did not consult a dietician; the remainder did not follow the prescribed diet plan.
CONCLUSIONS: The results of the research show that the hypotheses of a low incidence of EDs and a high level of knowledge about EDs was correct. In order to reduce the incidence of EDs and increase knowledge about them, nutritional education and information campaigns on EDs and their treatment should be introduced.

KEYWORDS

adolescents, eating disorders, frequency, knowledge, environmental influence

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STRESZCZENIE

WSTĘP: Współczesne produkty spożywcze podlegają ciągłemu postępowi technologicznemu w zakresie produkcji i przetwarzania. Rozwój wiedzy o żywności – która powinna być zdrowa, urozmaicona i łatwa w przygotowaniu – pozwala na jej ciągłe doskonalenie. Jednak rozwój ten prowadzi także do zaburzeń odżywiania (*eating disorders* – EDs). Również środowisko społeczne może wpływać na występowanie EDs i postrzeganie własnej sylwetki. Jednym z największych źródeł wpływu są media społecznościowe i tzw. influencerzy, którzy kształtują obraz ciała. Celem badania była ocena częstości występowania EDs oraz wiedzy na temat rodzajów EDs u młodzieży w wieku 13–19 lat zamieszkującej województwo śląskie. Hipotezy badawcze zakładały niską częstość występowania EDs i wysoki poziom wiedzy na ich temat.

MATERIAŁ I METODY: Badanie częstości występowania EDs oraz wiedzy na temat EDs w grupie wiekowej 13–19 lat prowadzono w okresie od maja do czerwca 2023 r. na reprezentatywnej grupie 400 osób zamieszkujących województwo śląskie. Próba obejmowała zarówno mężczyzn, jak i kobiety. W badaniu wykorzystano autorską ankietę internetową.

WYNIKI: Wśród respondentów, którzy zadeklarowali znajomość EDs, najwięcej zgłosiło znajomość anoreksji. Tylko 4% zadeklarowało, że po raz pierwszy doświadcza ED, natomiast 16% zmagało się z ED po raz drugi. Wśród osób z EDs aż 79% nie konsultowało się z dietetykiem; pozostałe nie stosowały się do zaleconej diety.

WNIOSKI: Wyniki badań potwierdzają prawdziwość hipotez o niskiej częstości występowania EDs i wysokiej wiedzy na ich temat. W celu zmniejszenia częstości występowania EDs i zwiększenia wiedzy na ich temat należy wprowadzić edukację żywieniową oraz kampanie informacyjne dotyczące EDs i ich leczenia.

SŁOWA KLUCZOWE

młodzież, zaburzenia odżywiania, częstość występowania, wiedza, wpływ środowiska

INTRODUCTION

Today's food products enjoy continual technological progress in their production and processing. With the development of knowledge about food, it can be constantly improved upon and developed. In fact, all methods used today serve to improve the sensory characteristics, nutritional values, and shelf life of food products, and even allow for so-called "modified food." As a result, food should be healthy, varied, and able to be prepared quickly. However, there is a problem here, in that the limitations in available time and willingness brings about the increasingly frequent use of fast-food chains or restaurants. One social group is people who want to improve their image by eating properly selected and modified foods [1] as well as by eating precisely defined amounts, which does not always meet the nutritional requirements of the body. Such a model of food consumption can lead to pathological consumption.

Eating disorders (EDs) of various types are also a contemporary phenomenon posing a challenge to public health care systems. According to Nelson's research, bulimia affects 0.1–1.4% of men and 0.3–9.4% of women [2]. Other studies from the 1980s show that, even then, the incidence of anorexia was 0.1–5.7% among teenage girls in Western countries [3]. Numerous studies show that there are many factors behind EDs. They may be caused by biological, psychological, behavioral, and even social and cultural phenomena [1]. In the youngest group, the most important role is played by the family and social environment, while in adolescence it is the changes occurring in the hormonal system and the influence of peers [4,5].

Social media platforms such as Instagram, Facebook, and others also have a very clear impact on one's perception of oneself and one's body image. As Suma [6] writes, "[s]ocial media portals have begun to act as transmitters of information, and have undoubtedly also begun to create certain trends and fashions. They have become an entertainment tool in themselves, offering interesting ways of spending free time." There is a kind of body cult among today's youth. Currently, what counts is one's figure, degree of muscle tone, and amount of body fat. Although the above-mentioned determinants can be considered positive, some people (especially sensitive ones) may take these determinants too seriously, and as a result, they may take radical steps to "finally please others," which can result in the emergence of eating behaviors that bear signs of pathology. This risk is even greater because "the so-called influencers play a very important role in creating an online image," as noted by Andrzejewski [7]. It is also worth mentioning that these influencers are often sponsored by corporations that benefit from the dissemination of specific behavioral patterns among the consumers of their products [7]. It is also common practice to use special computer-applied filters to make their photos or videos look perfect and to emphasize or create a perfect figure. Thus, striving to imitate unrealistic patterns leads to pathologized behavior of the recipients of online content. EDs are thereby becoming a serious health problem, especially among young people, which requires attention and action from public policies.

Eating disorders

EDs are disease entities most often characterized by appetite and food intake disorders. In this way, they can

be defined as pathological behaviors that focus on increasing or decreasing one's body weight. According to the World Health Organization (WHO) and the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), they are classified as mental disorders.

Types of eating disorders

The ICD-10 distinguishes nine disorders: F50 – anorexia nervosa, F50.1 – atypical anorexia nervosa, F50.2 – bulimia nervosa, F50.3 – atypical bulimia nervosa, F50.4 – overeating associated with other psychological factors, F50.5 – vomiting associated with other psychological factors, F50.8 – other eating disorders, and F50.9 – eating disorders, unspecified. However, the most socially recognizable eating disorders are anorexia, bulimia, orthorexia, and compulsive overeating.

Anorexia

Anorexia is defined as anorexia nervosa, a chronic disorder characterized by intentional weight loss, which is maintained by the person [8]. This disease is also manifested by a fear of gaining weight and the consequent emergence of obsessive thoughts about reducing body weight, basically without limit [8]. Emotional factors are dominant in this disease. They can arise through excessive demands from one's social environment [9]. According to ICD-10, the criteria for anorexia are intentional weight loss, a reluctance to gain weight during development, a refusal to maintain the lowest body weight for one's age, a strong fear of gaining weight, and disturbance in body perception [10]. Complications of anorexia nervosa include emaciation, undesirable changes in the central nervous system (difficulty concentrating, epilepsy, and cortical atrophy), disorders in the cardiovascular system, loss of muscle strength, and inhibition of the development of the reproductive system [11].

Bulimia

Bulimia, also known as bulimia nervosa, is characterized by the consumption of a large amount of food (and therefore calories) in one sitting and then taking action to reduce weight by, for example, inducing vomiting [9]. Risk factors for this disease may include both stress and one's social environment. These patients care about being attractive in terms of their figure, which is why they reach for methods to get rid of fat tissue. There are two types of bulimia. The first is the purging type, using laxatives or inducing vomiting. The second is the non-purging type, using fasting or very intensive physical exercise [9,12]. Complications of bulimia may include circulatory system disorders, electrolyte deficiencies, low levels of micro- and macroelements, disorders in the reproductive system, and disorders in the nervous system [13,14].

Orthorexia

Orthorexia, also known as orthorexia nervosa, is a term that was introduced by Sven Bratman relatively recently – in 1997 in the magazine *Yoga Journal* [15]. It involves following a diet that is very rigorous in terms of health. Such people give up "new food" and food containing preservatives or dyes, instead choosing purely organic products and food that is not genetically modified [16]. In addition to choosing healthy, natural products, these people often choose healthy methods of preparing meals, plan their diet in advance [17], and eat at strictly defined times [18]. In addition, there is frustration and a sense of guilt when these activities are disrupted or unfulfilled [19,20].

Compulsive overeating

Compulsive overeating is a disease characterized by the uncontrolled consumption of large amounts of food. The aim is to satisfy one's emotions, alleviate stress, or even cut oneself off from the problems of the outside world [21]. In the ICD-10, it is marked as "F50.4 – overeating associated with other psychological factors" [22]. The etiology of the disease is given as the lack of an appropriate "ability to cope with one's own problems and experiences" [21]. Observations have also confirmed that compulsive overeating runs in families andthat this is based on so-called imitation [23]. Looking closely at the classification of this condition in the ICD-10, it should be noted that in order to diagnose compulsive overeating, all of the following symptoms must appear:

– episodes of overeating that are not the result of hunger, combined with a lack of compensatory behaviors
– a strong urge to eat (especially during stress, sadness, and bad mood)
– a lack of inhibition and self-control over consumption in terms of quantity and quality
– difficulty interrupting an ongoing attack [22].

The most noticeable differences between compulsive overeating and bulimia are the initiating factor (in the case of compulsive overeating, it is often emotional arousal) and the use of tools for inducing vomiting (only in the case of bulimia) [21].

Body image and its determinants

Self-esteem about one's own body is one of a person's most important characteristics. Polish researcher Kulas [24] defined self-esteem as "a set of various judgments and opinions that an individual applies to himself. These judgments and opinions may concern both the current characteristics of the

individual and his potential capabilities." Body image is particularly important among adolescents. It is at this time that the greatest importance is attached to appearance [25]. The environment in which one finds oneself has a significant impact on one's body image. It is influenced by family, cultural considerations, peer group, traditional and social media, and psychological conditions.

Family

The attitudes that are emphasized, especially by parents when raising a child, form patterns of behavior that will be used by the child later in their lives [26]. In addition, the family shapes various health attitudes, informs children about health and diseases, and teaches hygiene and pro-health attitudes, as well as, unfortunately, anti--health attitudes [27]. Using their health competences, parents also shape the child's body image by creating opinions [28].

Culture

Different countries are characterized by their own culture. Following this line of reasoning, it can be observed that in Western countries, the emphasis on a slim figure dominates, while in countries in the east of Europe, being overweight is preferable to being slim; in these countries obesity is more accepted in society [29,30]. African American women also accept their bodies more, and even prefer a larger mass than Caucasians of the same age [30]. However, this is not a permanent element of culture and is constantly changing.

Peer group

Among young people, peers also play a significant role in shaping a person's body image. While some peers will not pay much attention to other people, others will either support or ridicule the other person. An obese person is often exposed to stigmatization and humiliation. For a child's mental health, this is a very difficult experience often associated with negative stereotypes [31].

Social media

In the modern world, almost everyone has contact with social media such as Facebook, Instagram, Snapchat, or TikTok. On these platforms, a lot of content promotes a perfect appearance and ideal body weight. Children and adolescents who visit these sites may come across such content. By absorbing it, a person may start to believe in the message and to treat what they have seen as the truth. Influencers, who are to a large extent celebrities or athletes, are very active on Instagram and, thanks to their fame, they are seen as idols and role models and their fans start to take their message seriously. Lesser-known or even completely unknown people also publish content on their profiles, in which they encourage people to change their figure or even their overall image and behavior. To build recognition, often all that is needed is a catchy name and appearance. "Idealized, often excessively slim women, beautified by plastic surgeons, are considered the queens of Instagram," notes Andrzejewski [7].

Treatment of eating disorders

EDs are most often psychological diseases and they have negative health consequences. They should be treated by doctors, psychotherapists, and experts in nutrition. Dieticians play a major role in this, not only to guide the patient in proper nutrition, but also to help them overcome inappropriate weight and improper nutritional status and to maintain proper condition after therapy. Treatment of these disorders is time--consuming and long-term [32].

Treating anorexia

In the treatment of anorexia, the main role is played by nutritional and psychological treatment. The patient should be brought to a body weight that is appropriate to the age and anthropometric characteristics of the person. One of the formulas that can be used to calculate the correct body weight is Broca's formula, which assumes that the ideal body weight in kilograms is a person's height in centimeters minus 100. In some cases of extreme malnutrition, nasogastric feeding is necessary [32]. If the malnutrition is not yet extreme, some recommendations for natural nutrition suggest using an individual plan based on three main meals and three snacks [33]. Psychotherapeutic treatment is also an important part of hospitalization. This method uses both individual and group therapy methods, e.g., with the person's family [34]. Special medications are also often used, both those that stimulate appetite and antipsychotics, such as olanzepin [32]. Appetite stimulants include cannabinoids, opiates, and tetrahydroxycannabinol, but different studies have reported different effects of these agents [35]. Another important step is to correct water and electrolyte imbalances that accompany this disease [36].

Treating bulimia

The treatment of EDs such as bulimia is difficult and long-term. It must be coordinated between a doctor, a psychologist, and a dietician and should consist of psychological, nutritional, and pharmacological treatment [36]. The initial stage should be to compensate for electrolyte imbalances and to protect against dehydration. Psychotherapy plays an important role here [37]. It should be a psycho-behavioral therapy [38], which allows the therapist to get to know the

patient and create an individual approach to them. It is also important because it allows for work on the patient's emotions and can significantly reduce those that lead to bulimia [39]. In this disorder, pharmacotherapy should also be used, with the aim of reducing the psychological aspect of bulimia. For this purpose, antipsychotic and antidepressant drugs are used [36]. On the other hand, the task of the dietician is to restore an appropriate body mass index (BMI), compensate for any nutritional deficiencies – including macro- and microelements [36] – and to normalize body weight and discontinue the patient's current activities [40].

Treating orthorexia

The treatment of orthorexia is primarily based on a diet that is properly composed by a dietician and aims to supplement all deficiencies [16]. In this ED, as in others, diet therapy is not sufficient. Therefore, psychological treatment and/or pharmacological treatment should also be used. Pharmacological treatment includes selective serotonin reuptake inhibitors; "however, there is a certain dissonance in the pharmacological treatment of patients with orthorexia: if a given person has an obsession with the purity and naturalness of the diet, they may be terrified by the need to introduce artificial substances, such as drugs, into the body," as noted by Dittfeld et al. [18].

Treating compulsive overeating

The treatment of compulsive overeating is based on diet therapy, psychotherapy, and pharmacotherapy. Psychological treatment plays a huge role here, aiming to reduce the psychological factor of this disease, thus reducing the psychopathological ED [41]. Self--treatment, i.e., self-medication using educational materials, also plays an important role here [42]. Pharmacotherapy involves the use of drugs that can reduce or even completely eliminate the psychological causes of the disease. The basic drug classes are antidepressants, antiepileptics, and anticonvulsants.

Assumptions and goals of the work

The aim of the study was to assess the frequency of EDs and the knowledge about types of EDs among adolescents aged 13–19 living in the Silesian Voivodeship.

This objective was supplemented by the following specific objectives:

– Obtaining information on the occurrence of EDs among respondents
– Determining the knowledge about types of EDs among respondents
– Determining whether there have been any changes in body image
– Determining whether one's BMI value can contribute to one's body image
– Determining whether changes in body image may be conditioned by one's social environment.

The following null hypotheses were adopted in the study:

– The frequency of EDs does not exceed 25% of the study group.
– Knowledge about EDs is at a high level, above the established threshold of 1.5 points.

MATERIAL AND METHODS

This study to assess the frequency of EDs and the knowledge about EDs among the 13–19-year-old population living in the Silesian Voivodeship was conducted in May–June 2023 on a group of 400 people. The sample consisted of both males and females. Silesian Voivodeship – a unit of local government and an administrative division of Poland – has an area of 12,333.09 km². According to data from Statistics Poland for 2022, it is inhabited by approximately 4,346,702 inhabitants, of which 429,949 (220,007 boys and 209,942 girls) fall within the range of the study population.

All respondents completed a survey consisting of six demographic questions and 24 main questions:

– about the respondent's perception of their figure
– about their intention to change their body weight
– to check whether this goal has been achieved
– to determine whether their social environment can influence their perception of their body
– to verify their knowledge of EDs
– to determine whether they are currently struggling with any EDs.

A convenience sample was used. Respondents were recruited through a link to the survey distributed on the social networking platform Facebook among youth groups living in the Silesian Voivodeship and through a circle of friends who had family members meeting the criteria. The data were analyzed using Microsoft Excel, using the following statistical methods: sum, average, minimum, maximum, Cramer's V contingency coefficient (used to determine the strength of the relationship between qualitative variables), the coefficient Chi-square, and the p-value for the Chi--square test.

In order to determine the respondents' knowledge about EDs, the following score thresholds were used:

– Low level of knowledge: less than 0.5 points
– Average level of knowledge: 0.6–1.5 points
– High level of knowledge: over 1.5 points
– Incorrect definition: N% * 1
– Correct definition: N% * 2.

RESULTS

The largest percentage were females (77%; n = 309), while 2% of the respondents did not want to provide their gender (Figure 1).
The largest age group was 19-year-olds (26%; n = 102) and the second largest group was people aged 16 (23%; n = 93; Table I).

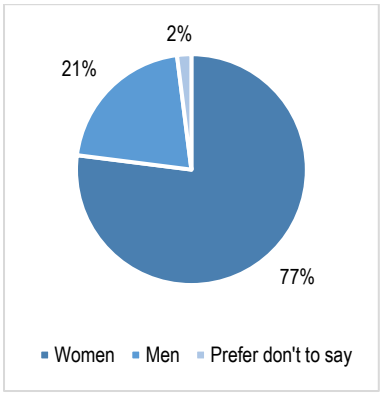

Fig. 1. Gender of respondents.

Table I. Age of respondents

Age of respondents (years)	Number of people	N (%)	Min/Max	Mean
13	3	1%		
14	19	5%		
15	65	16%		
16	93	23%	13 years/ 19 years	16.94 years
17	51	13%		
18	67	17%		
19	102	26%		

The height of the respondents was in the range of 135 cm to 200 cm. Only 1% (n = 4) of the study group was taller than 191 cm, while 78% (n = 312) were between 161 and 191 cm tall (Figure 2).

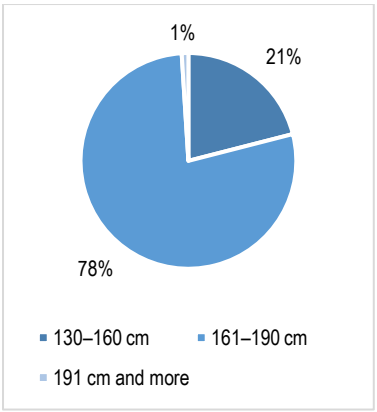

Fig. 2. Respondents' growth.

The body weight of the respondents ranged from 34.5 to 120.4 kg. The largest number of people (55%) weighed between 34 kg and 60 kg. Only 3% (n = 10) had a body weight greater than 91 kg (Figure 3).

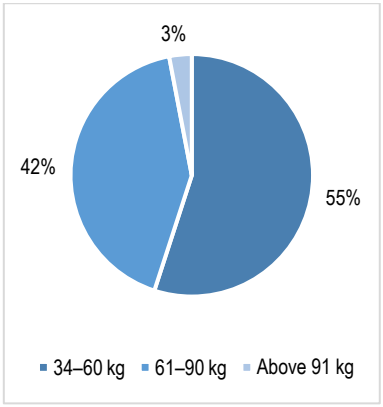

Fig. 3. Body weight of respondents.

The BMI and percentile index among the respondents varied. There were people with a normal BMI/percentile (64%), as well as those below the 10th percentile and with BMI below 18.4 kg/m^2 and those above the 90th percentile and a BMI above 25 kg/m^2 (Figure 4).

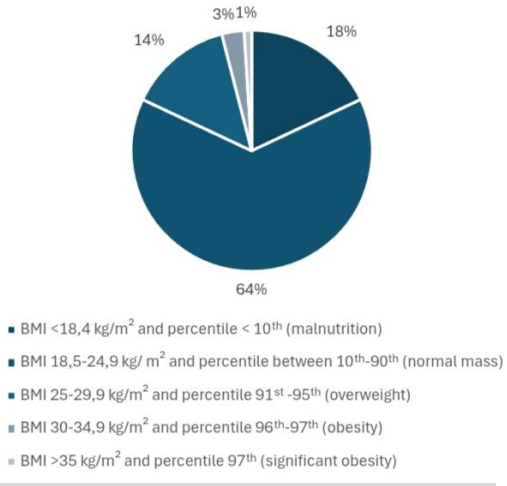

Fig. 4. Body mass index (BMI) and percentile of respondents.

The most common place of residence for respondents (41%; n = 165) was a city with more than 100,000 inhabitants. The smallest percentage (13%) of respondents came from towns with 50,000 to 100,000 inhabitants (Figure 5).
Seventy-one percent (n = 286) of the respondents indicated high school as their level of education. The smallest number (2%; n = 6) attended a vocational/trade school (Figure 6).

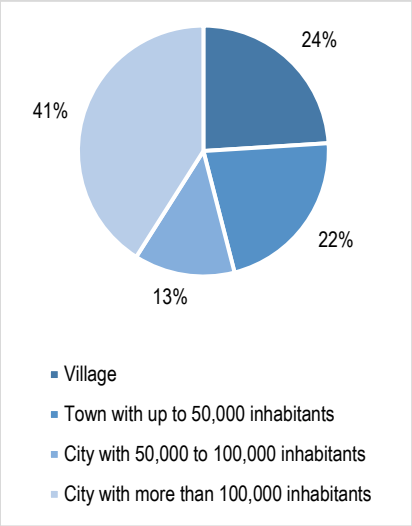

Fig. 5. Respondents' place of residence.

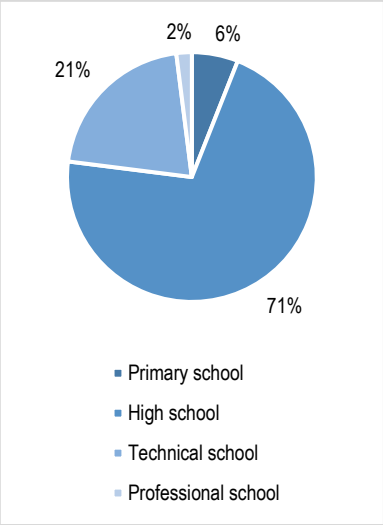

Fig. 6. Respondents' place of study.

Among all respondents with a normal BMI between 18.5 kg/m^2 and 24.9 kg/m^2 and between the 10th and the 90th percentiles, as many as 140 respondents (54%) considered their body shape to be appropriate. However, among the other respondents, only 30 (21%) considered their body shape appropriate (Table II).

Among the 140 respondents with a normal BMI who were positioned between the 10th and 90th percentiles and considered their body shape to be inappropriate, 66% (n = 92) considered themselves overweight, while only one person considered themselves underweight (Table III).

Table II. Respondents' perception of their body shape in relation to body mass index (BMI)/percentile

Figure based on BMI, WHO percentile charts, and OLA and OLAF studies	Number of people	N (%)	Respondent's perception of body shape	Number of people	N (%)
Appropriate	256	64%	appropriate	116	46%
			inappropriate	140	54%
Inappropriate	144	36%	appropriate	30	21%
			inappropriate	114	79%

WHO – World Health Organization; OLA – percentile grids for girls; OLAF – percentile grids for boys.

Table III. Perception of body shape by respondents with a normal body mass index (BMI)/percentile

Perception of body shape by respondents with a normal BMI who were between the 10th and 90th percentiles and considered their body shape to be inappropriate	Number of people	N (%)
Underweight	1	1%
Skinny	40	29%
Overweight	92	66%
Obese	7	5%

Of the 114 respondents who were aware that their body shape was abnormal based on BMI, the WHO percentile charts, and the percentile grids for girls (OLA) and for boys (OLAF) studies, 38 people indicated their body shape as thin, while the actual BMI and percentile indicated underweight. However, one person indicated their body shape as underweight, with the BMI/percentile indicating significant obesity. In the analysis of the relationship between the actual abnormal BMI/percentile and the perception of one's body shape, the p-value for Chi-square (105.4) was -0.000, which means that the relationship was statistically significant. The contingency coefficient was strong (Table IV).

Among the respondents with a BMI/percentile indicating a normal body mass, 98 perceived their figure as good (on a five-point scale) and 13 respondents as bad. Among the respondents with significant obesity, only one person perceived their figure as very good. The p-value for Chi-square (42.2584) was 0.0004, which means that the relationship was statistically significant; however, the strength of the relationship was weak, as indicated by the value of Cramer's V (Table V).

Table IV. Perception of body shape among respondents with abnormal body mass index (BMI)/percentile who considered their body shape inappropriate

Body shape according to BMI and percentile charts	Perception of body shape by respondents with abnormal BMI/percentile who considered their body shape to be inappropriate				Cramer's V	Correlation coefficient
	underweight	skinny	overweight	obese		
	number of people					
Underweight	2	38	12	2	0.56	strong
Overweight	0	1	42	4		
Obesity	0	0	4	6		
Severe obesity	1	0	0	2		

Table V. Perception of body shape by respondents on a five-point scale

Figure according to BMI and percentile charts	Perception of body shape					Cramer's V	Correlation coefficient
	1 (very bad)	2 (bad)	3 (neither bad nor good)	4 (good)	5 (very good)		
	Number of people						
Underweight	4	14	32	22	3	0.16	poor
Normal weight	13	41	81	98	23		
Overweight	5	20	19	9	2		
Obesity	3	3	4	1	0		
Severe obesity	1	1	0	0	1		

BMI – body mass index.

Among all respondents, 77% (n = 307) had intended to change their body weight in the past. Only 8% (n = 33) had no opinion (Figure 7).

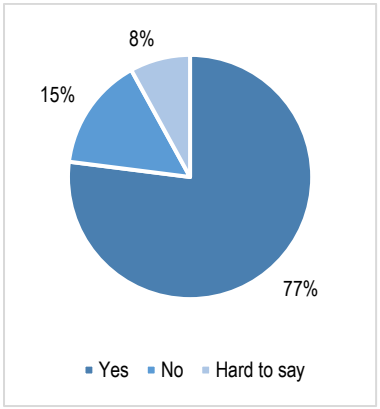

Fig. 7. Respondents' willingness to change body weight.

Of the 307 respondents who declared a desire to change their body weight, 86% (n = 264) wanted to lose weight, while only 43 people wanted to gain weight (Figure 8).

Among the respondents declaring the desire to change their body weight, only 36% (n = 112) achieved their intended goal (Figure 9).

Among the 64% of respondents who declared that they had not achieved their goal, the most common reason given was a lack of perseverance (n = 89), while the least common reason was a change of mind, which was declared by 19 respondents (Figure 10).

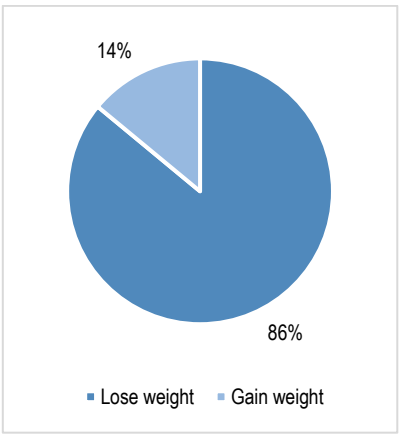

Fig. 8. Respondents' declaration regarding body weight change.

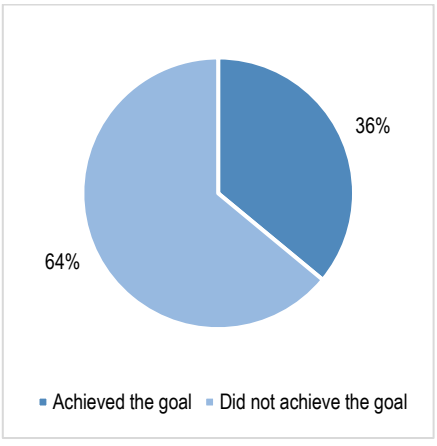

Fig. 9. Achievement of the respondents' goal to change body weight.

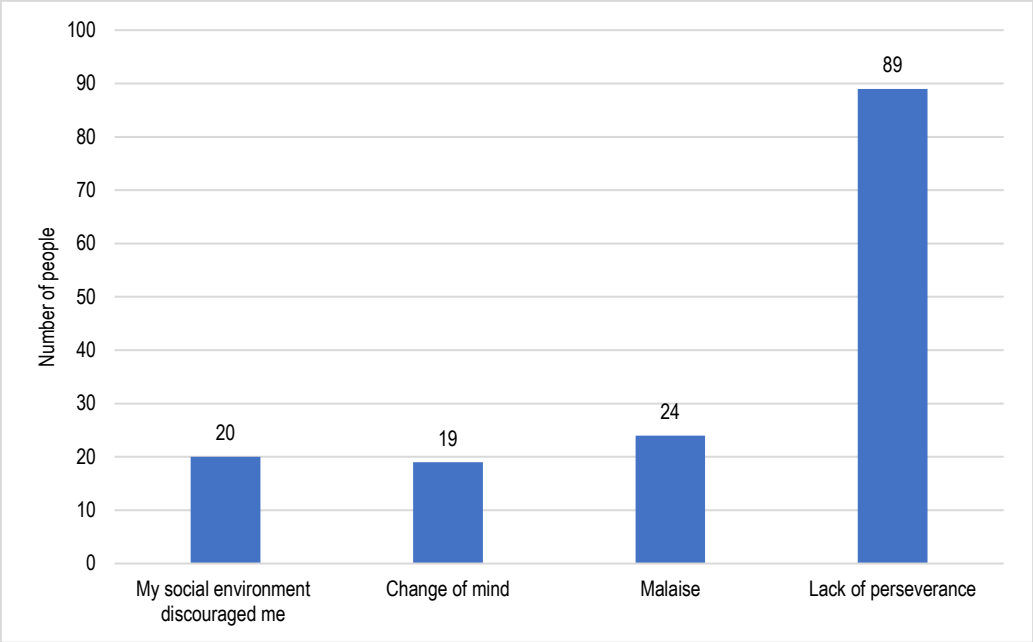

Fig. 10. Reasons for not achieving the goal.

Of all respondents, 94% (n = 378) declared that a person's social environment may influence their perception of their body shape (Figure 11).

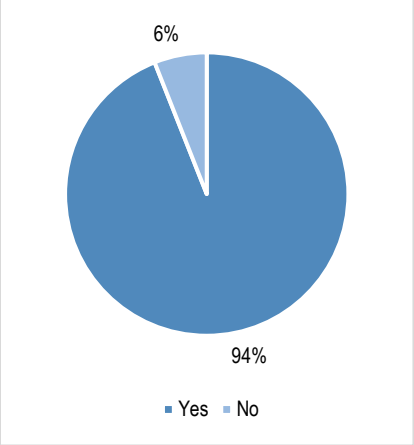

Fig. 11. Can one's social environment influence the perception of one's body shape?

Among the 378 respondents who claimed that a person's social environment has an impact on their perceived body shape, 40% (n = 152) claimed that the social environment has a positive impact to an average extent. On the other hand, a negative impact from the social environment was most commonly declared as very high (48%; n = 182; Table VI).

Table VI. Influence of one's social environment on the perception of one's body shape

Influence of one's social environment on the perception of one's body shape	Scale of influence	Number of people	N (%)
Positive	very low	34	9%
	low	76	20%
	medium	152	40%
	large	72	19%
	very large	44	12%
Negative	very low	9	2%
	low	11	3%
	medium	45	12%
	large	131	35%
	very large	182	48%

Among the 378 respondents who claimed that a person's social environment has an influence on their perceived body shape, 73% (n = 276) declared that they were subject to such influence, while 27% (n = 102) did not (Figure 12).

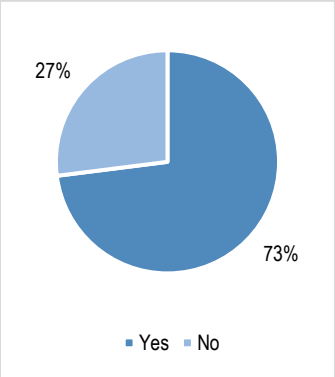

Fig. 12. Respondents influenced by their social environment.

Of the 276 respondents who reported being influenced by their social environment, 30% (n = 84) were influenced by social media. The second most common source of influence was family and friends (25% of responses for each option). Only one respondent (1.5%) experienced influence from traditional media (Table VII).

Table VII. Who or what influenced the respondents' body image

Who or what influenced the respondents' body image	Number of people	N (%)
Family	69	25%
Friends	70	25%
Social media	84	30%
Traditional media	1	1.5%
Pop culture	7	2.5%
Crush (girl/boy)	20	7%
Other	25	9%

Among all respondents, 84% (n = 337) were familiar with EDs. Only 16% (n = 63) declared that they were not familiar with EDs (Figure 13).

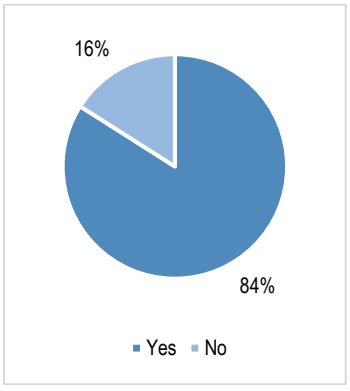

Fig. 13. Knowledge of eating disorders among respondents.

Among the respondents who declared having knowledge of EDs, the largest number (81.5%; n = 326) declared knowing about anorexia, followed by bulimia, which was declared by 318 respondents. The disorder least known among the respondents was orthorexia, which was declared by 95 respondents (Figure 14).

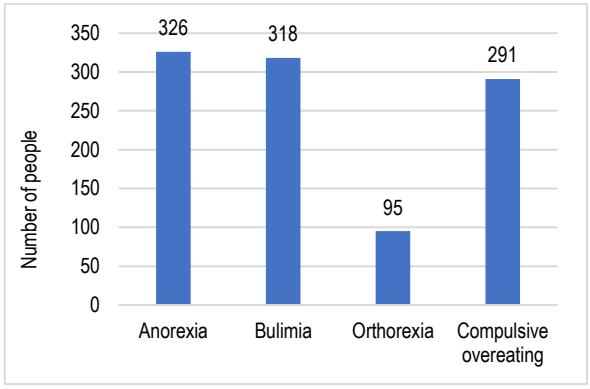

Fig. 14. Respondents' knowledge of individual eating disorders.

Among the 326 respondents who declared knowledge of anorexia, 54% (n = 177) provided the correct definition (Figure 15). The threshold score was 1.54 points.

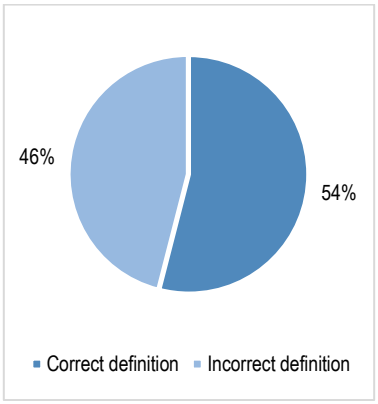

Fig. 15. Respondents correctly defining anorexia.

Of the 318 respondents who declared knowledge of bulimia, 85% (n = 269) provided the correct definition (Figure 16). The threshold score was 1.85 points.

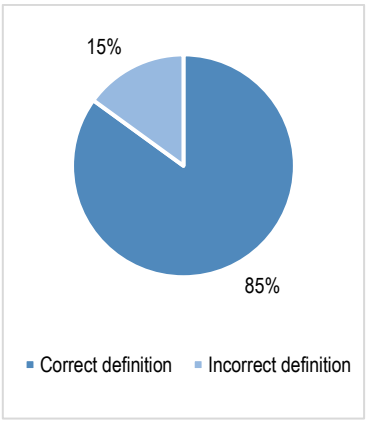

Fig. 16. Respondents correctly defining bulimia.

Among the 95 respondents who declared having knowledge of orthorexia, 96% (n = 91) provided a correct definition (Figure 17). The score threshold was 1.96 points.

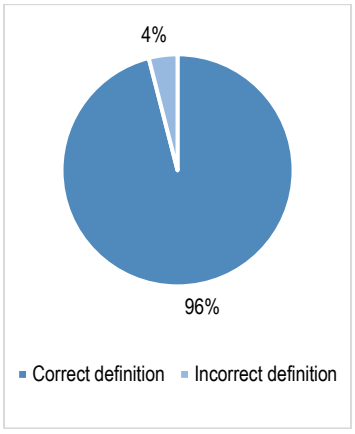

Fig. 17. Respondents correctly defining orthorexia.

Of the 291 respondents who declared having knowledge of compulsive overeating, 84% (n = 244) provided the correct definition (Figure 18). The score threshold was 1.84 points.

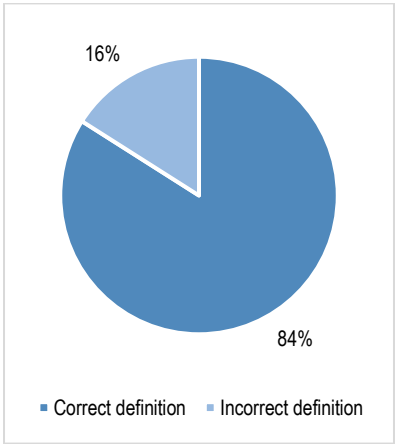

Fig. 18. Respondents correctly defining compulsive overeating.

Of all 400 respondents, 46% (n = 183) reported having never struggled with an ED. Only 4% (n = 15) reported that they were currently struggling with an ED for the first time, while 16% (n = 63) were doing so for the second time. In contrast, 21% (n = 86) did not know whether they were currently struggling with an ED (Figure 19).

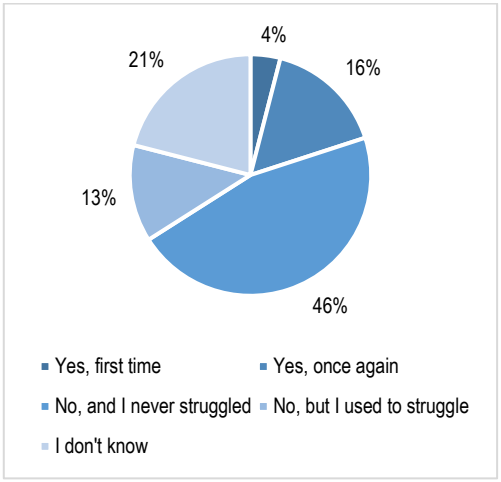

Fig. 19. Current eating disorders among respondents.

Among the respondents who currently had an ED, 44% (n = 34) suffered from compulsive overeating. The fewest (9%; n = 7) suffered from orthorexia (Figure 20).

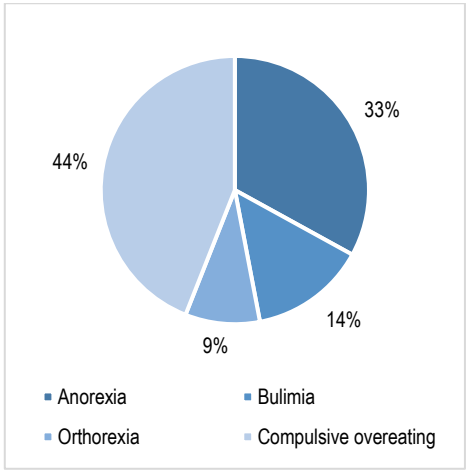

Fig. 20. Individual eating disorders among respondents.

Among the respondents currently with an ED, 77% (n = 60) had been struggling with it for more than one year. Only 9% (n = 7) had been struggling for less than six months (Figure 21).

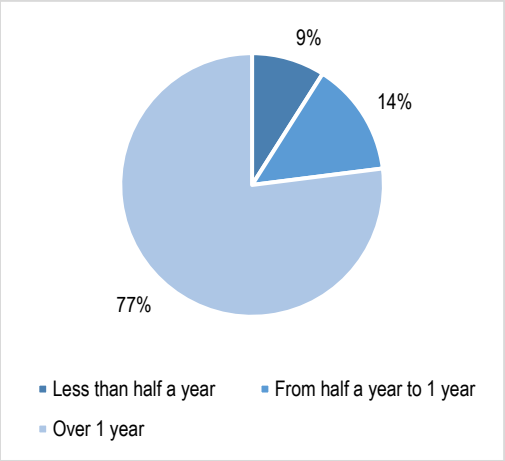

Fig. 21. Duration of eating disorders.

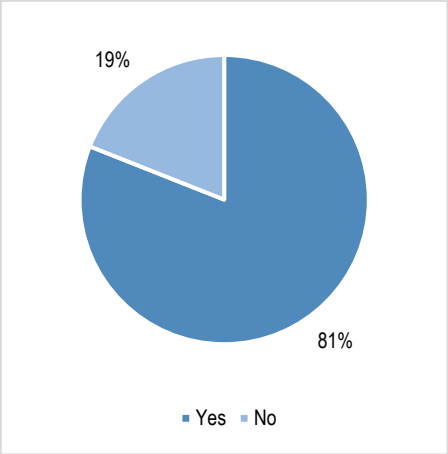

Fig. 23. Nutritional plans among respondents who consulted a dietician.

Among the respondents with EDs, 79% (n = 62) did not consult a dietitian (Figure 22).

Among those who received a nutritional plan from a dietitian, none followed it (Figure 24).

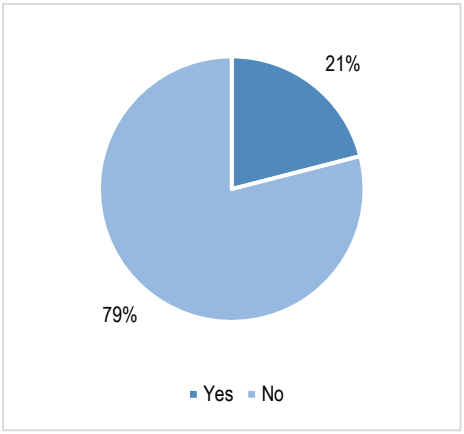

Fig. 22. Consultation with a dietician among respondents.

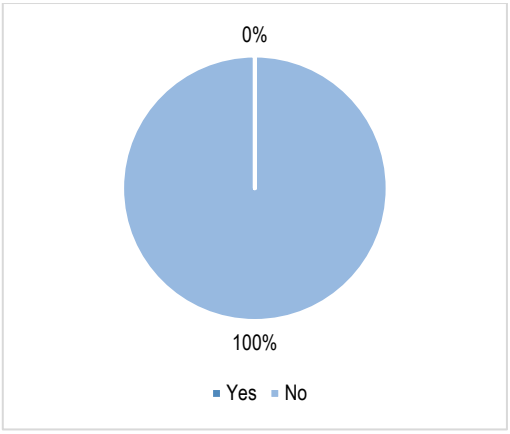

Fig. 24. Adherence to the assigned nutritional plan.

Of the 16 people who consulted a dietitian about their EDs, 81% (n = 13) received a nutritional plan (Figure 23).

The most common reason for not following the nutritional plans was the decision to quit, which was declared by seven people. The second reason (n = 6) was lack of motivation. Only two people declared that they had quit because the nutritional plan was too difficult (Figure 25).

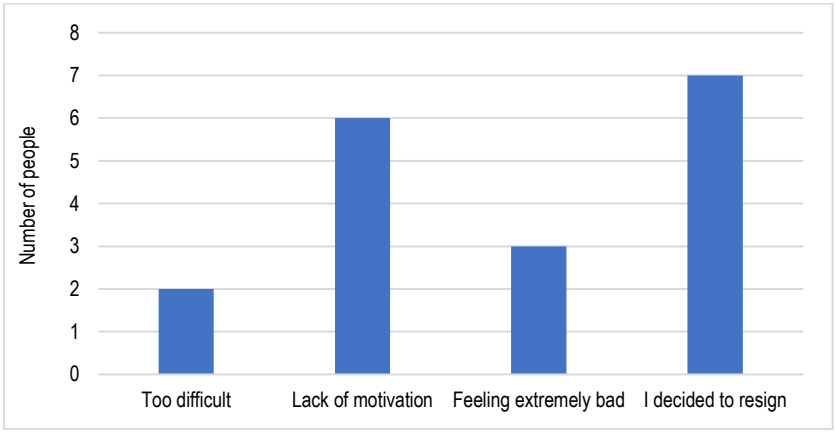

Fig. 25. Reasons for not following the nutritional plan.

DISCUSSION

EDs are a major problem today, affecting more and more people in society. Teenagers are particularly susceptible to them. These disorders have a negative impact on a person's health and functioning.

The study examined the frequency of EDs, the respondents' knowledge of ED terminology, and their perception of their body shape.

The research shows that regardless of gender, 20% of the adolescents were currently suffering from an ED. Similar results were obtained by Grajek et al. [43] in their work, in which they examined the frequency of EDs in a similar age range as that adopted in this study. The study involved 284 respondents (26% male and 74% female). They reported that 27% of the study group had an ED at the time, which is slightly above the adopted threshold of 25%. These differences are small, which may be related to the number of respondents or the period when surveys were distributed.

The problem of EDs is not limited to Poland, but also concerns other countries. Also, research conducted in Czechia by Duháčková [44] showed that of the total 82 respondents, EDs or their symptoms occurred in 18.4% of girls and 4.5% of boys, which is also a similar result to that of this study. During the COVID-19 pandemic, many people were forced to adopt a sedentary lifestyle due to lockdowns and the closure of many fitness clubs, gyms, and swimming pools, which could have contributed to the development of EDs or a greater tendency to suffer from them. The problem of restrictions was noticeable not only in Poland, but everywhere where the SARS-CoV-2 virus reached. A study by Napp et al. [45] showed that during the COVID-19 pandemic, the prevalence of ED symptoms in the study group was 17.12% among people aged 14–17, including 20.21% of girls and 13.7% of boys. The higher result among girls may be due to the desire to maintain or improve their pre--pandemic body weight despite not having access to the activities they took part in before the pandemic. Also, the lockdowns during COVID-19 brought a lot of uncertainty, stress, and social isolation, which could lead to an increased risk of EDs in women who are more sensitive.

Our research has shown that the majority of respondents perceive their body shape as very good or good – a positive finding in today's society, which is often bombarded with various insults and the trend of fitting in with others. Similar results were reported by Dymkowska-Malesa [46], in which 36.3% of the 56 respondents were satisfied with their figure. Such results may be related to puberty, when we want to please others at all costs and to be appreciated by our peers. Also, the research by Wojtyła-Buciora et al. [47] showed that out of 17,397 respondents, "22% of junior high school students, 27% of high school students and 33% of [university] students doubted their external assets". The differences may result from the experience and greater awareness of the respondents, which develop as they move from secondary school to higher education. It is also possible that university students are more inclined to compare themselves with others, which may affect the perception of their external assets. In a study by Wang et al. [48] showed that among 1,455 respondents over a period of 15 years (measured at four time-points, 5 years apart), body dissatisfaction was reported on average by 30% of women and 25% of men. In the cited study, it can be seen that the level of satisfaction with one's body shape is quite high. It should also be noted that the data was not collected once, but over a period of several years, and that the level of body shape satisfaction exceeded the level of dissatisfaction.

The current study shows that the vast majority of respondents know about EDs and can provide correct definitions of them, which is a very positive finding. Similar results were obtained by Żwirkowska et al. [49], which revealed that knowledge of EDs was declared by about 70% of the respondents. Widespread knowledge of EDs was also reported by Góral et al. [50], as knowledge about bulimia and anorexia was declared by 96% of the respondents. Also, the research of Myszkowska-Ryciak et al. [51] showed that "84% of girls in the youngest group, 94% in the group of 15–16-year-olds and all girls from the oldest group" knew the concept of anorexia and the vast majority also knew about the ED bulimia. Such a high proportion of adolescents with knowledge of EDs may be due to society's increasing awareness of complications and the introduction of information campaigns about them. Studies checking knowledge about EDs were conducted outside of Poland as well. A Czech study by Chadimová [52] showed that out of 103 respondents, over 46% indicated orthorexia as a "pathological necessity to remove unhealthy food from the menu". In a study by Hicks et al. [53] found that 63% of respondents correctly identified the definition of anorexia and 72% correctly indicated the definition of bulimia.

Based on our research and several other cited works and studies, it can be stated that the frequency of EDs among young people is 20% on average. EDs occur in both males and females, regardless of age or the time of the research. Our research and the cited studies show that the respondents' satisfaction with their figure varies and depends on their age and the time of the research. At the same time, the results of both our study and those cited above reveal a large percentage of respondents who have knowledge and familiarity with EDs.

CONCLUSIONS

1. The results of the research confirmed the hypothesis that the frequency of EDs among the respondents would not exceed 25%.
2. The hypothesis that the respondents would have a high level of knowledge about EDs was correct.
3. There were changes in body image among the respondents.
4. The respondents' BMI and percentile according to the WHO percentile charts and the OLA and OLAF studies may have contributed to the perception of their body shape.
5. Changes in body image may be conditioned by the influence of one's social environment.

In order for the frequency of EDs to be lower than the observed 20%, or at least maintained at a similar level and for knowledge about them to be equally high, information campaigns on EDs and their treatment should be introduced. Educating society on this subject would also help in identifying EDs in the early stages of their development and would encourage a conscious approach to healthy eating.

Authors' contribution

Study design – B. Palmowski, P. Romaniuk
Data collection – B. Palmowski
Data interpretation – B. Palmowski
Statistical analysis – B. Palmowski
Manuscript preparation – B. Palmowski, P. Romaniuk, W. Ficoń
Literature research – B. Palmowski, W. Ficoń

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PRACA ORYGINALNA
ORIGINAL PAPER

The impact of common chronic diseases on the severity of clinical symptoms of COVID-19

Wpływ powszechnych chorób przewlekłych na nasilenie objawów klinicznych COVID-19

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ABSTRACT

INTRODUCTION: Most available research on the etiopathogenesis of COVID-19 predominantly focuses on adult populations with chronic diseases in advanced stages – including severe respiratory and cardiovascular disorders, as well as oncological conditions – where correlations with the clinical course of the disease have been observed. The clinical course of COVID-19 is highly variable, ranging from asymptomatic or mild manifestations to severe respiratory and circulatory failure and death. The objective of the study was to assess whether common chronic diseases influence the severity of the clinical symptoms of COVID-19.

MATERIAL AND METHODS: A retrospective study was conducted on a group of 208 patients between October 2022 and February 2023. An author-designed questionnaire collected data on post-COVID-19 symptoms and their severity (mild, moderate, or severe), frequency, and links to comorbidities. Descriptive statistics were used, with significance set at $p < 0.05$. Comparisons of variables were made using the χ^2 test.

RESULTS: Among the patients, 50.48% had chronic diseases, of which 55% experienced mild symptoms of COVID-19 and 40% experienced moderate symptoms. In the group without chronic diseases (49.52%), mild symptoms were observed in 58% of patients and moderate symptoms in 36%. No significant correlation was found between chronic diseases and the severity of symptoms ($p = 0.809$).

CONCLUSIONS: No significant correlation was found between mild chronic diseases and the severity of COVID-19 symptoms. The type, severity, and duration of the conditions and the level of viremia influence the prognosis. Further studies are needed to consider additional factors, such as gender and age.

KEYWORDS

chronic comorbidities, COVID-19, clinical symptoms

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STRESZCZENIE

WSTĘP: Większość dostępnych raportów naukowych na temat etiopatogenezy COVID-19 koncentruje się głównie na populacjach dorosłych z zaawansowanymi stadiami chorób przewlekłych, w tym ciężkimi zaburzeniami układów oddechowego i sercowo-naczyniowego, a także schorzeniami onkologicznymi, w których zaobserwowano korelację z przebiegiem klinicznym choroby. Przebieg kliniczny COVID-19 jest bardzo zmienny, od bezobjawowych lub łagodnych objawów do ciężkiej niewydolności oddechowej i krążeniowej oraz zgonu. Celem badania była ocena, czy powszechne choroby przewlekłe wpływają na nasilenie objawów klinicznych COVID-19.

MATERIAŁ I METODY: Badanie retrospektywne prowadzono w grupie 208 pacjentów w okresie od października 2022 r. do lutego 2023 r. Autorski kwestionariusz zawierał dane dotyczące objawów po COVID-19 i ich nasilenia (łagodne, umiarkowane lub ciężkie), częstości występowania oraz związku z chorobami współistniejącymi. Zastosowano statystyki opisowe, przy istotności statystycznej $p < 0,05$. Porównania zmiennych dokonano za pomocą testu χ^2.

WYNIKI: Spośród pacjentów 50,48% cierpiało na choroby przewlekłe, z czego u 55% wystąpiły łagodne objawy COVID-19, a u 40% umiarkowane. W grupie bez chorób przewlekłych (49,52%) łagodne objawy zaobserwowano u 58%, a umiarkowane u 36%. Nie stwierdzono istotnej korelacji między chorobami przewlekłymi a nasileniem objawów ($p = 0,809$).

WNIOSKI: Nie stwierdzono istotnej korelacji między powszechnymi chorobami przewlekłymi a nasileniem objawów COVID-19. Rodzaj, nasilenie i czas trwania schorzeń, a także poziom wiremii wpływają na rokowanie. Konieczne są dalsze badania uwzgledniające dodatkowe czynniki, takie jak płeć i wiek.

SŁOWA KLUCZOWE

przewlekłe choroby współistniejące, COVID-19, objawy kliniczne

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has shown that the presence of lifestyle comorbidities – hypertension, diabetes, heart disease, and obesity – significantly increases the risk of severe COVID-19. Patients with these conditions are more likely to be hospitalized and to have post--COVID complications [1]. It has been shown that in most patients hospitalized due to COVID-19, the most common comorbidities were hypertension, diabetes, and obesity [2]. Meta-analyses show that chronic diseases, such as respiratory, cardiovascular, and metabolic diseases, significantly increase the risk of severe complications of COVID-19. In older people with comorbidities, the mortality rate was much higher: in the over-80 age group, the hospital mortality rate was 26.6% [2,3]. In the case of COVID-19, the most common comorbidities were cardiovascular diseases. Data on complications after COVID-19 emphasize the importance of early diagnosis and the monitoring of patients with chronic diseases to improve the prognosis in the case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [4]. Due to the wide range of clinical courses of COVID-19, symptoms are categorized as mild, moderate, severe, or critical. The first of them most often occur after 11 days of SARS-CoV-2 infection, with the median being about 4–5 days [5]. Patients who showed symptoms mostly had a mild or moderate course of the disease (81%), while 14% had a severe course and around 6% had a critical course [6]. Importantly, differences in the intensity of symptoms were observed between infections with individual strains – in the case of the omicron variant, the course is asymptomatic or mild, requiring hospitalization less often than the previous variants [7]. The mild form causes flu-like symptoms and may be only the initial phase of an incipient disease associated with viral replication [2]. This form most often includes headache, nasal congestion, cough, fever, loss or reduction in sense of smell (anosmia and hyposmia, respectively), disturbance of the sense of taste (dysgeusia), and muscle pain [8]. As variants of the virus emerged, the incidence of myalgia increased with a decreased incidence of anosmia and dysgeusia [6,8]. Rapid clinical deterioration was observed in some patients, probably due to an exacerbated immune response [2], and there were cases in which mild symptoms persisted for 12 months after diagnosis [9]. Moderate clinical symptoms are differentiated from mild symptoms based on abnormalities in chest imaging studies – mainly pneumonia. Dyspnea and a fever of $\geq 39.0°C$ that is resistant to paracetamol also appear [10]. In the severe course, in addition to the combination of the above-mentioned symptoms, tachypnea (a respiratory rate of ≥ 30 breaths per minute), hypoxia with a saturation of $< 93\%$, and significant pulmonary infiltrates occur [6,11]. Typically, this type of clinical picture is a consequence of the inflammation caused by the SARS-CoV-2 virus damaging the epithelium of type II pneumocytes. The inflammation results from increased release of proinflammatory cytokines such as IL-1β, IL-6, TNF-α, and IFN-γ [2,9]. The critical form of the severe course is characterized by acute respiratory distress syndrome (ARDS) and, as a result, multi-organ failure. ARDS appears about

8–9 days after the first symptoms appear. It is estimated that multi-organ failure may develop in about 2% of patients [6,9].

MATERIAL AND METHODS

In the study group (N = 208), 105 of the women had previously been diagnosed with chronic diseases, while the remaining 103 women had no history of disease. The decision to study the female population was informed by the subjective considerations of the researchers. The objective for subsequent studies is to direct the focus onto the male population. Chronic comorbidities in the patients included cardiovascular diseases – hypertension (15.66%), type 2 diabetes (14.50%), thyroid disease (20.48%), rheumatoid arthritis (6.02%), and allergies (20.48%). Other chronic conditions were reported by 24 women – 22.86% of the study group (Figure 1). There were no significant statistical differences in the incidence of chronic diseases, including hypertension, rheumatoid arthritis, and thyroid diseases in the patients.

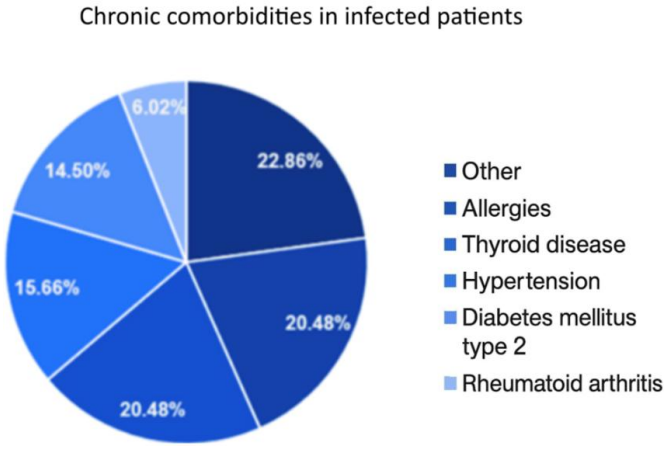

Fig. 1. Percentage of individual chronic diseases in the study group.

Study questionnaire

In the author's original questionnaire, respondents indicate clinical symptoms after SARS-CoV-2 infection. The demographic data (age, gender, education) were analyzed, as were comorbidities of various systems: the lungs and bronchi, e.g., bronchial asthma or chronic obstructive pulmonary disease; the genitourinary system, e.g., chronic cystitis; the heart and circulatory system, e.g., chronic heart failure, heart rhythm disorders, or coronary artery disease; the nervous system, e.g., neuralgia or concentration and memory disorders; the digestive system, e.g., stomach ulcers; the musculoskeletal system, e.g., degenerative diseases; diseases of the veins and peripheral arteries; hormonal disorders, e.g., hyperthyroidism or hypothyroidism; metabolic diseases, e.g., type 2 diabetes; autoimmune disorders, e.g., allergies and rheumatic diseases, e.g., rheumatoid arthritis. The place and time of infection with the SARS-CoV-2 virus were determined, the presence of the virus was confirmed by a diagnostic test (genetic, antigen, or antibody), and the clinical symptoms of COVID-19 were assessed, along with their severity (mild, moderate, or severe). The study group was divided into subgroups depending on the time of SARS-CoV-2 infection and the type and severity of clinical symptoms of COVID-19.

Statistical analysis

Statistical analysis was performed using the software program Statistica 12.0 (Krakow, Poland). Results were presented as means with standard deviation or percentages for nominal and ordinal scale data. Results with a p-value of less than 0.05 were considered statistically significant.

RESULTS

The majority of patients (56.73%) presented mild symptoms of COVID-19, regardless of the presence of chronic diseases (Table I). In the subgroup of patients with chronic diseases, 55.24% had mild symptoms, which was similar to those without chronic diseases (58.25%). Severe symptoms occurred in 5.29% of patients, with minimal differences between subgroups (chronic diseases – 4.76%, no chronic diseases – 5.83%).

Table I. Presence of chronic diseases and degree of symptoms after COVID-19

Degree of symptoms	Presence of chronic diseases*		Total (n, %)
	No (n, 95% CI)	Yes (n, 95% CI)	
Mild	60 (47.22–72.80)	58 (45.34–70.72)	**118 (56.73%)**
Moderate	37 (26.21–47.84)	42 (30.58–53.25)	**79 (38.36%)**
Severe	6 (1.25–10.82)	5 (0.62–9.36)	**11 (4.91%)**
Total (n, %)	**103 (49.52%)**	**105 (50.48%)**	**208 (100%)**

*p = 0.809, χ^2 test

Of the 105 women diagnosed with chronic disease, 55% had mild COVID-19 symptoms and 40% had moderate symptoms. In turn, among the women without chronic diseases (n = 103), mild symptoms dominated (58%), followed by moderate symptoms (36%). No statistical significance was observed (Figure 2).

Figure 3 presents the percentage distribution of participants with and without chronic comorbidities in the studied cohort. A total of 49.52% of individuals reported no chronic conditions, whereas 50.48% had at least one comorbidity.

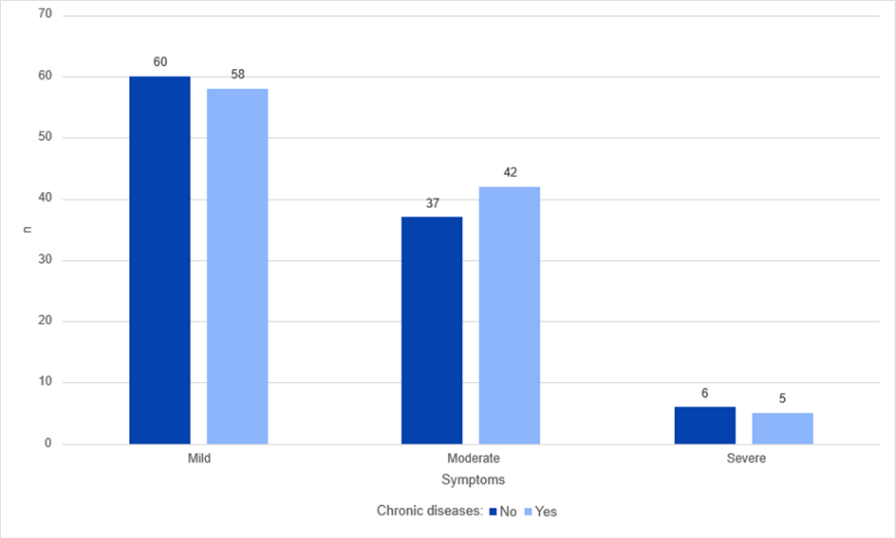

Fig. 2. Comparison of the occurrence of chronic diseases and the degree of symptoms after COVID-19 (*p = 0.809, χ^2 test).

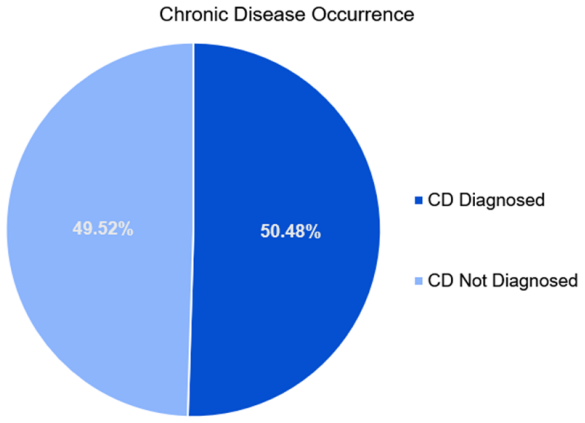

Fig. 3. Percentage of study group diagnosed with chronic diseases.

The diseases co-occurring with COVID-19 were ranked and assessed as percentages, as illustrated in Figure 1.

The chi-square test (χ^2) was used to compare the distribution of the degree of COVID-19 symptoms depending on the presence of chronic diseases. Since the calculated χ^2 value (0.809) was lower than the critical value (5.991), there was no basis to reject the null hypothesis. This means that no statistically significant relationship was found between the presence of chronic diseases and the severity of COVID-19 symptoms. This finding does not mean that such a relationship does not exist, but that sufficient evidence was not found to confirm the alternative hypothesis (which assumes the existence of a relationship).

DISCUSSION

Chronic diseases, according to the generally accepted definition, are characterized by a long-term course of a pathological condition with recurrent complaints after periods of improvement in the patient's health. They require continuous treatment and monitoring, often of the patient's vital signs and functional parameters by a specialist physician [12]. The COVID-19 pandemic, which directly contributed to the isolation of a group of patients with chronic diseases, had a negative impact on their general health – both somatic and mental. Fewer new cases of viral infection were detected, especially in this group of patients, which could be related to their isolation or asymptomatic course [13]. The most common chronic diseases that appeared in clinical statistics were diseases of civilization, e.g., diabetes, cardiovascular diseases, chronic lung diseases, and obesity. The analysis consisted of assessing the impact of their presence on the risk of severe COVID-19 [14]. One of the most common cardiovascular diseases in patients with COVID-19, during the pandemic and currently, is arterial hypertension [15]. Isolated hypertension is not an independent prognostic factor for the severity of the disease, but the co-occurrence of type 2 diabetes in patients significantly increased the risk of death in COVID-19 [16]. It has been suggested that hypertension may lead to a worsening of the course of SARS-CoV-2 infection, but this remains an open topic for further discussion and molecular mechanisms are still being sought to confirm these assumptions [17].

In our study, among the patients with hypertension, no direct correlation was found between the presence of this chronic disease and the severity of symptoms. A relationship with the co-occurrence of other risk factors, including age and other comorbidities, is suspected. Our study showed no statistical correlation between the occurrence of chronic diseases and the degree of clinical symptoms of COVID-19 ($p = 0.809$). Findings from other studies have suggested that less common chronic conditions may significantly worsen the clinical course of COVID-19. This impact largely depended on the characteristics of the study population as well as the severity and health consequences of the specific comorbid condition [18,19]. It has been indirectly shown that COVID-19 contributed to elevated blood pressure in patients who had not been ill before. However, the impact of the virus on the development of hypertension has not been confirmed [20], which was also documented in our work. However, some reports suggest that in patients with hypertension, COVID-19 is associated with a significant deterioration of their health [21]. This is most likely related to the occurrence of SARS-CoV-2--dependent chronic heart failure, which is significantly more severe in patients with high systolic blood pressure and less common in patients with high diastolic blood pressure. According to the latest reports, neglect of blood pressure treatment, especially in patients infected with SARS-CoV-2, often leads to the need for hospitalization in intensive care units, and in extreme cases there is a high risk of death [22]. Shalaeva et al. [23] suggest that despite the lack of a direct effect on the severity of symptoms, hypertension significantly prolongs their duration. Our work confirmed the lack of a direct effect of hypertension on the severity of symptoms associated with the course of the disease. However, it is noteworthy that Yoshihara [24] indicated no or a small causal relationship between hypertension and the exacerbation of clinical symptoms after SARS-CoV-2 infection. This suggests the need for further research to determine a specific relationship or lack thereof in a given clinical situation, the potential variability and individual dependence of which may additionally complicate the drawing of specific conclusions.

COVID-19 has also become a threat to patients with diabetes [25]. The immunological disorders that appear in the course of the disease itself – as well as the immune system response to SARS-CoV-2 infection – intensify inflammation, leading to glycemic disorders [26], which increases the probability of circulatory and respiratory failure in patients with a given clinical profile [27]. Patients with diabetes were at significantly higher risk of developing a more severe form of the disease. Symptoms of COVID-19 in this group may be less specific, which delays diagnosis and treatment. Maddaloni and Buzzetti [28] suggest developing separate risk scores for patients with diabetes to better assess their condition and to implement appropriate interventions that will be appropriately selected for a given patient, depending on their clinical condition. This is also because of the observed higher mortality rate (almost threefold) in coronavirus-infected patients with diabetes than in patients without diabetes [29]. Wu et al. [30] drew attention to the importance of chronic diseases in predisposing patients to a more severe course of the disease. Diabetes, circulatory and vascular diseases, and hypertension were the most common, and patients with these diseases were more susceptible to complications, including the development of acute respiratory distress syndrome. In turn, other studies have shown that in patients hospitalized due to COVID-19 infection, diabetes and heart disease had the strongest impact on the risk of death [31]. The presence of at least two chronic diseases predicted a worse course of COVID-19 and the patients had a higher risk of developing a severe course of the disease. The most common chronic diseases that worsened the course of infection were hypertension and diabetes, but this depended on the patient's age, the type, severity, and duration of chronic disease, and the

pharmacotherapy used [32,33]. Obese patients (body mass index (BMI) > 30) with comorbid cardiovascular disorders and diabetes showed higher mortality rates and a more severe course of COVID-19; a particularly high risk of complications was observed in people with cardiovascular diseases [34]. Szarpak et al. [35] drew attention to ischemic heart disease, in which a viral infection leads to the release of proinflammatory cytokines, which causes a disturbance in the homeostasis of the endothelium of blood vessels, especially cascades related to thrombocyte coagulation. The resulting clots are a direct cause of ischemic conditions due to embolic mechanisms, including ischemic disease, which is a direct threat to life.

Near the beginning of the COVID-19 pandemic, it was assumed that allergic diseases, including bronchial asthma, were one of the factors exacerbating the course of the disease and increasing susceptibility to infection. As the COVID-19 pandemic developed, it was noticed that the course of coronavirus was similar in patients with and without asthma. No difference in the frequency of hospitalization or mortality was observed between these groups [36], as in our study. Terry et al. [37] drew attention to the risk of infection, which was lower in people with asthma than in those without it, and one of the probable reasons was these patients' heightened awareness of the risk of infection and increased caution, where early isolation, social distancing, and personal hygiene played the main role. The opposite situation was observed in patients with chronic obstructive pulmonary disease (COPD), who have a high rate of hospitalization in intensive care units (ICUs). The essence of the problem is chronic inflammation causing impaired functionality of the respiratory epithelium. It induces a worse antiviral response, leading to reduced production of interferons, which makes patients more susceptible to infection. Increased expression of ACE2 in the epithelium facilitates the penetration of the SARS-CoV-2 virus into the lungs. Also, in COPD, hypoxia of the pulmonary vessels develops as a result of impaired lung ventilation, which is associated with increased prothrombotic potential. In SARS-CoV-2 infection, pulmonary clots form, which leads to hypoxia and ultimately to pulmonary embolism [38].

The criteria for the severity of clinical symptoms of COVID-19 in the questionnaires were the patients' subjective perceptions. Indirectly, the results indicated that the severity of COVID-19 symptoms may be influenced by various predisposing factors, such as age, genetics, lifestyle (i.e., diet and physical activity) and access to medical care – not only the co-occurrence of chronic diseases. However, it has been proven that coronavirus itself can also worsen the course of these diseases in patients who have already been diagnosed [39]. Our analysis did not confirm a statistically significant relationship between the presence of chronic diseases and the severity of COVID-19 symptoms in the women participating in this study. Of the 105 patients with chronic diseases, 55% had mild symptoms and 40% had moderate symptoms. In the subgroup without chronic diseases (n = 103), mild symptoms occurred in 58% and moderate ones in 36%. The lack of statistical significance suggests that the exclusive presence of chronic diseases did not directly affect the severity of the course of COVID-19.

While the results may prove useful in the assessment of health risks and the planning of therapeutic strategies, the factors contributing to a more severe course of the disease should be considered in the context of a wide spectrum of clinical parameters and not limited to only the presence of individual chronic diseases. Moreover, special attention should be given to the specific characteristics of the study population analyzed in the present research.

The survey was conducted exclusively among women who were relatively young and were not selected on the basis of any particular criteria. This may provide a rationale for the observed differences in comparison to other studies, where the participants were characterized by a much higher average age and fulfilled more specific criteria, such as BMI or the potential influence of other factors. Furthermore, the data encompassed subjective assessments by the researchers, which had the potential to restrict the analysis. In the future, it is recommended that further research be conducted to identify any additional factors that determine the course of the disease. This will allow for more precise adjustment of medical strategies to the specific needs of patients from different age groups.

CONCLUSIONS

1. No significant correlation with mild chronic diseases: In young women, no significant correlation was found between mild and moderate chronic diseases and the severity of clinical symptoms of COVID-19.
2. Impact of specific disease characteristics: The type, severity, and duration of chronic diseases play a key role in predicting the course of COVID-19, although the presence of such diseases alone does not necessarily determine the severity of infection.
3. The importance of viral load: In mild cases of COVID-19, the viral load is much lower than in patients with a severe disease course, indicating its key role in prognosis.
4. Study limitations and further research: The study was limited to individuals with chronic diseases who did not require hospitalization, which could have influenced the results. It is necessary to consider additional factors, such as gender and age, when planning medical strategies.

Authors' contribution

Study design – B. Pietrzyk, P. Dolibog, A. Joniec, T. Fajferek, J. Mikołajczyk
Data collection – T. Fajferek, B. Pietrzyk, A. Joniec, S. Kaczara, E. Kołodziej, J. Mikołajczyk, P. Dolibog
Data interpretation – B. Pietrzyk, A. Joniec, T. Fajferek, P. Dolibog
Statistical analysis – A. Joniec, T. Fajferek, S. Kaczara, E. Kołodziej, J. Mikołajczyk
Manuscript preparation – B. Pietrzyk, T. Fajferek, J. Mikołajczyk, P. Dolibog, A. Joniec, E. Kołodziej
Literature research – T. Fajferek, A. Joniec, J. Mikołajczyk, S. Kaczara, E. Kołodziej, P. Dolibog, B. Pietrzyk

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PRACA POGLĄDOWA
REVIEW

Hepatic portal venous gas in children: why ultrasound matters more than ever – a literature review

Gaz w żyle wrotnej u dzieci: dlaczego ultrasonografia ma dziś większe znaczenie niż kiedykolwiek – przegląd piśmiennictwa

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ABSTRACT

INTRODUCTION: Hepatic portal venous gas (HPVG) is a rare, yet alarming finding in pediatric patients that is historically linked to a mortality rate reaching 75%. However, advancements in imaging techniques now reveal that in many cases it is transient and benign. In this study, we focus on the growing role of ultrasonography in diagnosing pediatric patients with HPVG, highlighting its value in clinical practice.
MATERIAL AND METHODS: A literature review was conducted using PubMed and Google Scholar. The search terms were "hepatic portal venous gas," "pediatrics," "ultrasonography," "diagnostic imaging," "necrotizing enterocolitis," and related variations thereof.

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STATE OF KNOWLEDGE: HPVG can be detected by multiple imaging methods. Interestingly, ultrasonography stands out from the others for its high sensitivity in HPVG detection, lack of ionizing radiation, and real-time results. In pediatric patients, an extended ultrasound exam not only detects HPVG, but also enables clinicians to stratify risk by analyzing gas distribution patterns and other sonographic markers linked to poorer outcomes. Furthermore, ultrasound aids in refining differential diagnoses by tracking the flow of gas through the intricate branches of the portal venous system. Crucially, when HPVG detection via ultrasound is combined with Gordon's criteria, diagnostic accuracy for necrotizing enterocolitis improves significantly, reaching a specificity of 86% and a sensitivity of 90%. This highlights the growing indispensability of ultrasonography in pediatric care.
CONCLUSIONS: Ultrasonography is a powerful, non-invasive tool that enhances HPVG diagnosis and clinical decision--making. Given its advantages, we propose it as an imaging method of choice for the diagnosis of children with HPVG.

KEYWORDS

pediatrics, portal vein, ultrasonography

STRESZCZENIE

WSTĘP: Gaz w żyle wrotnej (*hepatic portal venous gas* – HPVG) jest rzadkim, lecz alarmującym objawem u pacjentów pediatrycznych, historycznie wiążącym się ze śmiertelnością sięgającą 75%. Jednak dzięki postępowi w technikach obrazowania można stwierdzić, że w wielu przypadkach ma on charakter przejściowy i łagodny. W badaniu skupiono się na rosnącej roli ultrasonografii w diagnostyce dzieci z HPVG, podkreślając jej znaczenie w praktyce klinicznej.
MATERIAŁ I METODY: Przeprowadzono przegląd literatury w bazach PubMed i Google Scholar. Użyto haseł: „hepatic portal venous gas", „pediatrics", „ultrasonography", „diagnostic imaging", „necrotizing enterocolitis" oraz ich wariantów.
STAN WIEDZY: HPVG można wykryć za pomocą różnych metod obrazowania. Spośród nich ultrasonografia wyróżnia się wysoką czułością, brakiem promieniowania jonizującego oraz możliwością uzyskania wyników w czasie rzeczywistym. U pacjentów pediatrycznych rozszerzone badanie ultrasonograficzne pozwala nie tylko na wykrycie HPVG, lecz także na ocenę ryzyka poprzez analizę wzoru rozkładu gazu i innych ultrasonograficznych markerów związanych z gorszym rokowaniem. Ponadto ultrasonografia ułatwia zawężenie diagnostyki różnicowej poprzez śledzenie przepływu gazu w skomplikowanych gałęziach układu wrotnego. Co istotne, połączenie wykrywania HPVG za pomocą ultrasonografii z kryteriami Gordona znacząco poprawia dokładność diagnostyczną martwiczego zapalenia jelit, osiągając 86% swoistości i 90% czułości. Podkreśla to rosnące znaczenie ultrasonografii w opiece pediatrycznej.
WNIOSKI: Ultrasonografia jest skutecznym, nieinwazyjnym narzędziem, usprawniającym diagnozowanie HPVG i wspierającym podejmowanie decyzji klinicznych. Ze względu na zalety badania proponujemy je jako metodę obrazowania pierwszego wyboru w diagnostyce dzieci z HPVG.

SŁOWA KLUCZOWE

pediatria, żyła wrotna, ultrasonografia

INTRODUCTION

In pediatric patients, ultrasonography (US) is one of the most commonly used imaging techniques, thanks to its non-invasiveness, low cost, lack of harmful ionizing radiation exposure, and real-time results [1,2]. Therefore, US is usually the first-line imaging method in children, especially for diagnosing abdominal diseases [1].

A rare ultrasonographic finding is hepatic portal venous gas (HPVG), first described in 1955 [3,4,5]. The mechanisms behind the appearance of gas in the portal system remain unclear. The most common theories are as follows:

1. Increased pressure in the intestines causes trapped air to move through the mural capillaries into the portal venous circulation.
2. Damage to the intestinal mucous membrane moves gas produced by microorganisms from the intestinal lumen to the portal system.
3. Bacteria in the abdominal cavity produce gas, bubbles of which pass into the circulation [3,4].

HPVG can be equated with life-threatening conditions such as bowel ischemia, necrotizing enterocolitis, or bowel wall rupture [3,4,6]. Less than 50 years ago, the mortality rate of patients with portal venous gas was as high as 75% [7]. However, due to technological development, the sensitivity of imaging machines has increased, which resulted in more frequent detection of HPVG, which in numerous cases turns out to be temporary and benign [3,4,6,8]. Non-surgical clinical conditions include food allergy, bowel inflammation, early postoperative period after liver transplantation, upper gastrointestinal barium examination, endoscopic procedures, umbilical vein cannulation, and more [3,4,6,9]. This has resulted in the fatality rate of patients with HPVG decreasing to 29–39% [10,11,12].

It is important to emphasize that HPVG is not a disease by itself and that its detection requires an extension of the diagnostic workup. In this study, we

will consider the increasing role of ultrasonography in diagnosing pediatric patients with HPVG.

MATERIAL AND METHODS

We conducted a comprehensive literature review using the databases PubMed and Google Scholar and the search terms "hepatic portal venous gas," "pediatrics," "ultrasonography," "diagnostic imaging," "necrotizing enterocolitis," and all variations related to these terms. The review focused on clinical trials, randomized controlled trials, meta-analyses, systematic reviews, and other review articles. Studies were selected based on their relevance to the topic and quality of evidence.

STATE OF KNOWLEDGE

HPVG imaging methods

Plain radiography

The most basic technique of visualizing gas in the portal venous circulation is plain radiography [4]. HPVG presents as branching peripheral radiolucencies in the liver parenchyma that extend up to 2 cm from the liver capsule [7]. However, the sensitivity of X-ray imaging in detecting HPVG is only 12.5%, since it requires the presence of copious amounts of gas [4]. As a result, the identification of this sign on radiography is correlated with a poor prognosis [4].

Computed tomography

Significantly better results in detecting HPVG can be achieved with computed tomography (CT) [4,12]. It allows for the demonstration of even small amounts of gas, thanks to the "lung window" function [4,8]. On a CT scan, HPVG emerges as tubular areas of decreased density in the liver tissue, branching up to 2 cm from the liver capsule [4,12]. The lumens are mainly visible in the non-dependent left lobe and anterior right lobe [4,13].

Ultrasonography

In US, HPVG manifests as hyperechoic, non--shadowing foci flowing through the portal vein or liver tissue, mainly in the non-dependent part of the liver [3,6,14]. Moreover, the use of Doppler and motion modes further increases the sensitivity of the examination [4,6,14,15]. In Doppler imaging, the hyperechoic gas generates characteristic sharp, bidirectional spikes superimposed on the portal vein wave pattern [6,14]. In motion mode, the hyperechoic gas creates typical linear signals, which imitate a "meteor shower" [14].

Comparison of ultrasonography and computed tomography

Hosokawa et al. [16] compared US and CT by describing 25 pediatric patients with suspected intestinal ischemia who were examined for the presence of HPVG using these two methods within 2 days. Forty percent of the ultrasound examinations revealed gas in the portal system, while only 16% of the CT exams did so. In addition, Chevallier et al. [17] reported on three patients with HPVG detected by US, who underwent abdominal CT within 15 minutes. In each case, the CT was negative for gas in the portal venous circulation, while the subsequent ultrasound examination was able to detect it. These results may indicate a higher sensitivity of US in the detection of HPVG compared to CT, which can be explained by the following factors:

1. the physical basis for gas detection – a small amount of gas can be easily detected by its high impedance on US, while a small volume of gas does not sufficiently alter the density to make it detectable on CT
2. the high blood solubility of the gas – the absence of accumulated gas bubbles prevents their visualization on CT, while US easily shows a small amount of gas
3. the time required for examination – CT is a one--time examination and gas bubbles that are large enough to be detected become untraceable while moving; US is performed over several minutes, which makes it possible to visualize flowing trapped air [17,18].

Computed tomography radiation risk

CT is the method of choice for detecting HPVG in adults, but not pediatric patients [3,4]. The explanation for this is that in children, CT has a significantly higher risk of adverse effects from a given dose of radiation [19]. This is due to their greater radiosensitivity (because of the greater proportion of dividing cells) and longer expected lifetime (during which radiation--induced tumors may develop) [19]. Moreover, due to the thinner torso and smaller cover of organs from the radiation exposure, pediatric patients need lower doses of radiation, which are surprisingly often not reduced [19,20]. As a result, the estimated organ dose after abdominal CT in children is much higher than in adults [19]. The situation is additionally complicated by the fact that CT machines show an absorbed dose of radiation during the scan using the volumetric CT dose index (CTDIvol), which was based on measurements performed on 16-cm or 32-cm phantoms and is independent of the actual patient's size [21]. This is particularly important for neonates, whose bodies are frequently much smaller than even the phantoms.

Strauss and Goske [21] showed that for an abdominal CT scan of an infant with a 6-cm-diameter trunk, the CTDIvol based on a 32-cm phantom indicates 30% of the real absorbed dose; the CTDIvol based on the 16-cm phantom indicates 80% of the real absorbed dose. With this in mind, it is not surprising that, according to research by Brenner et al. [22], the estimated lifetime attribute risk of death from cancer after abdominal CT in a 1-year-old child is estimated at 1 to 550.

Prognostic value of ultrasonography in patients with HPVG

HPVG patterns in ultrasonography

As mentioned before, the mere detection of HPVG does not determine the diagnosis, since it can be the first symptom of either terminal or harmless illnesses. Significantly, extended ultrasound examination after gas is detected in the portal vein system has been shown to help predict the patient's prognosis (Table I).

One study distinguished three patterns of HPVG on US:

1. dot-like pattern – branched distribution of hyperechoic foci throughout the liver; most of the liver tissue is visible, which corresponds to a small amount of gas in the portal venous system
2. streak-like pattern – streaky distribution of hyperechoic gas shadow extending to the peripheral part of the liver, but not reaching the liver capsule, which corresponds to a large amount of gas in the portal venous system
3. fruit-pulp-like pattern – crowded distribution of hyperechoic gas bubbles reaching up to 1 mm from the liver capsule; most of the liver tissue is almost invisible, which corresponds to the massive involvement of the portal venous system [9].

Interestingly, the dot-like pattern is associated with good prognosis and was commonly transitional in nature [9]. However, the streak-like and fruit-pulp-like patterns were correlated with poor prognosis and required aggressive treatment [9]. This can be explained by the fact that gas patterns on ultrasound are closely related to the amount of gas in the portal venous system – the more gas there is, the worse the prognosis [9].

Ultrasonographic risk factors in patients with HPVG

Moreover, precise ultrasound examination in a patient with HPVG can detect other features categorized as risk factors of poor outcome (Table I). Alexander et al. [23] provided an example ultrasound protocol that facilitates the determination of risk of surgery or death. The key components of the examination are an assessment of the bowel wall thickness, echogenicity, dilatation, and peristalsis, as well as the presence of bowel wall pneumatosis, ascites and its type, pneumoperitoneum, or HPVG. The most significant signs are evidence of bowel perforation, such as pneumoperitoneum, focal fluid collection, and complex ascites. In addition, bowel wall thinning, an absence of peristalsis, and perfusion should be taken seriously, as these symptoms may be associated with bowel necrosis, which can lead to perforation. Any of these discoveries requires surgical consultation and, in most cases, surgery due to their association with high mortality. The remaining findings, such as increased bowel perfusion, simple ascites, dilated bowel, HPVG, intestinal pneumatosis, or bowel wall thickening, are not necessarily signs of a serious condition [23].

Table I. Ultrasound results and their impact on prognosis (based on [9,23])

Sign associated with a poor prognosis
Streak-like pattern of HPVG
Fruit-pulp-like pattern of HPVG
Increased bowel wall echogenicity
Bowel wall thinning
Absent bowel peristalsis
Absent bowel wall perfusion
Pneumoperitoneum
Focal fluid collection
Complex ascites
Signs not associated with a poor prognosis
Dot-like pattern of HPVG
Increased bowel perfusion
Simple ascites
Pneumatosis intestinalis
Bowel wall thickening

HPVG – hepatic portal venous gas.

It should be noted that ultrasound alone cannot completely exclude severe disease, but in combination with additional clinical examinations, it facilitates the selection of patients requiring immediate treatment [23]. Furthermore, in case of uncertainty regarding the diagnosis, it enables monitoring of the disease state and the search for the signs classified as risk factors.

Ultrasonography in the diagnosis of patients with HPVG

Identification of HPVG origin by ultrasonography

Ultrasound examination has proven to be a useful diagnostic tool for patients with HPVG. Above all, tracing the gas flow along the branches of the portal vein system with US allows for the determination of the specific parts of the digestive tract from which HPVG originates [24]. For example, gas in the superior mesenteric vein indicates pathology in the small intestine, cecum, ascending colon, or transverse colon; gas in the splenic vein suggests pathology in the spleen or stomach; and gas in the inferior mesenteric vein indicates pathology in the descending or sigmoid colon [24]. This knowledge narrows the differential diagnosis, which increases the likelihood of early,

proper diagnosis and leads to more accurate treatment.

Ultrasonography for necrotizing enterocolitis diagnosis

Until recently, the presence of gas in the portal venous system was considered pathognomonic for necrotizing enterocolitis (NEC), a condition with an overall fatality rate of 23.5% in infants [23,25,26]. This high mortality rate is mainly due to the lack of definitive diagnostic criteria, which frequently leads to delays in diagnosis [23,26,27]. Currently, the most commonly used classification systems are Bell staging and a modified version based on the clinical picture and X-ray findings [27,28,29,30]. However, research shows that the specificity of the modified Bell staging in NEC diagnosis is only 11% [31]. Therefore, it is no surprise that this method is associated with numerous limitations [23,27,32]. Much better results in NEC diagnosis can be achieved using Gordon's criteria (Tables II and III) and ultrasound examination [31,32,33]. Gordon's classification has the main advantage of distinguishing acquired neonatal intestinal diseases in infants, which have a similar clinical course and are often confused [32]. On the other hand, ultrasound examination, which is a sensitive test for detecting HPVG, has satisfactory specificity in NEC diagnosis [4,31,33]. Importantly, Dördelmann et al. [33] reported a specificity of 86% and a sensitivity of 90% for NEC diagnosis by combining ultrasound HPVG detection with Gordon's criteria. It can therefore be assumed that the widespread use of these combined diagnostic methods may contribute to earlier diagnosis of NEC, potentially reducing its mortality and the risk of long-term complications, such as short bowel syndrome or neurodevelopment impairment [25].

Table II. Gordon's criteria for the diagnosis of acquired neonatal intestinal diseases in infants weighing < 1250 grams (based on [32])

Parameter	Feeding intolerance of prematurity	Viral enteritis	Spontaneous intestinal perforation	Necrotizing enterocolitis
Age	< 2 weeks	> 2 weeks	< 2 weeks	> 2 weeks
Feeds (ml/kg/day)	< 80	> 120	< 40	> 80
Clustering	–	+	–	–
Bloody stools	–	+	–	Uncommon
Coagulopathy	–	Related to severity	–	Related to severity
Pneumatosis	–	Common	–	+
Pneumoperitoneum	–	30–40%	100%	20–30%
Ileus	–	Not initially	Variable	+
Surgical finding	None	Ascites, bowel necrosis, distal pneumatosis	Focal perforation of ileum or jejunum	Pneumatosis, mural necrosis
Histological finding	None	Mucosal obliteration, necrosis, inflammation, edema	Robust mucosa, focal necrosis at site of perforation, less inflammation	Mucosal obliteration, necrosis, inflammation, edema
Pathogens	None	Rotavirus, enterovirus	No spec. pathogen	Enterobacteria

Table III. Gordon's criteria for the diagnosis of acquired neonatal intestinal diseases in infants weighing > 1250 grams (based on [32])

Parameter	Cow's milk protein allergy	Viral enteritis	Spontaneous intestinal perforation	Necrotizing enterocolitis
1	2	3	4	5
Age	> 6 weeks	> 2 weeks	< 1 week	< 1 month
Feeds (ml/kg/day)	Cow's milk product	> 120	Unrelated	> 80
Clustering	–	+	–	–
Bloody stools	+	+	–	+
Coagulopathy	–	Related to severity	–	Related to severity
Pneumatosis	Possible	Possible	–	+
Pneumoperitoneum	Rare	Uncommon	+	Less common
Ileus	–	–	Occasional	+

cd. tab. III

1	2	3	4	5
Surgical finding	Ascites, bowel necrosis, distal pneumatosis	Ascites, bowel necrosis, distal pneumatosis	Focal perforation of ileum or jejunum	Pneumatosis, mural necrosis
Histological finding	Mucosal obliteration, eosinophilic inflammation, edema, necrosis	Mucosal obliteration, necrosis, inflammation, edema	Robust mucosa, focal necrosis at site of perforation, less inflammation	Mucosal obliteration, necrosis, inflammation, edema
Pathogens	None	Rotavirus, enterovirus	No spec. pathogen	No spec. pathogen

Limitations of ultrasonography

It should be remembered that despite the numerous advantages of using ultrasonography in pediatric patients with HPVG, this method also has numerous limitations. The result of an ultrasound examination is influenced by multiple variables, such as the patient's condition or the clinician's experience. The barriers to examination on the patient's part include excessive intestinal gas, obesity, and – particularly in children – a lack of cooperation in holding their breath or crying during the examination [1,14,15]. The rarity of HPVG in patients is also significant, as it can result in less training of clinicians in the detection of this symptom, which limits its detection [3].

Another problem is that there is a group of diseases that resemble HPVG on US examination [14]. One condition frequently confused with HPVG is pneumobilia, which also presents as intrahepatic hyperechogenicity [14,34,35]. However, to make the correct diagnosis, it is crucial to be aware that for HPVG, because of the blood flow direction in the portal vein, gas mainly distributes in the peripheral part of the liver, while for pneumobilia, because of the bile flow direction, gas tends to accumulate centrally, further than 2 cm from the liver capsule [6,15]. Other diseases that should be distinguished from HPVG include air in the intrahepatic inferior vena cava and liver abscess [14]. It is important to underscore that all of these conditions require different types of treatment. Therefore, the physicians performing ultrasound examinations must be very familiar with the principles of differentiating between these diseases.

CONCLUSIONS

HPVG is a rare discovery that may be associated with many conditions and does not necessarily indicate a serious illness. We propose US as an imaging method of choice in diagnosing pediatric patients with HPVG, as it is highly sensitive to gas detection, enables the selection of patients with poor prognosis, and helps with diagnosis. We believe that the wider use of US will improve the treatment of pediatric patients with abdominal diseases.

Authors' contribution

Study design – K. Ceglarz, S. Pucyło

Data collection – K. Ceglarz, S. Pucyło, M. Skweres, J. Pielaciński

Manuscript preparation – K. Ceglarz, S. Pucyło, M. Nieczyporuk

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PRACA ORYGINALNA
ORIGINAL PAPER

The influence of fluid restriction on the patient's water distribution during video-assisted thoracoscopy (VATS) – A preliminary report

Wpływ restrykcji płynowej na dystrybucję wody u pacjenta podczas wideotorakoskopii (VATS) – doniesienie wstępne

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ABSTRACT

INTRODUCTION: The principles of optimal perioperative fluid therapy in thoracic surgery have been discussed for many years due to its possible role in pulmonary complications. The aim of the study was to perform a preoperative analysis of bioelectrical impedance (BIA) in patients undergoing video-assisted thoracoscopic surgery (VATS) using one-lung ventilation.

MATERIAL AND METHODS: The study comprised 14 adult patients (11 men and 3 women). BIA was applied to measure total body water (TBW), intracellular body water (ICW), and extracellular body water (ECW) prior to the operation and after the patient's return to the ward. The patients were grouped according to the total water received during the surgery per kilogram of body weight. The accepted cut-off value for restrictive fluid therapy was < 6.5 ml/kg of all fluids received during surgery.

RESULTS: A small elevation of TBW was observed after the surgeries as compared to preoperational values. In restrictive fluid therapy, the values raised from 46.55% (95% CI: 41.58; 51.58) to 46.92% (95% CI: 42.92; 51.32), while for liberal volumes of fluids given during the procedures, the values grew from 37.26% (95% CI: 37.97; 41.56) to 37.63% (95% CI: 33.82; 41.43). However, the differences were not statistically significant (p = 0.983) and fluctuations in the intracellular and extracellular water were unremarkable in both groups.

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CONCLUSIONS: Restrictive fluid therapy does not affect intracellular and extracellular water distribution in patients undergoing VATS.

KEYWORDS

VATS, water distribution, video-assisted thoracoscopy, total body water, bioelectrical impedance analysis, restrictive fluid therapy, perioperative fluid therapy, TBW

STRESZCZENIE

WSTĘP: Zasady prowadzenia optymalnej płynoterapii okołooperacyjnej w trakcie zabiegów torakochirurgicznych są przedmiotem debaty od wielu lat z powodu możliwego związku z rozwojem powikłań płucnych. Celem badania była analiza wpływu płynoterapii restrykcyjnej z użyciem impedancji bioelektrycznej (*bioelectrical impedance analysis* – BIA) u pacjentów poddawanych operacjom wideotorakoskopowym (*video-assisted thoracoscopic surgery* – VATS) z wentylacją jednym płucem.
MATERIAŁ I METODY: Badanie przeprowadzono u 14 dorosłych pacjentów (11 mężczyzn i 3 kobiety). Za pomocą BIA dokonywano pomiarów wody całkowitej (*total body water* – TBW), wewnątrzkomórkowej (*intracellular body water* – ICW) i zewnątrzkomórkowej (*extracellular body water* – ECW) przed operacją oraz po powrocie pacjenta na salę chorych. Pacjentów podzielono ze względu na całkowitą ilość płynów otrzymanych podczas operacji w przeliczeniu na kilogram masy ciała. Za wartość graniczną dla restrykcyjnej płynoterapii przyjęto < 6,5 ml/kg wszystkich płynów podanych podczas operacji.
WYNIKI: Po zabiegach obserwowano niewielki wzrost ilości TBW w porównaniu z wartościami przedoperacyjnymi. Dla restrykcyjnej płynoterapii wartości wzrosły z 46,55% (95% CI = 41,58; 51,58) do 46,92% (95% CI = 42,92; 51,32), natomiast w przypadku dowolnej ilości podanych płynów z 37,26% (95% CI = 37,97;41,56) do 37,63% (95% CI = 33,82; 41,43). Jednak różnice te nie były istotne statystycznie (p = 0,983). Wahania w ilości wody wewnątrzkomórkowej i zewnątrzkomórkowej w obu grupach były nieznaczne.
WNIOSKI: Płynoterapia restrykcyjna nie wpływa na dystrybucję wody wewnątrzkomórkowej i zewnątrzkomórkowej u pacjentów poddawanych VATS.

SŁOWA KLUCZOWE

VATS, dystrybucja wody, wideotorakoskopia, całkowita zawartość wody w organizmie, analiza impedancji bioelektrycznej, płynoterapia restrykcyjna, płynoterapia okołooperacyjna, TBW

INTRODUCTION

The guidelines for optimal perioperative fluid therapy during thoracic surgery have been discussed for many years due to possible development of pulmonary complications [1,2,3,4,5]. Pulmonary complications have been recognized as a cause of markedly poorer recovery after thoracic procedures and constitute a major burden to the healthcare system, including increased costs [6,7]. For a long time now, restrictive fluid supply has been considered an optimal regimen that can restrict the development of pulmonary complications. However, such opinions have also been contested for potential association with other complications, e.g., organ hypoperfusion leading to dysfunction and failure, particularly manifested in acute renal insufficiency [8]. On the other hand, the evaluation of water distribution has been found helpful in assessing the risk of complications such as infection or edema [9,10]. An effective method for estimating body composition, particularly the distribution of water, body fat, and muscle mass, is bioelectrical impedance analysis (BIA). It involves the flow of a weak electric current through the body, the voltage of which is measured to calculate the body's impedance, or its ability to attenuate the current. It has been established that fat does not conduct electricity, and that fat-free body mass is considered a conductive volume that helps electric current flow due to the conductivity of electrolytes dissolved in water. Impedance is made up of resistance and reactance. In biological systems, resistance is due to the total water in the body, while reactance occurs because of the capacitance of the cell membrane. This allows us to measure the values of cellular water as well as extracellular water [11]. This method has been used in research to estimate and analyze changes in disorders of various types of diseases, including in critically ill patients [12,13,14]. The objective of this study was to evaluate the effect of restrictive fluid therapy on water distribution in patients undergoing video-assisted thoracoscopy (VATS) with one-lung ventilation (OLV), using BIA.

MATERIAL AND METHODS

The study comprised 14 adult patients (11 men and 3 women; mean age: 60.5 ± 9.574) undergoing VATS for diagnostic or therapeutic reasons. The mean weights recorded in the liberal and restrictive fluid therapy groups were 72.65 kg (± 7.21 kg) and 79.48 kg

(± 11.52 kg), respectively. Similarly, the mean heights were 169.25 cm (± 5.11 cm) and 177.83 cm (± 4.26 cm), respectively. The study was approved by the Bioethical Committee of the Medical University of Silesia (No. PCN/0022/KB1/08/II/20). All the surgeries were scheduled in advance. The American Society of Anesthesiologists (ASA) scale was used to qualify the patients into groups II or III (Table I). Anesthesia was uniform in both groups and entailed IV administration of propofol (Propofol-Lipuro B. Braun, Germany), fentanyl (Fentanyl WZF, Polfa Warszawa S.A., Poland), and cis-atracurium (Cisatracurium Kalceks AS Kalceks, Latvia). OLV was ensured with a Robertshaw double lumen endotracheal tube. Anesthesia was supported by sevoflurane (Sevoflurane Baxter, Baxter SA, Belgium) at a dosage of 2% v/v and fractional doses of fentanyl and cis-atracurium. FiO_2 1.0 was used during ventilation. The duration of the procedure ranged between 40 and 100 min (average 63.88 min). The patients were grouped according to the total water received during the surgery per kilogram of body weight. They were assigned to groups at random by tossing a coin. The test group included patients receiving targeted fluid therapy (n = 8). The accepted cut-off value for restrictive fluid therapy was < 6.5 ml/kg of all fluids received during surgery. The patients received Sterofundin ISO balanced full electrolyte solution (B. Braun Melsungen AG, Germany). Body composition was evaluated with an Accuniq BC310 analyzer (SELVAS Healthcare Inc., South Korea) in a standing position following the manufacturers' instructions. To avoid measurement errors, the results were automatically calculated using three different frequencies (5, 50, and 250 kHz). The measurements were taken in the evening preceding the surgery and after the patient's return to the ward (before oral hydration was administered). The statistical analysis was conducted with the software program Statistica 12. Normal data distribution was assessed using the Kolmogorov–Smirnov test. In order to compare variables between the groups, ANOVA was used for repeated measures, with the results presented as mean values and standard deviation. Post hoc analysis made use of the Bonferroni test. The accepted cut-off for statistical significance was $p < 0.05$.

Table I. Qualification of patients for individual groups by American Society of Anesthesiologists (ASA) scale grading

ASA grading	Number of patients (n)
II	8
III	6
IV	–

RESULTS

Water distribution was evaluated taking into consideration the parameters of total body water (TBW), intracellular body water (ICW), and extracellular body water (ECW). A statistically significant difference was observed between the test group and the control group for each of these parameters. The average TBW value for the group receiving restrictive volumes of fluids was 46.73%, while the controls showed a mean value of 37.45%. Respectively, the groups' observed values for ICW were 27.75% and 22.19%, while for ECW they were 18.99% and 15.26%. The values of all parameters were markedly higher in the test group as compared to the controls (Table II).

Table II. Comparison of mean total, intracellular, and extracellular body water in the test and control groups

Group	TBW (p = 0.007)	ICW (p = 0.007)	ECW (p = 0.007)
Test group (1) < 6.5 ml/kg	**46.73%** (95% CI = 42.07; 51.40)	**27.75%** (95% CI = 24.91; 30.58)	**18.99%** (95% CI = 17.09; 20.88)
Controls (2) > 6.5 ml/kg	**37.45%** (95% CI = 33.40; 41.49)	**22.19%** (95% CI = 19.74; 24.64)	**15.26%** (95% CI = 13.61; 16.90)

TBW – total body water; ICW – intracellular body water; ECW – extracellular body water.

Both groups showed some increase in TBW following the surgery over the preoperative values (Table III). In restrictive fluid therapy, the values were 46.55% and 46.92%, respectively; for liberal fluid supply, they were 37.26% and 37.63%, respectively. However, the differences were not statistically significant (p = 0.983). Fluctuations in the intracellular-to-extracellular-water ratio were unremarkable in both groups. ICW levels in the patients supplied with fluids at a volume of < 6.5 ml/kg amounted to 27.51% before the surgery and 27.98% afterwards. The controls showed mean values of 22.14% and 22.24%, respectively (Table IV). Such results did not correspond to the level of statistical significance chosen for the study. The p-value for ICW amounted to 0.464. Similarly, measurements of ECW were 19.03% prior to surgery and, paradoxically, as high as 18.94% after the procedures. In the control group, these values were 15.12% and 15.38%, respectively (Table V).

Table III. Comparison of total body water (TBW) prior to and after surgery in the test and control groups

Group	Time	Mean (%)	-95.00% (%)	+95.00% (%)	p
Test group (1) < 6.5 ml/kg	TBW preoperative	46.55	41.58	51.51	0.983
	TBW postoperative	46.92	42.52	51.32	
Controls (2) > 6.5 ml/kg	TBW preoperative	37.26	32.97	41.56	
	TBW postoperative	37.63	33.82	41.43	

Table IV. Comparison of intracellular body water (ICW) prior to and after surgery in the test and control groups

Group	Time	Mean (%)	-95.00% (%)	+95.00% (%)	p
Test group (1) < 6.5 ml/kg	ICW preoperative	27.51	24.59	30.43	0.464
	ICW postoperative	27.98	25.19	30.77	
Controls (2) > 6.5 ml/kg	ICW preoperative	22.14	19.61	24.67	
	ICW postoperative	22.24	19.82	24.66	

Table V. Comparison of extracellular body water (ECW) prior to and after surgery in the test and control groups

Group	Time	Mean (%)	-95.00% (%)	+95.00% (%)	p
Test group (1) < 6.5 ml/kg	ECW preoperative	19.03	16.96	21.10	0.264
	ECW postoperative	18.94	17.20	20.68	
Controls (2) > 6.5 ml/kg	ECW preoperative	15.12	13.33	16.91	
	ECW postoperative	15.38	13.87	16.89	

DISCUSSION

Our study analyzed bioelectric impedance in patients undergoing thoracoscopic surgery according to the adopted method of perioperative fluid therapy. Our results indicate no effect of the volume of supplied crystalloids on body water distribution after the selected thoracic surgeries. Both restrictive and liberal volumes of fluid resulted in unremarkable fluctuations in water parameters, with a minor increase in TBW after the surgery. Also, no statistical fluctuations in ICW and ECW were observed.

The available literature fails to illustrate multiple studies in the area of this important, nevertheless controversial issue. A similar study was carried out upon resection of the esophagus, where fluid dynamics was evaluated during the perioperative period. The authors suggested the potential for forecasting the occurrence of infection on the basis of BIA. Contrary to our study, the volumes of ECW and the ECW/TBW ratio were elevated during the postoperative period [9]. Another analysis was carried out by Wu et al. [15] in a retrospective, single-center observational study comprising 446 adults undergoing minimally invasive lobectomy. The participants supplied with crystalloids were divided into four groups depending on the volume of fluid per kilogram of body weight during one hour of the procedure, while the patients receiving colloids were divided into three groups. The results illustrate that both restrictive and liberal fluid therapy with crystalloids led to a worse course in the postoperative period and a greater incidence of complications. Interestingly, similar negative effects were observed in the patients who did not receive colloids or when their supply was strictly limited. The study bears numerous limitations, however, including a long list of exclusions for the subjects; therefore, any final conclusions should be approached very cautiously. The exact effect of colloids during thoracic surgery remains unclear. Studies on colloid therapies have drawn some conflicting conclusions, but they comprised inconsistent groups of patients suffering from different predominant conditions [16,17,18,19,20]. A possible alternative seems to be a targeted therapy, though it demands additional hemodynamic monitoring. Also, the benefits themselves are not clear, as the results originate from studies in areas other than thoracic surgery with OLV [21,22,23,24]. Numerous authors claim that fluid therapy should be an individually selected regimen managed by an interdisciplinary team to take into consideration the predominant condition, any concomitant diseases, and the general health status of the patient [15,25,26]. The concept of BIA is a recent development in thoracic surgery research. A team of researchers in Italy have utilized BIA to identify a substantial occurrence of fluid retention subsequent to lobectomy. Their conclusion was that BIA constituted an accessible, reproducible, and non-invasive technique for the assessment and early detection of fluid retention. The present study found no correlation

between fluid retention and the duration of anesthesia, gender, age, blood loss, or body mass index [27]. Another study used BIA in a repeat lobectomy with the VATS method, with the objective of measuring the effect of tumor removal on body weight [28].

CONCLUSIONS

Adequate perioperative fluid therapy is considered key to reducing postoperative pulmonary complications. There is no proven effect of restrictive fluid therapy on water balance in patients undergoing VATS.

Limitations

When interpreting the results of this study, it is important to consider its limitations. The measurements were obtained using a device that has only been employed on two occasions in the context of scientific studies. The measurement was taken in a standing position, which is not feasible for a significant number of thoracic surgery patients immediately after surgery. The random selection of patients in the small sample could have influenced the results. Therefore, it is necessary to conduct further studies comprising a larger cohort of patients.

Authors' contribution

Study design – S. Białka, J. Zalejska-Fiolka
Data collection – P. Wichary, D. Kowalski, M. Czaja
Data interpretation – S. Białka, P. Wichary, D. Kowalski
Statistical analysis – S. Białka, P. Wichary, D. Kowalski
Manuscript preparation – P. Wichary, D. Kowalski, S. Mika
Literature research – P. Wichary, D. Kowalski, S. Mika

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OPIS PRZYPADKU
CASE REPORT

Too late for prevention, too early for disease – invasive cervical cancer in a 28-year-old woman

Zbyt późno na profilaktykę, zbyt wcześnie na chorobę – inwazyjny rak szyjki macicy u 28-letniej kobiety

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ABSTRACT

Cervical cancer is one of the most common gynecological malignancies worldwide. The main risk factor is persistent infection with oncogenic types of human papillomavirus (HPV), particularly types 16 and 18. The disease is rarely observed in young women and progresses slowly. In its early stages is often asymptomatic, which may delay diagnosis and worsen prognosis. This paper presents the case of a 28-year-old woman who reported recurrent intermenstrual bleeding and postcoital vaginal spotting. Initial clinical evaluation revealed a palpable mass and tenderness in the region of the right adnexa, raising suspicion of a tumor in that area, which was confirmed by ultrasonographic examination. Further imaging and histopathological evaluation confirmed invasive squamous cell carcinoma of the cervix, with infiltration of adjacent structures and a concurrent neoplastic lesion of the right adnexa what made it inoparable. This case highlights the importance of regular cervical cancer screening and timely diagnostic evaluation, particularly in younger women, whose symptoms may be nonspecific. Early detection significantly improves the chances of effective treatment and long-term survival.

KEYWORDS

cervical cancer, abnormal uterine bleeding, oncological prevention, HPV infection

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STRESZCZENIE

Rak szyjki macicy jest jednym z najczęstszych nowotworów ginekologicznych na świecie. Głównym czynnikiem ryzyka jest przewlekła infekcja onkogennymi typami wirusa brodawczaka ludzkiego (*human papillomavirus* – HPV), szczególnie 16 i 18. Choroba rzadko występuje u młodych kobiet, a jej rozwój postępuje wolno. We wczesnym stadium często przebiega bezobjawowo, co może opóźniać rozpoznanie i pogarszać rokowanie. W pracy przedstawiono przypadek 28-letniej pacjentki, która zgłosiła się z powodu nawracających krwawień międzymiesiączkowych oraz plamień kontaktowych. Wstępna ocena kliniczna wykazała obecność oporu i tkliwości w rzucie przydatków prawych – podejrzenie zmiany guzowatej w tej okolicy, potwierdzonej w badaniu ultrasonograficznym. Dalsza diagnostyka obrazowa i histopatologiczna potwierdziła obecność inwazyjnego raka płaskonabłonkowego szyjki macicy z naciekiem na sąsiednie struktury oraz współistniejącą zmianą nowotworową przydatków prawych, co uniemożliwiło leczenie operacyjne. Na podstawie opisanego przypadku należy podkreślić znaczenie regularnych badań przesiewowych i szybkiej diagnostyki w kierunku raka szyjki macicy, zwłaszcza u młodszych kobiet, u których objawy mogą być mało charakterystyczne. Wczesne wykrycie nowotworu znacznie zwiększa szanse na skuteczne leczenie oraz przeżycie.

SŁOWA KLUCZOWE

rak szyjki macicy, nieprawidłowe krwawienia z dróg rodnych, profilaktyka onkologiczna, wirus HPV

INTRODUCTION

Cervical cancer ranks among the most frequent gynecological cancers globally. The most significant risk factor is persistent co-infection with high-risk human papillomavirus (HPV) subtypes, primarily types 16 and 18. In the early stages, the disease may be completely asymptomatic. However, symptoms such as intermenstrual bleeding, vaginal spotting or bleeding after sexual intercourse, and visible changes to the cervix should raise clinical concern [1].

CASE REPORT

A 28-year-old woman presented to the Outpatient Department of the hospital with abnormal intermenstrual bleeding – current bleeding with clots had persisted for four days. She reported spontaneous episodes of bleeding for approximately eight months, along with postcoital vaginal spotting and right-sided sciatica-like pain. The patient had a cytology result indicating the absence of cells from the cervical canal and the presence of HPV 16 infection.

On physical examination, slight vaginal bleeding was noted, and the cervix appeared firm on palpation. There was also a palpable mass and pain during palpation in the area of the right adnexa – raising suspicion of a tumor in this region. Transvaginal ultrasound revealed a hypoechoic cyst, most likely originating from the right adnexa measuring 50 × 50 × 45 mm. Additionally, there was a structure next to the uterus which could be pathological tube (Figure 1) and a mass located in the retroperitoneal space adjacent to the right iliopsoas muscle, measuring 47 × 39 mm (Figure 2). Diagnostic imaging was extended to include computed tomography (CT), which also showed irregular thickening of the cervix, and confirmed all the pathological lesions observed on ultrasonography.

Due to the patient's increasing pain, a decision was made to perform laparoscopy, during which the enlarged right fallopian tube with the tumor was removed. No other abnormalities in the right adnexa were observed intraoperatively. The postoperative specimen was sent for histopathological examination.

Due to continued moderate vaginal bleeding and the absence of a cytology result, cervical canal curettage and cervical biopsy were performed. An abundant tissue sample was obtained from the cervical canal and cervix, suspicious for neoplastic changes. The specimen was sent for histopathological examination.

Repeated ultrasound evaluation revealed right-sided hydronephrosis and enlarged lymph nodes (not seen at the beginning) in the tissue surrounding the cervix (Figures 3 and 4). These findings were confirmed on contrast-enhanced magnetic resonance imaging (MRI), which revealed thickening of the uterine walls, cervix, and bilateral parametria, along with heterogeneous enhancement of the right adnexal mass and adjacent lymph nodes. Laboratory tests showed mild anemia (Hb 10.3 g/dL) and elevated inflammatory markers (CRP 58 mg/L). Renal function was within normal limits.

Histopathological analysis confirmed cervical squamous cell carcinoma (non-keratinizing, G2, p16+, CK5/6+, Ki-67 > 50%) and a poorly differentiated epithelial neoplasm of the right adnexa with an inconclusive immunoprofile (ER−, p53+, CDX-2−). The patient was referred for multidisciplinary oncologic evaluation and treatment planning.

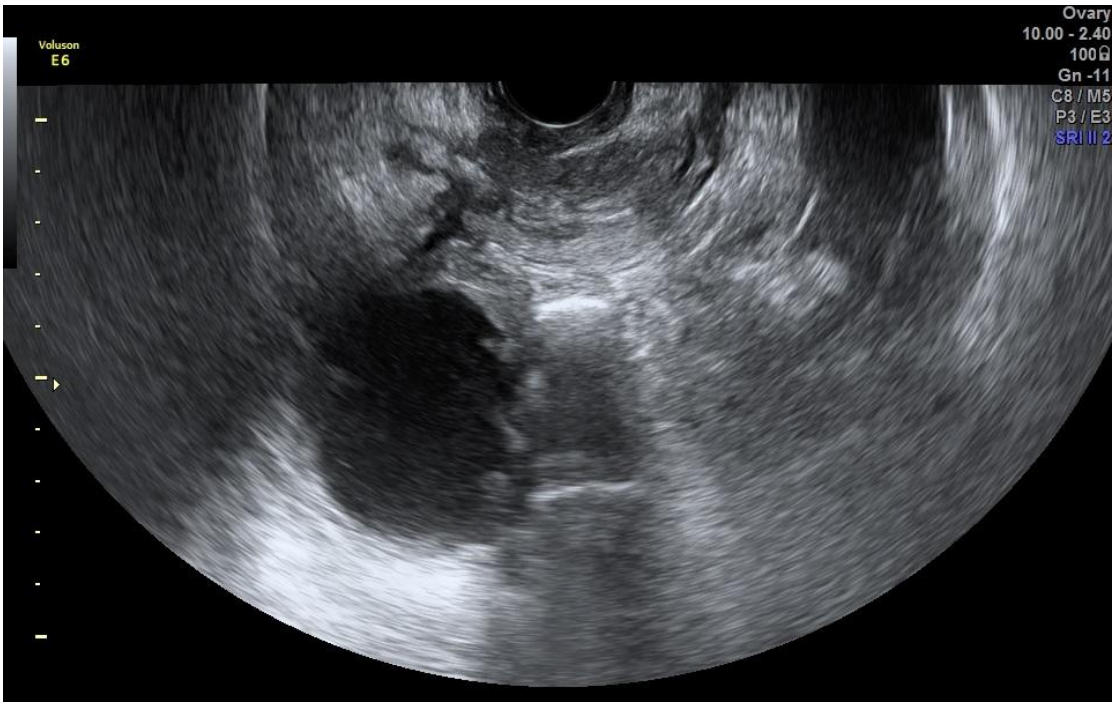

Fig. 1. Right adnexal lesion – right fallopian tube (preoperative).

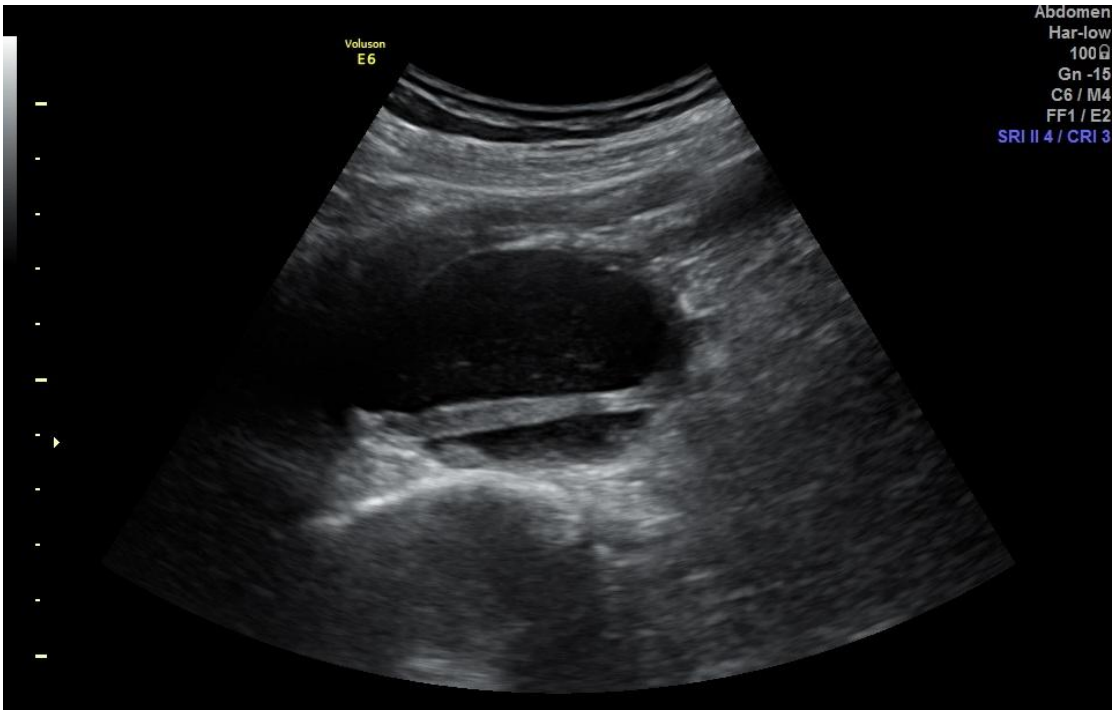

Fig. 2. Cyst in the iliopsoas muscle with the sciatic nerve passing through it.

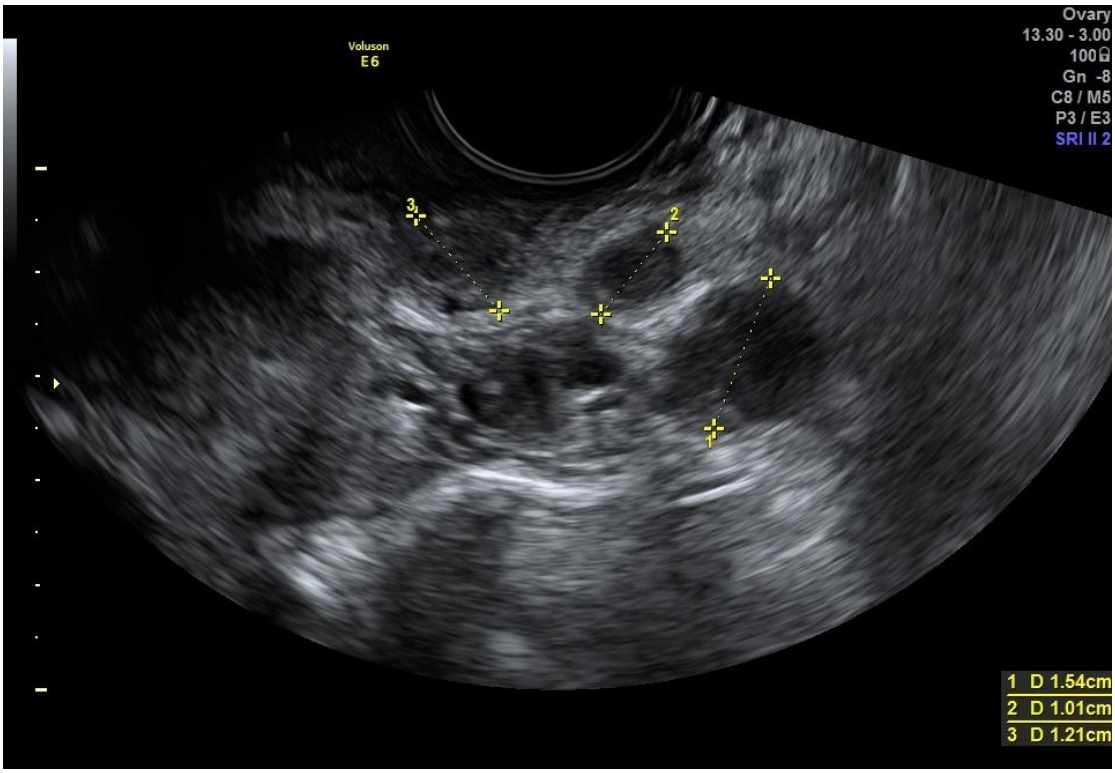

Fig. 3. Left peri-adnexal lymph nodes (post-laparoscopy).

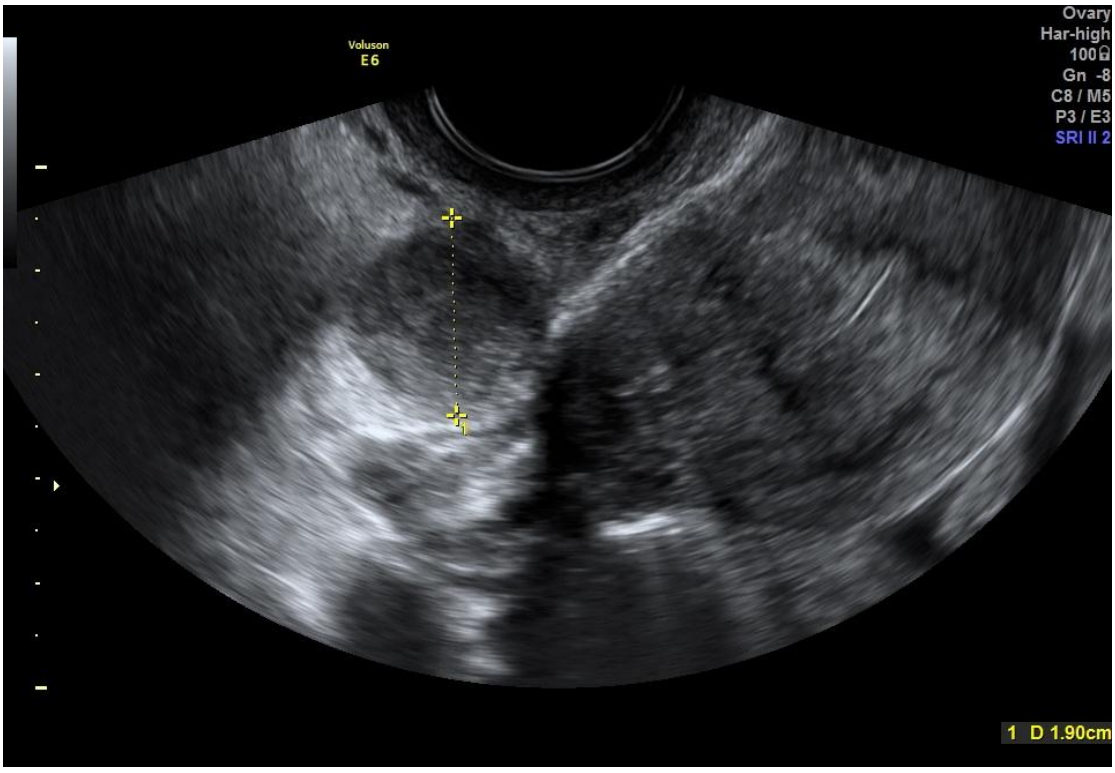

Fig. 4. Right adnexal mass (lymph node) adherent to the uterus.

DISCUSSION

Cervical cancer is the fourth most commonly diagnosed malignancy among women globally [1]. In Poland, population-based screening programs include cervical cytology and HPV testing [2]. However, compared to Western Europe, screening coverage remains low, contributing to higher incidence and mortality rates [3]. This can be explained by the low percentage of women reporting for preventive examinations, which may result from low social awareness of the risk of not taking preventive measures [4]. Early symptoms are often nonspecific, including acyclic bleeding and postcoital spotting [5], which hinders timely diagnosis and worsens prognosis.

Key risk factors are related to HPV infection and include early onset of sexual activity, multiple sexual partners, and a history of sexually transmitted infections. Additional contributors include high endogenous estrogen levels (e.g., in obesity), low socioeconomic status, smoking, and genetic predisposition [5,6,7,8,9,10,11].

HPV-induced carcinogenesis typically occurs at the squamocolumnar junction of the cervix, where persistent infection disrupts the host immune response and cell cycle regulation. This leads to dysplastic cell proliferation and progression to invasive cancer [1,12]. The most common histologic type is squamous cell carcinoma (~75%), followed by adenocarcinomas (~25%), including adenosquamous variants [13,14]. These tumors originate from cervical intraepithelial neoplasia (CIN), carcinoma in situ (CIS), or adenocarcinoma in situ (AIS) [1]. Rare histologic subtypes include neuroendocrine tumors, small cell carcinomas, rhabdomyosarcomas, and lymphomas [15,16,17,18].

Diagnosis relies on speculum examination and cervical cytology with HPV genotyping. Colposcopy with targeted biopsy and endocervical curettage is indicated in cases of abnormal cytology or visible lesions. Imaging modalities such as CT, MRI, or PET-CT are essential for staging based on FIGO and TNM systems [1,19,20].

Treatment options vary by disease stage and include surgery, radiotherapy, and chemoradiation [1]. Prognosis is favorable in early-stage disease (44% of cases), with a 5-year survival rate of up to 92%. This drops to 60% in locally advanced cases and 19% in cases with distant metastases [1].

CONCLUSIONS

This case underscores the nonspecific nature of early cervical cancer symptoms and emphasizes that young women are not immune to the disease. Considering the natural progression of HPV-related cervical neoplasia, robust screening efforts and public health education remain critical. Furthermore, it is important for clinicians to ensure the quality of the collected cytology sample, as it determines the accuracy of the diagnosis. Despite available programs, patients participation remains suboptimal, and increasing awareness is vital to improving early detection and outcomes.

Authors' contribution

Study design – S. Woźniak
Data collection – T. Bryś, B. Rembielak-Stawecka
Manuscript preparation – T. Bryś
Literature research – T. Bryś, B. Rembielak-Stawecka, S. Woźniak
Final approval of the version to be published – B. Rembielak-Stawecka, S. Woźniak

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PRACA ORYGINALNA
ORIGINAL PAPER

Dietary patterns and cardiovascular risk in adolescent males: An epidemiological study among high school students in Silesia, Poland

Wzorce żywieniowe a ryzyko sercowo-naczyniowe u nastoletnich chłopców: badanie epidemiologiczne wśród uczniów szkół średnich w województwie śląskim

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ABSTRACT

INTRODUCTION: Cardiovascular diseases (CVDs) are a major cause of mortality globally, including in Poland. Their risk factors include both non-modifiable (e.g., age or genetics) and modifiable elements (e.g., diet and physical activity). Among the latter, diet plays a pivotal role in prevention. Poor dietary habits – such as high intake of saturated fats and low consumption of fruits and vegetables – significantly increase CVDs risk. The aim of this study was to assess the risk of developing CVDs among adolescents based on their dietary habits.

MATERIAL AND METHODS: The research, conducted in May 2024, involved 583 male students from School No. 10 in Zabrze, Poland. An anonymous questionnaire gathered information on eating habits, meal composition, food preparation, and seasoning practices. Statistical analysis was carried out using Microsoft Excel, including chi-square tests and correlation analysis.

RESULTS: The results showed that 78.8% of participants had a normal body mass index (BMI), 14.1% were overweight, and 2% were obese. About 50% rated their nutritional knowledge as good. A moderate positive correlation was found between nutritional knowledge and physical activity ($r = 0.34$; $p < 0.05$). While daily vegetable consumption was 54%, fruit consumption was slightly lower, at 48%. A high intake of saturated fats and insufficient consumption of fruits and vegetables were significantly linked to increased CVDs risk ($\chi^2 = 34.36$; $p < 0.0001$).

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CONCLUSIONS: Despite normal BMI values among participants, the findings highlight the need to strengthen nutrition education. The unbalanced dietary pattern and excessive intake of saturated fats justify implementing preventive measures aimed at reducing cardiovascular risk and promoting healthier habits in adolescents.

KEYWORDS

risk factors, adolescents, cardiovascular diseases, nutritional education, dietary habits

STRESZCZENIE

WSTĘP: Choroby układu krążenia (*cardiovascular diseases* – CVDs) są główną przyczyną zgonów na świecie, również w Polsce. Czynniki ryzyka obejmują zarówno czynniki niemodyfikowalne (np. wiek, genetyka), jak i modyfikowalne (np. dieta, aktywność fizyczna). Spośród tych ostatnich dieta odgrywa kluczową rolę w profilaktyce. Niezdrowe nawyki żywieniowe – takie jak wysokie spożycie tłuszczów nasyconych i niskie spożycie owoców i warzyw – znacznie zwiększają ryzyko CVDs. Celem badania była ocena ryzyka rozwoju CVDs u młodzieży na podstawie ich zachowań żywieniowych.
MATERIAŁ I METODY: Badanie przeprowadzono w maju 2024 r. w grupie 583 uczniów płci męskiej z Zespołu Szkół nr 10 w Zabrzu. Zastosowano anonimową ankietę dotyczącą nawyków żywieniowych, składu posiłków, metod przygotowywania potraw oraz sposobów przyprawiania. Analizy statystyczne przeprowadzono w programie Microsoft Excel, wykorzystując testy chi-kwadrat oraz analizę korelacji.
WYNIKI: Wyniki wskazały, że 78,8% badanych miało prawidłowy wskaźnik masy ciała (*body mass index* – BMI), 14,1% miało nadwagę, a 2% było otyłych. Około 50% badanych oceniło swoją wiedzę na temat żywienia jako dobrą. Stwierdzono umiarkowaną dodatnią korelację między wiedzą na temat żywienia a aktywnością fizyczną ($r = 0,34$; $p < 0,05$). Dzienne spożycie warzyw wyniosło 54%, a owoców nieco mniej, bo 48%. Nadmierne spożycie tłuszczów nasyconych i niewystarczające spożycie owoców i warzyw były istotnie związane ze zwiększonym ryzykiem CVDs ($\chi^2 = 34,36$; $p < 0,0001$).
WNIOSKI: Pomimo prawidłowych wartości BMI u badanych wyniki wskazują na potrzebę intensyfikacji działań związanych z edukacją żywieniową. Niezbilansowana dieta i nadmierne spożycie tłuszczów nasyconych uzasadniają wdrażanie działań profilaktycznych ukierunkowanych na ograniczenie ryzyka sercowo-naczyniowego i kształtowanie zdrowych nawyków wśród młodzieży.

SŁOWA KLUCZOWE

czynniki ryzyka, młodzież, choroby sercowo-naczyniowe, edukacja żywieniowa, nawyki żywieniowe

INTRODUCTION

Cardiovascular diseases (CVDs) encompass a broad spectrum of circulatory system disorders, including heart diseases, blood vessel disorders, and metabolic disturbances, which represent a significant health concern in developed countries and remain the leading cause of death worldwide. In 2019, nearly 18 million deaths were attributed to CVDs, including 6.5 million cases among individuals under the age of 70 [1,2,3]. In 2020–2021 in Poland, these diseases were the primary cause of death, emphasizing the need for effective preventive measures [4].

CVD risk factors are classified as non-modifiable and modifiable. Non-modifiable factors include sex, age, and genetic predispositions [5]. Women are less frequently affected by CVDs, yet when they occur, they are associated with worse prognoses and higher mortality rates [6,7]. Age also plays a crucial role, with its impact amplified by other factors such as obesity, hypertension, and diabetes [8]. Genetic factors, both polygenic and monogenic, significantly influence CVD development. An example of a monogenic disease that increases the risk of premature cardiovascular complications is familial hypercholesterolemia (FH) [9,10].

Modifiable risk factors, such as diet, physical activity, body weight, and substance use, have a substantial impact on CVD development [11]. Regular physical activity improves insulin sensitivity, reduces blood pressure, and enhances endothelial function, reducing the risk of CVDs [12,13,14]. Conversely, excessive body weight, particularly visceral obesity, leads to severe metabolic disturbances and mechanical strain on the heart, increasing the risk of atherosclerosis and hypertension [15,16,17].

Diet plays a crucial role in CVD prevention. Excessive consumption of saturated fatty acids, trans isomers, and highly processed foods promotes elevated low-density lipoprotein cholesterol (LDL-C) levels and the development of atherosclerosis [18,19,20]. On the other hand, a diet rich in plant protein, fiber, and unsaturated fatty acids is associated with a lower risk of CVDs [21,22]. Excessive salt and simple carbohydrate intake can raise blood pressure and lead to dyslipidemia [23,24,25].

Effective dietary models for CVD prevention include the DASH and Mediterranean diets. The DASH diet (Dietary Approaches to Stop Hypertension)

emphasizes the consumption of vegetables, fruits, whole grains, and low-fat dairy products and the restriction of sodium. Studies have shown that this diet lowers blood pressure and LDL-C levels and reduces systemic inflammation [26,27]. The Mediterranean diet, rich in olive oil, fish, nuts, and legumes, also contributes to improved lipid profiles and reduced cardiovascular risk [28,29].

Health education plays a key role in both primary and secondary CVD prevention. Promoting healthy habits, including a proper diet and regular physical activity, helps patients make informed health decisions [30]. Early health education among children and adolescents, including nutritional education, aims to establish long--term positive health habits that reduce CVD risk in adulthood [31].

Adolescence is a crucial period in human development, during which dietary habits likely to persist into adulthood are established. Moreover, optimal nutritional intake during this stage is essential to support full growth potential and reduce the risk of developing noncommunicable diseases, including CVDs [32]. Notably, women are generally less likely to develop CVDs than men, which underscores the importance of incorporating dietary education focused on CVD prevention, particularly for adolescent males [33].

In summary, a comprehensive approach to CVD prevention should involve interdisciplinary actions based on health education, regular physical activity, and a well-balanced diet. Implementing such strategies at both the individual and societal levels can significantly reduce the global burden of these diseases, improve quality of life, and reduce health care costs.

The aim of this study was to conduct a comprehensive analysis and assessment of the risk of developing CVDs among school-aged adolescents in the context of dietary habits, considering diet quality, the frequency of consumption of specific food groups, the nutritional value of meals, and the adherence of dietary habits to current nutritional guidelines. The study aimed to identify dietary factors that may contribute to an increased risk of CVDs.

MATERIAL AND METHODS

Study design

The study group consisted of 583 male students attending high schools in the Polish region of Silesia. The sample was randomly selected from all available groups of students within the school. To ensure random selection, a stratified random sampling method was employed: each high school was treated as a separate stratum and groups were randomly selected within each stratum to achieve a balanced representation of various school types and educational profiles across the region. The representativeness of the sample was verified by comparing demographic and academic performance variables with regional statistical data provided by Statistics Poland. The selected sample size was calculated to achieve a 95% confidence level with a 10% margin of error. The formula used for this step was $n = (Z^2 \times p \times (1-p)) / E^2$, where n is the required sample size, Z is the Z-value (1.96 for a 95% confidence level), p is the estimated proportion of the population (0.5 for maximum variability), and E is the margin of error (0.10). The resulting sample size was 96.04, rounded up to 99 participants for greater reliability. To further verify representativeness, the chi--square test was conducted to compare the distributions of age, academic performance, and school type between the sample and the population. The p-values exceeded 0.05, indicating no statistically significant differences, confirming the representativeness of the sample. Questionnaires were distributed in each selected group during school hours with the consent of the school principal. This procedure minimized the risk of self-selection bias and ensured high response rates.

Research tool

The study used a questionnaire based on the Food Frequency Questionnaire (FFQ), designed to assess the frequency of consuming specific food groups, as well as food preparation methods and selection of condiments. The process of validating the tool included a pilot study with a group similar to the target population, which allowed the questionnaire to be refined in terms of the relevance and comprehensibility of the questions. The reliability of the questionnaire was assessed using Cronbach's alpha, which was 0.85, indicating high internal consistency of the tool. The stability of the results was confirmed by the test-retest correlation, which reached 0.82. The questionnaire was designed in accordance with the scientific literature, where FFQ tools are widely recognized as effective in studies of adolescents' eating habits, enabling a reliable assessment of their diet and potential health risk factors [34,35].

Research ethics

The study obtained approval from the Bioethics Committee of the Medical University of Silesia in Katowice (No. BNW/NWN/0052/KB/295/23/24, issued on 14 December 2023). The research was conducted in adherence with the principles of scientific research ethics. Participation in the study was entirely voluntary, and students had the right to withdraw at any stage without providing a reason. Personal data was not collected, and the results were presented collectively, ensuring the participants' anonymity. The study was carried out with the informed consent of the school

principal, ensuring compliance with the institution's internal regulations. It posed no physical or psychological risk to the participants. Approval from the ethical committee was not required for this specific aspect of the study, as per the Polish Medical Profession Act (Dz.U. 1997 No. 28, item 152, as amended) and the Declaration of Helsinki, due to its questionnaire-based nature. Data such as height and body weight were self-reported, eliminating the need for any intrusive procedures, such as bioimpedance measurement. The study design ensured that all ethical and legal requirements were upheld.

Data analysis

The data was subjected to quantitative analysis using Microsoft Excel. The analysis included coding responses by assigning numerical values to each answer and calculating descriptive statistics (means and standard deviation) and correlation coefficients. Statistical tests were performed, including the chi--square test for frequency comparisons and Pearson's correlation coefficient for relationships between variables. The analysis also involved calculations for the odds ratio of cardiovascular risk in the study group. Results with a p-value of < 0.05 were considered statistically significant.

RESULTS

An expanded analysis of the study, conducted on a diverse group of respondents, revealed a detailed distribution of body mass index (BMI) classifications and their associations with various health and lifestyle factors. The results indicate that 64.8% of the participants had a BMI within the normal range, suggesting a healthy body weight. However, 20.2% were classified as overweight, 7% as obese, and 8% as underweight (Figure 1). Comparing BMI distribution patterns, most respondents fell within the normal range, but nearly one in six struggled with excess body weight, emphasizing the importance of weight management education.

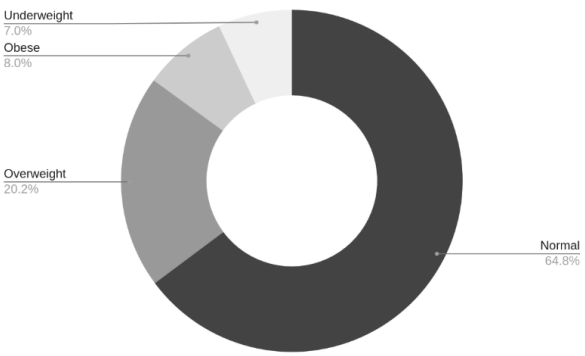

Fig. 1. Percentage distribution of the group by body mass index (BMI).

The self-assessment of nutritional knowledge varied, with 50% of the participants rating their knowledge as good, 32% as moderate, and 18% as poor. A positive correlation was observed between higher self-assessed nutritional knowledge and healthier BMI levels ($r = 0.28$; $p < 0.05$), suggesting that education on nutrition could influence weight management behavior (Table I).

Table I. Comparison of respondents' body mass index (BMI) and nutritional knowledge

BMI	n (%)	Nutritional knowledge	n (%)	r	p-value
Normal	64.8	Good	50		
Overweight and obese	27.2	Moderate	32	0.28	0.05
Underweight	8	Poor	18		

Physical activity levels were diverse, with 31% of respondents reporting very high activity, 21% high activity, 28% moderate activity, and 20% low to very low activity. A significant positive relationship was found between physical activity levels and BMI within the normal range ($r = 0.42$; $p < 0.01$; Table II). Further, nutritional knowledge and physical activity showed a moderate positive correlation ($r = 0.34$; $p < 0.05$), reinforcing the connection between health literacy and lifestyle choices.

Table II. Comparison of respondents' body mass index (BMI) and physical activity

BMI	n (%)	Physical activity	n (%)	r	p-value
Normal	64.8	High	52		
Overweight and obese	27.2	Moderate	28	0.42	0.01
Underweight	8	Low	20		

In terms of dietary habits, the consumption of cereal products was high, with 87% of respondents regularly consuming them, including 38% daily and 49% several times a week. Fruit consumption was also frequent, with 48% consuming fruit daily and 39% several times a week. Vegetable consumption surpassed fruit intake, with 54% consuming vegetables daily and 37% several times a week. The statistical analysis showed a significant difference in favor of vegetable consumption ($p < 0.05$). Those who consumed fruits and vegetables more frequently demonstrated healthier BMI levels and lower cardiovascular risk markers.

In terms of beverage preferences, 82% of the participants primarily drank mineral, table, or spring water, while 32% consumed fruit and vegetable juices regularly. Daily energy drink consumption was reported by only 12%, indicating a generally low intake of such products, which aligns with healthier consumption patterns.

Regarding meat consumption, poultry was the most consumed, with 52% selecting chicken or turkey as their primary choice, while 29% indicated uncertainty about their meat preferences. Fish consumption was reported by 19% of participants at least once a week, while red meat was consumed weekly by 34%.

The consumption of fats in the diet revealed that butter was the most frequently used fat, reported by 42% of respondents, while 27% used vegetable oils. Uncertainty about fat consumption was noted by 15% of participants. A chi-square test identified a significant association between butter consumption and higher BMI levels ($\chi^2 = 19.56$; $p < 0.01$).

The consumption patterns of salty snacks and sweets varied. Fast food, instant products, and salty snacks were consumed several times a month by 69% of the respondents and several times a week by 22%. The consumption of sweet snacks was higher among boys, with 44% consuming sweets multiple times a week and 14% reporting daily consumption. Excessive consumption here was associated with higher BMI and lower physical activity levels ($r = 0.29$; $p < 0.05$).

The data revealed that 52% of the respondents could not estimate their daily intake of salt, while the remaining participants reported consuming at least one teaspoon per day. Excess salt consumption was associated with higher reported blood pressure levels among the participants over 25 years of age ($r = 0.31$; $p < 0.01$).

Further analysis highlighted that 42% of respondents fell into a high-risk group for CVDs due to poor diet quality, excessive body weight, and low fruit and vegetable intake. A chi-square test confirmed a significant association between saturated fat consumption and cardiovascular risk ($\chi^2 = 34.36$; $p < 0.0001$). Moreover, a logistic regression model identified high BMI, low physical activity, and frequent processed food consumption as significant predictors of cardiovascular risk (OR = 2.3, CI 95% [1.7–3.2], $p < 0.001$; Table III).

Table III. Cardiovascular risk predictors in the study group

Cardiovascular risk predictors	OR	CI	p-value
High BMI	2.3		0.001
Low physical activity	2.1		0.001
Poor nutritional knowledge	N/A		NS
Consumption of processed foods	2.5	95%	0.001
Consumption of saturated fats	N/A		NS
High salt intake	N/A		NS
Consumption of sweet snacks	1.9		0.001

BMI – body mass index; OR – odds ratio; CI – confidence interval.

DISCUSSION

Adolescence is a critical period for establishing lifelong health behaviors, including dietary patterns and physical activity levels. Given the increasing prevalence of obesity and related health conditions among adolescents worldwide, it is essential to investigate factors that influence nutritional habits and their potential impact on cardiovascular health. This study explored dietary behaviors, nutritional knowledge, and physical activity patterns among adolescents, shedding light on both positive trends and areas requiring targeted health education. The findings contribute to the broader discourse on health promotion among adolescents and provide insight for public health interventions aimed at fostering balanced nutrition and reducing cardiovascular risk in this population.

The study reported that 78.8% of the participants maintained a BMI within the normal range, while 14.1% were classified as overweight and 2% as obese. These findings mirror global trends reported by the World Health Organization (WHO), which highlights a rising prevalence of adolescent obesity, particularly in developed nations, where high-calorie diets often lack nutritional quality [23]. The self-reported nature of the BMI data used in this study could have introduced an underreporting bias, as observed in previous population health surveys comparing self-reported and measured BMI values [36].

The percentages of overweight and obese adolescents in the study group were 14.1% and 2%, respectively, which are lower than the global figures provided by the WHO. The organization indicates that globally, the prevalence of overweight and obesity among adolescents has increased significantly in recent years, reaching values above 20% in some regions [23]. The lower results obtained in our study may be due to regional differences, the level of health education, and cultural habits. At the same time, it should be taken into account that the results may be underestimated in part due to the survey methodology, in which the participants self-reported their weight and height. This approach runs the risk of underestimating BMI due to the tendency to underreport weight or overestimate height. In addition, the study group were at a developmental age characterized by dynamic changes in height and weight. These factors may further affect the final interpretation of the results. Although the incidence of overweight and obesity in the study group was lower than the global average, the problem still affects one sixth of the participants. This underscores the need for further educational and preventive measures, especially in terms of reducing

the consumption of high-calorie products and promoting physical activity.

Nutritional knowledge was found to have a moderate positive correlation with physical activity. This association is consistent with findings from previous studies emphasizing the role of health literacy among adolescents in promoting healthier lifestyle choices, including increased physical activity and improved diet quality [37,38]. However, the cross-sectional design of the study precludes causal inferences. Longitudinal studies are recommended to clarify the directionality of these relationships.

The study also revealed a difference between intake of vegetables (54% daily consumption) and fruits (48% daily consumption). This imbalance contrasts with national dietary guidelines advocating balanced intake from both groups due to their combined nutritional benefits, including fiber, antioxidants, and essential vitamins [39]. Increased fruit consumption has been associated with a reduced risk of CVDs in multiple cohort studies [40]. This indicates a potential area for targeted dietary education focusing on balanced consumption of fruits and vegetables. The high proportion of the study group who consume vegetables (54%) and fruits (48%) daily is a positive result in the context of WHO data, which emphasizes the importance of regularly consuming these food groups in terms of preventing CVD [40]. The difference between vegetable and fruit consumption may be related to their greater availability, lower price, or regional taste preferences. Dietary recommendations point to the need for a balanced intake of both groups of products due to their complementary nutritional values, such as fiber, vitamins, and antioxidants [39]. Further educational efforts should focus on raising awareness of dietary balancing and eliminating barriers to accessing fruit, especially among groups with lower economic status.

Regarding beverage consumption, most participants (82%) reported regular water intake, with only 12% consuming energy drinks daily. This positive trend diverges from European data showing energy drink consumption rates as high as 40% among adolescents [41]. The low intake of energy drinks in this study is encouraging, as the high caffeine and sugar content of such beverages has been linked to increased cardiovascular risk, including hypertension and arrhythmia [42]. The noticeably low percentage of daily consumption of energy drinks (12%) in the study group represents a positive departure from European data, which indicate that up to 40% of adolescents regularly consume such products [4]. This result may be related to a greater emphasis on health education in the region, the relatively limited availability of sweetened beverages, or a preference for water, which was the main choice of 82% of the participants. However, it is worth expanding the research in this area to explore what environmental and social factors may be influencing youth preferences in Poland. Further efforts should focus on maintaining these positive trends by promoting healthy habits in this population.

The survey questions regarding fat revealed that 42% of the respondents preferred butter as their primary fat source, while only 27% used vegetable oils. Butter, rich in saturated fats, has been strongly associated with elevated LDL cholesterol levels and heightened cardiovascular risk [4]. In contrast, unsaturated fats from vegetable oils, such as olive oil, have demonstrated cardioprotective properties [43]. These findings suggest the need for improved nutritional education that promotes healthier fat choices among adolescents.

Salt consumption also emerged as a concern, with 52% of participants unable to estimate their intake and the remainder reporting a minimum of one teaspoon daily. Excessive salt consumption has been consistently linked with hypertension, a major risk factor for cardiovascular events [26]. The WHO has recommended global strategies for salt reduction as a cost-effective intervention for improving cardiovascular health in the population [44].

The study identified a significant relationship between high saturated fat intake, low fruit and vegetable consumption, and increased cardiovascular risk. This observation is in line with extensive epidemiological evidence that plant-based diets low in saturated fats are protective against CVDs [28,34,45].

The strengths of this study include its relatively large and diverse sample size, the use of standardized questionnaires, and the application of validated statistical techniques. However, limitations such as self-reported data and a cross-sectional design should be noted. Self-reported dietary behaviors often result in the underreporting of unhealthy choices due to social desirability bias [46].

To address the identified cardiovascular risk factors in adolescents, targeted interventions are essential. Our study highlights the need for comprehensive educational programs that promote a balanced diet and regular physical activity. Evidence from previous studies indicates that school-based health education initiatives can effectively reduce cardiovascular risk by encouraging healthier lifestyle choices among adolescents [4,18–42]. These programs should focus on reducing the intake of saturated fats and processed foods, increasing awareness about balanced fruit and vegetable consumption, and emphasizing the importance of regular exercise. Implementing such interventions could significantly mitigate the risks identified in this study, particularly for adolescents with high BMI, low physical activity levels, and poor dietary habits. The behaviors of adolescents, including dietary habits and physical activity levels, play a crucial role in determining their long-term cardiovascular

health. Our study demonstrates a significant association between these behaviors and increased cardiovascular risk. Adolescents with high BMI, low physical activity, and excessive consumption of saturated fats exhibited an odds ratio (OR) of 2.3 (95% CI [1.7–3.2], $p < 0.001$) for developing CVDs. These findings align with the existing literature, which emphasizes that unhealthy habits formed during adolescence can persist into adulthood, significantly elevating the risk of cardiovascular events later in life [4,23,26,28,30–44]. Preventive measures targeting this age group are therefore critical. Early interventions, such as providing nutritional education and promoting active lifestyles, are effective strategies for reducing the future burden of CVDs. Such measures could contribute to fostering long-term healthy behaviors, thereby reducing the incidence of cardiovascular events in adulthood.

Future research should aim for more objective measures of dietary intake, such as food diaries, biomarker analysis, and repeated measures to ensure accuracy. Broader studies incorporating multiple regions would enhance the generalizability of the findings. Interventional studies focusing on dietary education, particularly addressing the consumption of healthy fats and balanced fruit and vegetable intake, could further validate these findings.

Strengths and limitations

The study included a relatively large and diverse sample size, providing a solid base for analysis. Quantitative data collection and statistical analysis were conducted using established methods, ensuring reliability. A wide range of dietary habits and health-related variables were examined, allowing for comprehensive insights. However, the self-reported nature of the data may have introduced a response bias or inaccurate reporting of dietary habits. The study focused on a specific population, limiting the generalizability of the results to other groups. The cross-sectional design prevents the establishment of causal relationships between variables. Additionally, some participants expressed uncertainty regarding their dietary choices, which could have affected the accuracy of the findings.

CONCLUSIONS

Most participants had a healthy BMI, but there was a significant minority facing overweight and obesity issues, which may require targeted interventions. There was a moderate, positive correlation between nutritional knowledge and physical activity levels, indicating that better-informed individuals tend to engage in more physical activity. Vegetable consumption was significantly higher than fruit consumption, suggesting the need for balanced dietary education focusing on both food groups. The strong preference for water and low consumption of energy drinks is a positive trend in beverage choices. Poultry was the most frequently consumed meat, but a significant portion of the respondents were uncertain about their meat consumption habits, indicating a need for better dietary awareness. The preference for butter over vegetable oils and the uncertainty about fat consumption could be addressed through targeted nutritional education emphasizing healthy fat choices.

The findings highlight the importance of comprehensive nutritional education to address gaps in knowledge and promote healthier eating patterns.

Authors' contribution

Study design – M. Szymańska, M. Grajek
Data collection – M. Szymańska, K. Krupa-Kotara, K. Sobczyk
Data interpretation – M. Szymańska, K. Krupa-Kotara, K. Sobczyk
Statistical analysis – M. Szymańska, B. Nowak
Manuscript preparation – M. Grajek
Literature research – M. Szymańska, K. Krupa-Kotara, K. Sobczyk, B. Nowak

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PRACA POGLĄDOWA
REVIEW

The influence of social media and digital technologies on adolescent mental health – A literature review

Wpływ mediów społecznościowych i technologii cyfrowych na zdrowie psychiczne młodzieży – przegląd piśmiennictwa

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ABSTRACT

Social media has become an integral part of adolescents' daily lives, offering new ways to connect, express oneself, and access support. However, growing concerns highlight its potential risks to mental health. This paper explores the relationship between social media use and psychological well-being in young people, considering both the benefits and the drawbacks. This review draws on recent literature to examine the psychological impact of digital engagement among adolescents and young adults. It investigates areas such as social media addiction, emotional health, body image, and the influence of online communities. Excessive social media use is associated with increased rates of anxiety, depression, low self-esteem, and sleep problems and is often linked to social comparison and fear of missing out. At the same time, social media can serve as a valuable tool for emotional connection, peer support, and identity formation – particularly for marginalized or vulnerable groups. The addictive nature of these platforms, however, remains a significant concern. The influence of social media on adolescent mental health is complex and multifaceted. While the risks are well-documented, the potential for positive impact should not be overlooked. Encouraging mindful and balanced use, addressing problematic behaviors, and supporting digital literacy may help young people navigate online spaces in healthier, more resilient ways.

KEYWORDS

mental health, adolescents, social media, digital technologies, internet addiction

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STRESZCZENIE

Media społecznościowe stały się integralną częścią życia młodzieży, oferując nowe możliwości nawiązywania relacji, wyrażania siebie i uzyskiwania wsparcia. Jednocześnie rosną obawy dotyczące ich potencjalnego negatywnego wpływu na zdrowie psychiczne. Celem artykułu była analiza powiązań między korzystaniem z mediów społecznościowych a dobrostanem psychicznym młodych osób, uwzględniając zarówno korzyści, jak i zagrożenia. Artykuł opiera się na aktualnej literaturze, analizując wpływ cyfrowego zaangażowania na zdrowie psychiczne nastolatków i młodych dorosłych. Skupiono się na takich kwestiach, jak uzależnienie od mediów społecznościowych, emocjonalność, wizerunek ciała oraz rola społeczności internetowych. Nadmierne korzystanie z mediów społecznościowych wiąże się ze zwiększonym ryzykiem wystąpienia lęku, depresji, niskiej samooceny i problemów ze snem, często wynikającymi z porównywania się z innymi i lęku przed wykluczeniem. Z drugiej strony media społecznościowe mogą pełnić pozytywną rolę – umożliwiają nawiązywanie relacji, wsparcie rówieśnicze i kształtowanie tożsamości, szczególnie w przypadku grup marginalizowanych. Problem uzależnienia od tych platform pozostaje jednak dużym wyzwaniem. Wpływ mediów społecznościowych na zdrowie psychiczne młodzieży jest złożony i wielowymiarowy. Choć zagrożenia są dobrze udokumentowane, nie należy pomijać potencjału mediów. Promowanie świadomego i zrównoważonego korzystania z internetu, reagowanie na problematyczne zachowania i wspieranie kompetencji cyfrowych może pomóc młodym ludziom poruszać się w przestrzeni internetowej w zdrowszy i bardziej świadomy sposób.

SŁOWA KLUCZOWE

zdrowie psychiczne, młodzież, media społecznościowe, technologie cyfrowe, uzależnienie od internetu

Introduction

In recent years, mental health has taken a central place in public discourse, with increasing recognition of its critical role in overall well-being. The emergence of digital technologies and social media has had a huge impact on how people connect, form relationships, and engage with the world [1]. Communication applications have become an inseparable part of life, especially for adolescents and young adults [2]. While social media can offer meaningful connections and mental health support, growing evidence suggests that they also pose serious risks to adolescents' well-being [1]. With adolescents spending increasingly more time online, often several hours daily, concerns about the psychological consequences of such habits are rising [3].

Research regarding screen time and mental health has been inconsistent. Some studies show a substantial association between time spent online and poor well--being, while others find it to be irrelevant or beneficial [4]. On the one hand, social media platforms can cultivate social connection and provide emotional support and access to mental health resources [5]. Adolescents value the relationships built online and the comfort provided by their online peers [6]. On the other hand, evidence suggests associations between social media use and increased risks of depression, anxiety, and loneliness [7]. Adolescents frequently exposed to idealized images and unrealistic lifestyles reported lower self-esteem, increased body dissatisfaction, and a higher incidence of eating disorders [8].

Studies showed that by 2024, over 95% of teenagers in developed countries owned a smartphone and nearly 90% used social media daily, often as their primary means of communication and emotional regulation [9]. Research has also shown that frequent engagement with online platforms is associated with poor sleep quality, difficulty falling asleep, and sleep disturbances [10]. Social media's addictive nature, fueled by constant notifications, can interfere with everyday responsibilities, aggravating existing mental health issues. The growing lack of control over social media use is beginning to impact the everyday functioning of young people and is cause for concern [11].

In light of the growing awareness about the negative psychological effects of excessive digital media use, the concept of a *digital detox* – voluntarily refraining from using smartphones and social media for a set period – has gained increasing attention in both clinical and public health settings. Recent studies suggest that even short-term disconnection from social media platforms can lead to significant improvements in mood, attention, sleep quality, and overall well--being, particularly among adolescents and young adults [12].

By exploring both beneficial and adverse outcomes, as well as the concept of social media addiction, this article aims to provide a nuanced understanding of how digital engagement affects the psychological well-being of adolescents and young adults in contemporary society.

The negative impact of social media on adolescents' mental health

The negative impact of social media, which significantly affects the mental health of young people, is an increasing problem in the modern world [13]. Adolescents are almost constantly using or thinking about social media platforms, highlighting their deep integration into the daily lives of this age group [14]. A 2024 study revealed a concerning correlation: teenagers aged 12–15 who spent more than 3 hours a day in the virtual world of social media experienced twice the risk of negative mental health outcomes,

including an increase in symptoms of depression and anxiety [15]. The world of social media skillfully creates and showcases positive aspects of life, joyful moments, and the flawless appearance of influencers who become role models and objects of fascination for adolescents.

Young people, who are often not fully aware of the curated nature of this virtual reality, constantly compare their daily lives with these unrealistic standards. One of the key mechanisms resulting from this negative impact is the continuous self-comparison with idealized images of others [16]. Many young individuals begin to feel dissatisfied with their bodies and experience pressure to always be happy and slim [17]. Social media platforms generate a sense of inadequacy, lower self-esteem, and lead to constant comparisons with peers, often based on a superficial online image [18]. A study conducted on 7th- and 8th-grade students showed that as many as 51.7% of girls and 45% of boys reported experiencing an eating disorder, characterized by strict physical exercise and skipping meals [8]. Moreover, a significant majority of the respondents with eating disorders had active social media accounts – 75.4% of girls and 69.9% of boys had at least one such account, further emphasizing the potential role of these platforms in shaping negative patterns and attitudes [8]. A 2022 WHO study showed that many adolescents have difficulty controlling their social media use, resulting in negative consequences [19]. Individuals living with highly stigmatized mental illnesses, such as schizophrenia, schizoaffective disorder, or bipolar disorder, are unfortunately susceptible to online hate due to their condition [20]. The anonymity and widespread reach of the internet can embolden individuals to express discriminatory views and engage in harmful behavior, from making derogatory comments to outright harassment [21]. This online vitriol exacerbates the existing societal stigma, potentially leading to more social isolation, psychological distress, and a reluctance to seek or adhere to treatment among those affected. All of the above demonstrates that social media has a negative impact on young people, leading to lower self-esteem, poorer well-being, and increasing envy, which negatively affects young people's mental health [22]. Social media use is also associated with severe psychological distress [23].

Social media as a tool for connection and support

The negative impact of social media on mental health needs to be acknowledged. However, there could be benefits to using social media that could contribute to the well-being of some individuals.

As human beings, we need to connect with people and have meaningful relationships with them [24]. One of the opportunities that social media provides is the ability to meet new people. This is especially important for teenagers during puberty, because socialization is a part of the process of becoming an adult [25]. Making friends online is less stressful for adolescents than meeting in person [26].

Additionally, social media creates a space where people with stigmatized diseases such as schizophrenia, schizoaffective disorder, or bipolar disorder can support each other. They can share personal experiences and problems, as well as seek advice and help in overcoming the challenges associated with living with a particular disease [27]. Access to social media enables individuals with stigmatized disorders to reach out for comfort when they are struggling, while allowing them to maintain anonymity [27].

For people with serious mental illnesses, it is important to feel like they belong to a group. This can have a positive impact on their well-being and even on their recovery [27]. Social media allows users to form support groups, helping them feel less isolated in their condition and providing access to educational resources about it. This is crucial in combating the stigma surrounding certain diseases such as ADHD, which is imposed by people who lack experience with these illnesses [25].

LGBTQ+ adolescents often turn to social media to seek emotional support – and to help others in need. Being able to express and build their identity online is also beneficial to this group [28].

Social media provides a place for conversations about mental health. If used mindfully, it can be beneficial for promoting positive well-being [6]. Some adolescents suggested that social media could be used to spread awareness about issues that could impact one's mental health [29]. Online forums are a safe space for users to overcome concerns regarding seeking professional help when suffering from physical or mental health problems [6]. In a culture focused on celebrities' online lives, when a public figure shares their experiences with mental health challenges, it can promote learning about mental illnesses [29]. The accessibility of social media can help provide therapy for adolescents with mental health disorders, even those living in isolated locations [30]. Increased anonymity online contributes to the help-seeking process because it promotes self-disclosure [31].

Research among adolescents hospitalized for suicidal behavior showed that the participants valued humorous content available on social media. The entertainment that social media provides improved their mood [5].

Other research shows that young people use social media as a distraction from difficult situations [32].

Online groups can also connect people with similar interests, including art, politics, science, nature, and others [5].

When used mindfully, social media can serve as a tool for maintaining connections and accessing mental health support. It also provides opportunities for self-expression and personal growth.

Social media addiction and its impact on adolescents

In the modern digital era, social media has become an integral part of everyday life. As of 2024, more than five billion individuals around the world were active on social media; this figure is expected to surpass six billion by 2028 [33]. Facebook, Instagram, and YouTube are currently the three most widely used social media platforms globally, attracting billions of active users each month [34]. Although social media offers various benefits to many users, its excessive use can, in some cases, lead to behavioral addiction, which further adversely affects mental health.

The scale of this phenomenon is significant. Globally, an estimated 210 million people may be affected by internet or social media addiction [35]. Young people are particularly vulnerable, as shown in a study in which over 50% of teenagers in the United States believe it would be difficult for them to give up social media entirely [3]. Surprisingly, the overall prevalence of problematic social media use did not increase since the onset of the COVID-19 pandemic, except in low--income countries, where it is significantly higher [36]. Social media addiction can be defined as a pattern of excessive, uncontrollable use of social media platforms that interferes with everyday responsibilities, strains personal relationships, and can have harmful effects on both psychological and physical health [37]. It has been characterized by the six core symptoms commonly associated with addiction: salience, tolerance, mood modification, relapse, withdrawal, and conflict [38].

A growing body of research has highlighted the psychological consequences of social media overuse, especially among adolescents. A study conducted in Thailand examined 972 high school students and found that 41.9% met the criteria for addiction to Facebook, while 21.9% reported general mental health problems. The students identified as having an addiction were significantly more likely to experience symptoms such as depression, anxiety, and social dysfunction. Notably, they were 1.7 times more likely to report mental health concerns than their non-addicted peers. The study also revealed that greater levels of addiction were associated with increased psychological distress [39]. Moreover, it has been found that Facebook addiction significantly predicts higher narcissistic behavior and lower levels of self-esteem [40].

Another concerning finding comes from a large-scale study conducted across six European countries that investigated the psychosocial effects of social networking site use among 10,930 adolescents aged 14–17. The results revealed that 70% of the participants used social media on a daily basis and nearly 40% engaged with it for two or more hours per day. Heavier social media use was associated with higher levels of internalizing problems such as anxiety, depression, and somatic complaints. Furthermore, it correlated with lower academic performance and reduced participation in offline activities, particularly among younger adolescents. However, older adolescents who used social media more intensively showed slightly higher levels of offline social competence, suggesting that age may moderate both the risks and benefits of social media use [41].

Addressing social media addiction requires a multifaceted approach, combining therapeutic methods with preventive strategies. A study from Helwan University demonstrated that cognitive--behavioral therapy significantly reduced addictive behavior among students by targeting cognitive distortions and improving coping skills [42]. In addition, digital tools like self-monitoring apps and software for setting time limits can help users manage their screen time and develop healthier habits. These tools offer accessible support and complement traditional therapy [43].

Conclusions

The analysis of the current literature indicates that social media exerts both negative and positive effects on the mental health of young people. Excessive use of social networking platforms is associated with an increased risk of depression, anxiety, low self-esteem, body dissatisfaction, and eating disorders. Continuous exposure to idealized images leads adolescents to negative self-comparisons and feelings of inadequacy. Additionally, behavioral addiction to social media exacerbates emotional dysfunction, academic decline, and social withdrawal. Nevertheless, the studies reviewed herein highlight that social media can serve as a valuable source of social support, identity formation, and mental health education, particularly among marginalized populations. Online communities offer opportunities for positive interactions, peer support, and psychoeducation. Addressing the impact of social media on young people requires a balanced approach that combines preventive education, the promotion of healthy digital habits, and therapeutic interventions such as cognitive-behavioral therapy.

While the research consistently demonstrates strong associations between social media use and various mental health challenges in adolescents, a closer examination reveals notable methodological limitations. Many of the cited studies rely on cross-sectional designs and self-reported data. Although these approaches are useful for identifying patterns, they significantly limit the ability to draw causal inferences. It remains unclear whether social media use contributes to psychological distress, or whether adolescents already experiencing mental health difficulties are more likely to engage heavily with digital platforms. This potential bidirectional relationship is seldom examined directly and thus further investigation is warranted. Large-scale surveys and meta-analyses offer valuable statistical

insights and high external validity, yet they often overlook important contextual factors such as family dynamics, school environment, and cultural influences. In contrast, qualitative studies provide depth by capturing adolescents' lived experiences and motivations; however, their findings are often limited in generalizability due to small or demographically narrow samples.

Despite the expanding body of literature on the psychological impact of social media, several key gaps remain. Future research should focus on specific subpopulations, such as adolescents with pre-existing mental health conditions, neurodivergent individuals, or those from socioeconomically disadvantaged backgrounds – groups that may be particularly vulnerable to negative digital influences. Longitudinal studies are especially needed to capture the developmental trajectory of social media's effects over time, particularly during early adolescence, a critical period for identity formation. Furthermore, future investigations should consider the role of mediating factors, including parental involvement, digital literacy initiatives in schools, cultural differences, and broader community-level interventions.

Empowering adolescents to use social media mindfully is crucial for supporting their mental well-being and fostering resilience in the digital environment, laying the foundation for healthier digital habits that can positively influence their psychological development well into adulthood.

Authors' contribution

Study design – A. Zalewska, W. Hariasz

Manuscript preparation – A. Zalewska, W. Hariasz, K. Gądek, A. Lichodij, M. Michałek, M. Drobik, M. Kozieł

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PRACA ORYGINALNA
ORIGINAL PAPER

Characteristics of diabetic patients based on the Silesian Intensive Care Unit Registry

Charakterystyka pacjentów z cukrzycą na podstawie Śląskiego Rejestru Oddziałów Intensywnej Terapii

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ABSTRACT

INTRODUCTION: Diabetes mellitus (DM), a chronic condition, contributes to heightened hospitalizations, disability, and early mortality due to related complications. This study aimed to explore the incidence, clinical traits, and prognostic implications of DM in patients treated in Silesian intensive care units (ICUs).
MATERIAL AND METHODS: The paper is a retrospective, multicenter study containing patient data from the Silesian Intensive Care Unit Registry. Patients were treated in multi-profile ICUs in the Silesian Voivodeship. The registry collected clinical data of patients before admission to the ICU during hospitalization, as well as the results of ongoing treatment. To determine the effect of diabetes on the variables analyzed (51 variables), patients were divided into two groups: patients with a history of DM (regardless of its type) and patients without DM. Intergroup differences were compared for quantitative variables using parametric (Student's t-test) or non-parametric (Mann–Whitney U) tests, depending on the type of distribution.
RESULTS: The study population of 25,456 included 6,393 patients (25.1%) with DM. DM patients were typically older (71 vs. 64 years, $p = 0.001$) and predominately female (49% vs. 39%, $p < 0.001$). Statistically significant comorbidities amongst DM patients included coronary artery disease (OR = 2.96), hypertension (OR = 3.62), chronic renal failure (OR = 4.29; requiring dialysis, OR = 2.98), and morbid obesity (OR = 4.01), all with $p < 0.001$. Primary reasons for ICU admission in DM patients were notably multiple organ failure (OR = 1.18), shock (OR = 1.20), and infection/sepsis (OR = 1.35/1.16), each with $p < 0.001$. An elevated risk of ICU death by 24% was observed in DM patients ($p < 0.001$).
CONCLUSIONS: These findings underscore the substantial influence of DM on the clinical presentation and therapeutic outcome in critically ill patients, regardless of its role as a comorbidity rather than a primary admission cause.

KEYWORDS

diabetes mellitus, intensive care, infections, perioperative care, cardiovascular complications

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STRESZCZENIE

WSTĘP: Cukrzyca (*diabetes mellitus* – DM) jest chorobą przewlekłą, której powikłania są przyczyną dodatkowych hospitalizacji, inwalidztwa i przedwczesnych zgonów. Celem pracy była ocena częstości występowania, cech klinicznych i rokowania pacjentów z DM leczonych w śląskich oddziałach intensywnej terapii (*intensive care units* – ICUs).

MATERIAŁ I METODY: Praca jest retrospektywnym, wieloośrodkowym badaniem wykorzystującym dane pacjentów ze Śląskiego Rejestru Oddziałów Intensywnej Terapii. Pacjenci byli leczeni w wieloprofilowych ICUs na terenie województwa śląskiego. Rejestr gromadził dane kliniczne pacjentów przed przyjęciem na ICU, w trakcie hospitalizacji, a także wyniki prowadzonego leczenia. Aby określić wpływ cukrzycy na analizowane zmienne (51 zmiennych), pacjentów podzielono na dwie grupy: pacjenci z DM w wywiadzie (niezależnie od jej typu) i pacjenci bez DM. Różnice międzygrupowe porównywano w przypadku zmiennych ilościowych za pomocą testów parametrycznych (test t-Studenta) lub nieparametrycznych (test U Manna–Whitneya), zależnie od typu rozkładu.

WYNIKI: Spośród 25 456 chorych DM występowała u 6393 (25,1%). Pacjenci z DM byli starsi (71 vs. 64 lata, $p = 0,001$), częściej były to kobiety (49% vs. 39%, $p < 0,001$). U pacjentów z DM znamiennie częściej występowały ($p < 0,001$): choroba wieńcowa (OR = 2,96), nadciśnienie tętnicze (OR = 3,62), przewlekła niewydolność nerek (OR = 4,29; z koniecznością dializoterapii, OR = 2,98) oraz otyłość olbrzymia (OR = 4,01). Wśród pierwotnych przyczyn przyjęcia na ICU istotnie częstsze były ($p < 0,001$): niewydolność wielonarządowa (OR = 1,18), wstrząs (OR = 1,20) oraz infekcja/sepsa (OR = 1,35/1,16). U pacjentów z DM stwierdzono zwiększone o 24% ryzyko zgonu na ICU ($p < 0,001$).

WNIOSKI: Wyniki podkreślają istotny wpływ DM na stan kliniczny i efekt leczenia krytycznie chorych, nawet jeżeli pozostaje ona chorobą współistniejącą, a nie głównym powodem hospitalizacji.

SŁOWA KLUCZOWE

cukrzyca, intensywna terapia, infekcje, opieka okołooperacyjna, powikłania sercowo-naczyniowe

INTRODUCTION

Diabetes mellitus (DM) is a global health problem. In 2019, the disease is estimated to affect about 463 million adults globally. That number is expected to rise to 700 million by 2045 [1]. In the intensive care unit (ICU) setting, both acute metabolic conditions caused by DM decompensation and complications resulting from long-standing disease are treated. DM is rarely the main reason for ICU admission, more often it is a comorbid condition, e.g., among patients with sepsis, 10–30% had this diagnosis in their medical history [2]. Complications of DM can have a significant impact on quality of life and increase the risk of premature death. The high prevalence of DM and its complications is also associated with increased morbidity and mortality among hospitalized patients [3,4,5]. Patients with DM who require intensive care are at increased risk of complications such as infections, kidney failure, cardiovascular disease [6,7,8,9]. Early identification and therapy of DM is crucial to improving patient outcomes.

In this study, we analyzed the characteristics of patients with DM who were treated in the ICU. The analysis included a significant cohort of critically ill patients and a wide range of data from the Silesian Intensive Care Unit Registry, focusing on both the demographic structure, clinical characteristics and prognosis of patients.

MATERIAL AND METHODS

The paper is a retrospective, multicenter study containing patient data from the Silesian Intensive Care Unit Registry. Patients were treated in multi-profile ICUs in the Silesian Voivodeship. The registry was in operation from 2010 to 2019, and reporting was supervised by the Silesian Branch of the Polish Society of Anesthesiology and Intensive Care. All ICUs in the Silesian Voivodeship (37 wards) had access to the database. Patient reporting was voluntary. An estimated 50% of units took an active part in the database. The form allowed the selection of multiple answers, as well as the addition of a description in non-standard situations. The registry collected clinical data of patients before admission to the ICU, during hospitalization, as well as the results of ongoing treatment. A detailed description regarding the registry was published previously [10]. To determine the effect of diabetes on the variables analyzed (51 variables), patients were divided into two groups: patients with a history of DM (regardless of its type) and patients without DM.

Statistical analysis was performed using Statistica 13. Quantitative variables were presented as mean ± SD or median (IQR), while qualitative variables were presented as percentages. Intergroup differences were compared for quantitative variables using parametric (Student's t-test) or non-parametric (Mann–

–Whitney U) tests, depending on the type of distribution. The distribution of the study population was verified using the Kolmogorov–Smirnov test. Quantitative data were analyzed using the Chi-square test. To assess the association of qualitative variables, odds ratios and their 95% confidence intervals were calculated. Statistically significant values were considered at $p < 0.05$.

RESULTS

In the described cohort of critically ill patients (n = 25456), patients with a history of DM accounted for 25.1% (n = 6393). Patients with DM were older (71, IQR 63–78 vs. 64, IQR 53–75 years, p = 0.001), and were more often female (49% vs. 39%, p < 0.001). Table I includes clinical data on patients' burdens before admission to the ICU. Patients with DM were significantly more likely (p < 0.001) to have coronary artery disease (OR = 2.96), heart failure (OR = 2.78), hypertension (OR = 3.62), chronic respiratory failure (OR = 1.41), chronic renal failure (OR = 4.29; including the need for dialysis, OR = 2.98), cerebrovascular incidents (OR = 1.67), and morbid obesity (OR = 4.01).

Patients with diabetes were most often admitted to the ICU from non-surgical wards (36.6%), for the rest of the wards the distribution was similar (Table II).

Tables III and IV address the reasons for ICU admission. In both the group of patients with and without DM, the most common direct reasons for admission were respiratory failure (91.1%, OR = 1.23), circulatory failure (66.5%, OR = 1.38) and disorders of consciousness (53.3%, OR = 1.00). No statistically significant difference in direct reasons for ICU admission was noted only for disorders of consciousness.

Table V shows the clinical data of patients at the time of ICU admission. The majority of patients (p < 0.05) were: intubated (OR = 1.1), mechanically ventilated (OR = 1.12) and required infusion of catecholamines (OR = 1.2).

During treatment in the ICU (Table VI), patients with DM required statistically more frequent (p < 0.05): infusion of catecholamines (OR = 1.3), mechanical ventilation (OR = 1.11), non-invasive ventilation (OR = 1.23), dialysis therapy (OR = 1.99), continuous renal replacement therapy (OR = 1.58), antibiotic therapy (OR = 1.33).

30.1% of patients with diabetes were discharged with good neurological outcome (Table VII), compared to 34% of patients without a history of diabetes (p < 0.001, OR = 0.83). Patients with DM had a 24% higher risk of death in the ICU (p < 0.001; Table VIII).

Table I. Pre-intensive care unit (ICU) admission clinical data

Variable	All patients	Patients with DM	Patients without DM	P	OR (95%CI)
Coronary artery disease	10496 (41.2%)	3901 (61.0%)	6595 (34.6%)	< 0.001	2.96 (2.79–3.14)
Heart failure	8848 (34.8%)	3377 (52.8%)	5471 (28.7%)	< 0.001	2.78 (2.62–2.95)
Hypertension	13252 (52.1%)	4757 (74.4%)	8495 (44.5%)	< 0.001	3.62 (3.39–3.85)
Chronic respiratory failure	3162 (12.4%)	982 (15.4%)	2180 (11.4%)	< 0.001	1.41 (1.30–1.53)
Chronic kidney failure	3750 (14.7%)	1963 (30.7%)	1787 (9.4%)	< 0.001	4.29 (3.99–4.61)
Dialysis	321 (1.3%)	159 (2.5%)	162 (0.85%)	< 0.001	2.98 (2.39–3.71)
Cerebrovascular accident	1902 (7.47%)	664 (10.4%)	1238 (6.5%)	< 0.001	1.67 (1.51–1.84)
Cachexia	903 (3.6%)	137 (2.14%)	766 (4.02%)	< 0.001	0.52 (0.44–0.63)
Severe obesity	1457 (5.72%)	800 (12.5%)	657 (3.4%)	< 0.001	4.01 (3.60–4.47)

DM – diabetes mellitus; p – value; OR – odds ratio; CI – confidence interval

Table II. Source of intensive care unit (ICU) admission

Variable	All patients	Patients with DM	Patients without DM	p	OR (95%CI)
Operating theatre	6298 (24.7)	1372 (21.5%)	4926 (25.8%)	< 0.001	0.78 (0.73–0.84)
Emergency department	6393 (25.1%)	1109 (20.9%)	5284 (26.2%)	< 0.001	0.74 (0.69–0.80)
Surgical department	5123 (20.1%)	1316 (20.6%)	3807 (19.9%)	0.28	1.04 (0.96–1.11)
Non-surgical department	7413 (29.1%)	2337 (36.6%)	5076 (26.6%)	< 0.001	1.59 (1.50–1.69)
Another intensive care unit	384 (1.5%)	78 (1.2%)	306 (1.6%)	0.03	0.76 (0.59–0.97)
Ambulance	946 (3.7%)	181 (2.8%)	765 (4.01%)	< 0.001	0.70 (0.59–0.82)

DM – diabetes mellitus; p – value; OR – odds ratio; CI – confidence interval

Table III. Primary intensive care unit (ICU) admission diagnosis

Disease entity	All patients	Patients with DM	Patients without DM	p	OR (95%CI)
Acute respiratory failure	19004 (74.6%)	4800 (75.1%)	14204 (74.5%)	0.33	1.03 (0.97–1.10)
Exacerbation of chronic respiratory failure	2057 (8.1%)	639 (10.0%)	1418 (7.4%)	< 0.001	1.38 (1.25–1.52)
Circulatory insufficiency	11921 (46.8%)	3359 (52.3%)	8652 (44.8%)	< 0.001	1.36 (1.28–1.44)
Multiple trauma	3305 (13.0%)	925 (14.5%)	2380 (12.5%)	< 0.001	1.18 (1.09–1.29)
Shock	7643 (30.0%)	2105 (32.9%)	5538 (29.0)	< 0.001	1.20 (1.13–1.27)
Spinocerebellar ataxia	6129 (24.1%)	1694 (26.5%)	4435 (23.4%)	< 0.001	1.19 (1.12–1.27)
Obtunded consciousness	10069 (39.5%)	2566 (40.1%)	7503 (39.3%)	0.26	1.03 (0.98–1.10)
Post-surgical complications	7809 (30.7%)	1831 (28.6%)	5978 (31.3%)	< 0.001	0.88 (0.83–0.94)
Antiphospholipid syndrome	387 (1.5%)	80 (1.3%)	307 (1.6%)	0.04	0.78 (0.60–0.99)
Acute neurological conditions	1931 (7.6%)	339 (5.3%)	1592 (8.4%)	< 0.001	0.61 (0.54–0.69)
Severe metabolic disorders	1394 (5.5%)	415 (6.5%)	979 (5.1%)	< 0.001	1.28 (1.14–1.44)
Infections	4828 (18.9%)	1443 (22.6%)	3385 (17.8%)	< 0.001	1.35 (1.26–1.45)
Sepsis	1808 (7.1%)	503 (7.9%)	1305 (6.8%)	0.006	1.16 (1.04–1.29)

DM – diabetes mellitus; p – value; OR – odds ratio; CI – confidence interval

Table IV. Direct admission diagnosis

Variable	All patients	Patients with DM	Patients without DM	p	OR (95%CI)
Circulatory insufficiency	15474 (60.1%)	4248 (66.5%)	11226 (58.9%)	< 0.001	1.38 (1.30–1.47)
Respiratory failure	22858 (89.8%)	5825 (91.1%)	17033 (89.3%)	< 0.001	1.23 (1.11–1.35)
Renal failure	4688 (18.4%)	1654 (25.9%)	3034 (15.9%)	< 0.001	1.84 (1.72–1.97)
Multiple trauma	1142 (4.49%)	91 (1.4%)	1051 (5.5%)	< 0.001	0.25 (0.20–0.31)
Metabolic disorders	5083 (20.0%)	1582 (24.8%)	3501 (18.4%)	< 0.001	1.46 (1.37–1.56)
Obtunded consciousness	13522 (53.1%)	3405 (53.3%)	10117 (53.1%)	0.77	1.00 (0.95–1.07)

DM – diabetes mellitus; p – value; OR – odds ratio; CI – confidence interval

Table V. Status upon admission

Procedure	All patients	Patients with DM	Patients without DM	p	OR (95%CI)
Use of catecholamines	11432 (44.9%)	3091 (48.4%)	8341 (43.7%)	< 0.001	1.20 (1.14–1.27)
Unconsciouss	17324 (68.1%)	4342 (67.9%)	12982 (68.0%)	0.82	0.99 (0.93–1.06)
Mechanical ventilation	18889 (74.2%)	4843 (75.8%)	14046 (73.4%)	< 0.001	1.12 (1.05–1.19)
Intubated	19423 (76.3%)	4957 (77.5%)	14466 (75.9%)	0.006	1.10 (1.03–1.18)

DM – diabetes mellitus; p – value; OR – odds ratio; CI – confidence interval

Table VI. Clinical data of intensive care unit (ICU) stay

Procedure	All patients	Patients with DM	Patients without DM	p	OR (95%CI)
Application of catecholamines	18606 (73.1%)	4912 (76.8%)	13694 (71.8%)	< 0.001	1.30 (1.22–-1.39)
Intubation	16490 (64.8%)	4167 (65.2%)	12323 (64.6%)	0.41	1.03 (0.97–1.09)
Tracheostomy	4186 (16.4%)	1100 (17.2%)	3086 (16.2%)	0.057	1.08 (1.00–1.16)
Invasive ventilation	21020 (82.5%)	5346 (83.6%)	15674 (82.2%)	0.009	1.11 (1.03–1.19)
Non-invasive ventilation	1195 (4.7%)	346 (5.4%)	849 (4.5%)	0.002	1.23 (1.08–1.40)
Dialysis	533 (2.1%)	211 (3.3%)	322 (1.7%)	< 0.001	1.99 (1.67–2.37)
Continuous replacement dialysis	2726 (10.7%)	910 (14.2%)	1816 (9.5%)	< 0.001	1.58 (1.45–1.72)
Antibiotic therapy	20531 (80.6%)	5358 (83.8%)	15173 (79.6%)	< 0.001	1.33 (1.23–1.43)
Extracorporeal membrane oxygenation	119 (0.47%)	23 (0.36%)	96 (0.5%)	0.15	0.7 (0.45–1.13)

DM – diabetes mellitus; p – value; OR – odds ratio; CI – confidence interval

Table VII. Neurological outcome

Variable	All patients	Patients with DM	Patients without DM	p	OR (95%CI)
Good	8419 (33.0%)	1925 (30.1%)	6494 (34.0%)	< 0.001	0.83 (0.78–0.88)
Moderate disability	6393 (25.1%)	778 (25.2%)	5615 (25.1%)	0.96	1.00 (0.92–1.09)
High disability	1821 (7.15%)	434 (6.79%)	1387 (7.27%)	0.19	0.92 (0.83–1.04)
Vegetative condition	6393 (25.1%)	225 (21.1%)	6168 (25.3%)	0.002	0.79 (0.68–0.92)

DM – diabetes mellitus; p – value; OR – odds ratio; CI – confidence interval

Table VIII. Mortality rate of patients in intensive care unit (ICU)

Variable	All patients	Patients with DM	Patients without DM	p	OR (95%CI)
Mortality in ICU	11064 (43.5%)	3031 (47.4%)	8033 (42.1%)	< 0.001	1.24 (1.17–1.31)

DM – diabetes mellitus; p – value; OR – odds ratio; CI – confidence interval

DISCUSSION

DM is a significant clinical problem in patients treated in the ICU. The purpose of this study was to analyze the impact of this disease on the course of hospitalization and the prognosis of patients. In our study, we showed that patients with diabetes mellitus are characterized by worse treatment outcomes compared to a group of patients without a history of DM. In the patient population of the Silesian Intensive Care Unit Registry, the prevalence of diabetes was high, affecting 25.1% of patients. In a meta-analysis by Siegelaar et al. [9] it was demonstrated that an average of 19% of patients hospitalized in multi-profile ICUs are diagnosed with diabetes. Obesity is one of the main risk factors for developing type 2 DM [11]. The debilitating effect of obesity was also confirmed in our study; the percentage of patients with grade III obesity was nearly four times higher among patients with DM than among patients without DM. In contrast, non--modifiable risk factors include female gender and age [11]. These assumptions confirm our results, i.e. there were more women and elderly patients in the study group. Patients with DM were most often brought to the ICU from non-surgical wards. It can be concluded that this is due to more frequent exacerbation of chronic diseases and decompensation of the general condition. The main complications of diabetes mellitus, due to the adverse effects of hyperglycemia on vascular endothelial function, are primarily broad cardiovascular complications [12,13]. We showed that patients with DM already at the time of admission to the ICU were more likely to have additional medical conditions, especially cardiovascular, renal and pulmonary diseases. They were also admitted in a worse clinical condition, as they significantly more often required intubation, mechanical ventilation and infusion of catecholamines. Such observations have also been confirmed in many other papers [6,14]. The primary reasons for ICU admission included acute respiratory failure, circulatory failure, impaired consciousness, shock and infections. This translates, into the number of procedures performed during hospitalization such as renal replacement therapy, the need for catecholamines, mechanical ventilation and antibiotic therapy. All these procedures are significantly more frequent in DM patients. Our study showed that patients with diabetes were 17% less likely to be discharged from the ICU in good neurological condition compared to patients without DM. DM is a risk factor for stroke, peripheral neuropathy and, through hypo and hyperglycemic incidents, the development of cognitive impairment [4,15]. However, despite the more numerous complications and worse response to the treatment used, not all studies could confirm that DM increases mortality in critically ill patients. In a meta-analysis of 141 publications by Siegelaar et al. [9] it was demonstrated that DM had no effect on increased mortality, except in cardiac surgery patients. In our study, patients with DM had a 24% higher risk of death than patients without diabetes. The overall death rate was higher than the national average and stood at 47.4%. According to the National Institute of Public Health in Poland, the ICU mortality rate among the general patient population in 2012 was 42% [16].

CONCLUSIONS

There are some limitations to our study. It is a retrospective paper in which data were entered by numerous individuals, which may affect the quality of the information included. In terms of diabetes, variables showing absolute glycemic values and the breakdown by disease type were missing, which is extremely important, given the different characteristics of patients with type 1 and type 2 diabetes. Nevertheless, the large group of patients and the very large number of variables analyzed make it possible to trace patients from the moment they are admitted to the ICU to the end of their treatment. This makes it possible to characterize the needs and risks associated with

hospitalization of patients with DM within the ICU. The above results highlight the significant impact of DM on the clinical status and outcome of critically ill patients, even if it remains a comorbid condition and not the main reason for ICU admission.

Authors' contribution

Study design – Ł. Krzych, D. Bednarski
Data collection – Ł. Krzych
Data interpretation – D. Bednarski
Statistical analysis – D. Bednarski
Manuscript preparation – D. Bednarski, Ł. Krzych
Literature research – D. Bednarski

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KOMUNIKAT O WYNIKACH BADAŃ
BRIEF REPORT

Orexin receptor-1 expression in adult rodent neurogenic regions: evidence from the subgranular zone and the median eminence

Ekspresja receptora oreksynowego-1 w regionach neurogenezy dorosłych gryzoni: strefie podziarnistej oraz wyniosłości pośrodkowej

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ABSTRACT

INTRODUCTION: Orexin signaling plays a vital role in regulating autonomic and cognitive functions, including sleep-wake cycles, feeding, and memory. Orexin receptor-1 (OX_1R), a key component of this system, may also influence adult neurogenesis. This study examined OX_1R expression in both the classic (hippocampal) and non-classic (hypothalamic) neurogenic regions of the adult rodent brain.
MATERIAL AND METHODS: Adult rodent brains were fixed, paraffin-embedded, and sectioned coronally. Immunohistochemistry and immunofluorescence were performed using antibodies against OX_1R, DCX, and TUC-4, followed by fluorophore- or diaminobenzidine-based detection. Negative controls were included to ensure specificity.
RESULTS: OX_1R-positive cells were localized primarily to the subgranular zone (SGZ) of the dentate gyrus and β2 tanycytes of the median eminence showed uniform OX_1R expression in both somata and vascular-directed processes. Morphological variation was observed between species, with diverse perikaryon shapes in mice and predominantly elongated, multipolar forms in rats.
CONCLUSIONS: This study revealed, for the first time, region-specific OX_1R expression in the SGZ in β2 tanycytes of the median eminence. These findings suggest a potential role for orexin signaling in adult neurogenesis.

KEYWORDS

orexin, adult neurogenesis, hippocampus, tanycytes

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STRESZCZENIE

WSTĘP: Sygnalizacja oreksynergiczna odgrywa kluczową rolę w regulacji funkcji autonomicznych i poznawczych, w tym cyklu snu i czuwania oraz przyjmowania pokarmu. Receptor oreksyny-1 (*orexin receptor-1* – OX_1R), pierwszoplanowy element tego układu, może również wpływać na neurogenezę w mózgu dojrzałym. W przedstawionym badaniu zbadano ekspresję OX_1R zarówno w klasycznych (hipokamp), jak i nieklasycznych (podwzgórze) regionach neurogennych mózgu dorosłych gryzoni (szczurów i myszy).

MATERIAŁ I METODY: Mózgi dorosłych gryzoni utrwalono, zatopiono w parafinie i skrojono w płaszczyźnie poprzecznej. Badania immunohistochemiczne i fluorescencyjne wykonano z wykorzystaniem pierwszorzędowych przeciwciał selektywnych względem OX_1R, DCX i TUC-4, a następnie przeciwciał drugorzędowych sprzężonych z fluorochromami lub w reakcji diaminobenzydyny. W celu zapewnienia swoistości uwzględniono kontrole negatywne.

WYNIKI: Komórki OX_1R-pozytywne zlokalizowano głównie w strefie podziarnistej (*subgranular zone* – SGZ) zakrętu zębatego, β2-tanycyty wyniosłości pośrodkowej wykazywały jednorodną ekspresję OX_1R zarówno w ich ciałach komórkowych, jak i w wypustkach okołonaczyniowych. Zaobserwowano istotne zróżnicowanie morfologiczne neuronów OX_1R-pozytywnych między badanymi gatunkami gryzoni – u myszy dominowały perykariony różnokształtne, natomiast u szczurów komórki wydłużone i wielobiegunowe.

WNIOSKI: Badanie to po raz pierwszy ujawniło specyficzną dla regionu ekspresję OX_1R w SGZ hipokampa oraz w β2-tanycytach wyniosłości pośrodkowej podwzgórza. Wyniki sugerują potencjalną rolę sygnalizacji oreksynowej w regulacji neurogenezy w mózgu dojrzałym.

SŁOWA KLUCZOWE

oreksyna, neurogeneza w mózgu dojrzałym, hipokamp, tanycyty

INTRODUCTION

Neurochemical research on brain neuropeptides involved in the regulation of adult neurogenesis has emerged as a highly dynamic area in contemporary neuroscience. Two well-established neurogenic niches have been identified in the vertebrate brain: the subgranular zone (SGZ) of the dentate gyrus and the subventricular zone (SVZ) beneath the ependyma of the lateral ventricles. The SGZ gives rise to granule neurons within the hippocampus, while the SVZ produces progenitor cells that migrate via the rostral migratory stream to the olfactory bulb, where they differentiate into specialized sensory interneurons. The SGZ niche is primarily composed of astrocytes and capillary endothelial cells, both of which are abundantly represented in this layer of the dentate gyrus [1,2]. In addition to these canonical regions, two potential sites of adult neurogenesis have recently been found within the hypothalamus: the hypothalamic ventricular zone (HVZ), situated along the lateral walls of the third ventricle, and the hypothalamic proliferative zone (HPZ), composed primarily of median eminence tanycytes [3,4] whose somata are situated along the floor of the third ventricle. Based on their anatomical distribution and the expression of specific markers related to lineage and differentiation, radial glia-like tanycytes are classified into four subtypes: α1, α2, β1, and β2 [5]. α1 tanycytes are found at the ventromedial and dorsomedial nuclei of the hypothalamus, α2 tanycytes are in the vicinity of the arcuate nuclei, and the β1 and β2 types are situated along the HVZ (ventral tanycytic zone) of the third ventricle [6], but extend their processes into the median eminence, in the tuberal region of the hypothalamus [7]. Notably, β2 tanycytes are characterized by their remarkable sensitivity to circulating hormones, metabolic regulators, and nutritional signals. Their somata, embedded in the ependymal lining, are optimally placed to detect molecular cues from the cerebrospinal fluid (CSF), while their elongated processes extend toward the median eminence, where they may interact with blood-borne signals [8]. Given their strategic location at the interface between the CSF and hypothalamic vasculature, β2 tanycytes could be well positioned to respond to neuropeptides such as orexins. Tanycytes comprising the HVZ – including β2 tanycytes in both rats and humans – express several neural precursor markers, including nestin [9], Sox2 [10], vimentin [11], and doublecortin-like protein [12], suggesting a role in adult neurogenesis.

In parallel, orexins exert broad regulatory effects across the central nervous system, influencing diverse physiological domains from sleep and homeostasis to memory, emotions, and reward [13,14]. Orexinergic perikarya, which co-express glutamate and dynorphine, are localized exclusively in the perifornical area and the lateral and posterior hypothalamus [15,16,17]. Their axons target multiple brain regions, including key neurogenic areas such as the hippocampus and the olfactory bulb [18,19]. Orexins act via two G-coupled receptors, known as OX_1R (orexin receptor-1) and OX_2R, showing significant homology among mammalian species [20]. OXRs have been identified in various brain regions, including the prefrontal and limbic cortices, the hippocampus, the amygdala, the bed nucleus of stria terminalis, and several hypothalamic and brainstem nuclei [21,22].

Building on recent evidence which suggests that certain hypothalamic orexin neurons project to neurogenic regions in the rat brain [23], we hypothesized that cells

within both the SGZ and the hypothalamic subependymal zone – particularly β2 tanycytes – may be responsive to orexins via OX_1R signaling. This hypothesis is supported by the anatomical and functional profile of β2 tanycytes: they are strategically positioned to sense hormonal and nutritional cues from both the CSF and the blood and they express multiple markers of neural precursors. These characteristics make them compelling candidates for mediating the neurogenic effects of orexins in the hypothalamus.

Thus, if β2 tanycytes express OX_1R, they could serve as intermediaries through which orexins regulate adult neurogenesis, energy homeostasis, or hormonal feedback in hypothalamic circuits. To explore this possibility, we investigated OX_1R expression within both classic (hippocampal SGZ) and non-classic (hypothalamic median eminence) neurogenic zones.

MATERIAL AND METHODS

Animals

Male Sprague–Dawley rats and mice (N = 5 each) from the Medical University of Silesia Experimental Centre were housed at a temperature of 22°C with a regular 12/12 light/darkness cycle and access to standard Murigran chow and water *ad libitum*. The research was approved by the Local Ethical Commission for Animal Experimentation at the Medical University of Silesia (No. 36/2012) and all experimental procedures were conducted according to the NIH Guide for Care and Use of Animals.

Immunohistochemistry

The animals were quickly anesthetized with isoflurane inhalation and sacrificed. The brains were excised, fixed by immersion for 48 h in 4% paraformaldehyde PBS (pH 7,2–7,4) at 4°C, dehydrated via graded alcohols at room temperature, cleared in xylene, embedded in paraffin, and finally sectioned on a microtome (Leica Microsystems, Germany) in the coronal plane (-2.00 to -2.80 mm from the bregma) into 7-μm thick slices, according to standard rat brain atlases.

For immunofluorescence, after blocking with 0.1% Triton X-100 (Sigma, T-7878) and 10% serum (horse normal serum for orexin, Vector Labs), sections were incubated overnight at 4°C with rabbit antibody against rat orexin-1 receptor (1:2000, Abcam). Additional antibodies against adult neurogenesis markers were applied: goat anti-rat DCX (Santa Cruz Pharmaceuticals, 1:1000) and rabbit anti-rat TUC-4 (Abcam, 1:1000). Primary antibodies were followed by fluorochrome-conjugated secondary antibodies: goat anti-rabbit FITC (1:200, Abcam) for 1 h at 4°C. Finally, the sections were mounted on glass slides with DAPI-containing medium and coverslipped.

For diaminobenzidine (DAB) single staining, blocking (0.1% Triton X-100 and 10% serum) and administration of primary antibodies (1:1000) were followed by biotynylated anti-rabbit/anti-goat secondary antibodies for 30 min, and then an avidin-biotin-horseradish peroxidase complex (Vectastain ABC kit, Vector Labs) for another 30 min, before DAB was used to complete the reaction (1–2 min). The brain sections were dehydrated, mounted on glass slides with medium, and coverslipped. Sections incubated with rabbit/mouse IgG instead of primary antibody were used as negative controls in order to check the specificity of primary antibodies. All images were captured and analyzed with Nikon Coolpix optic systems and processed using Image ProPlus software (Media Cybernetics, USA). The same planes of the brain were chosen from each set of slides. On each section, we analyzed the morphology of immunopositive and immunonegative cells from the entire area of the dentate gyri and lateral hypothalamic regions.

RESULTS

Upon examining the hippocampal area of both mouse and rat brains, a distinct number of granular cells in the dentate gyrus exhibited OX_1R immunoreactivity. The highest aggregation of OX_1R-positive cells was observed almost exclusively within the SGZ, known as the classic site of adult neurogenesis. The OX_1R--immunoreactive cells in the mouse dentate gyri displayed a relatively wide spectrum of shapes: round, oval, fusiform, and even triangular (pyramidal) perikaryal, from which short dendrites sometimes emerged (Figure 1[A–F]). In the rat brain, oval, multipolar, and elongated OX_1R-immunoreactive somata were most common (Figure 1[G–H]). In the hypothalamus, the inner median eminence layer showed distinct, regular OX_1R expression. Columnar cell bodies and long processes running toward blood vessels indicated uniform, mild OX_1R immunoreactivity (Figure 2).

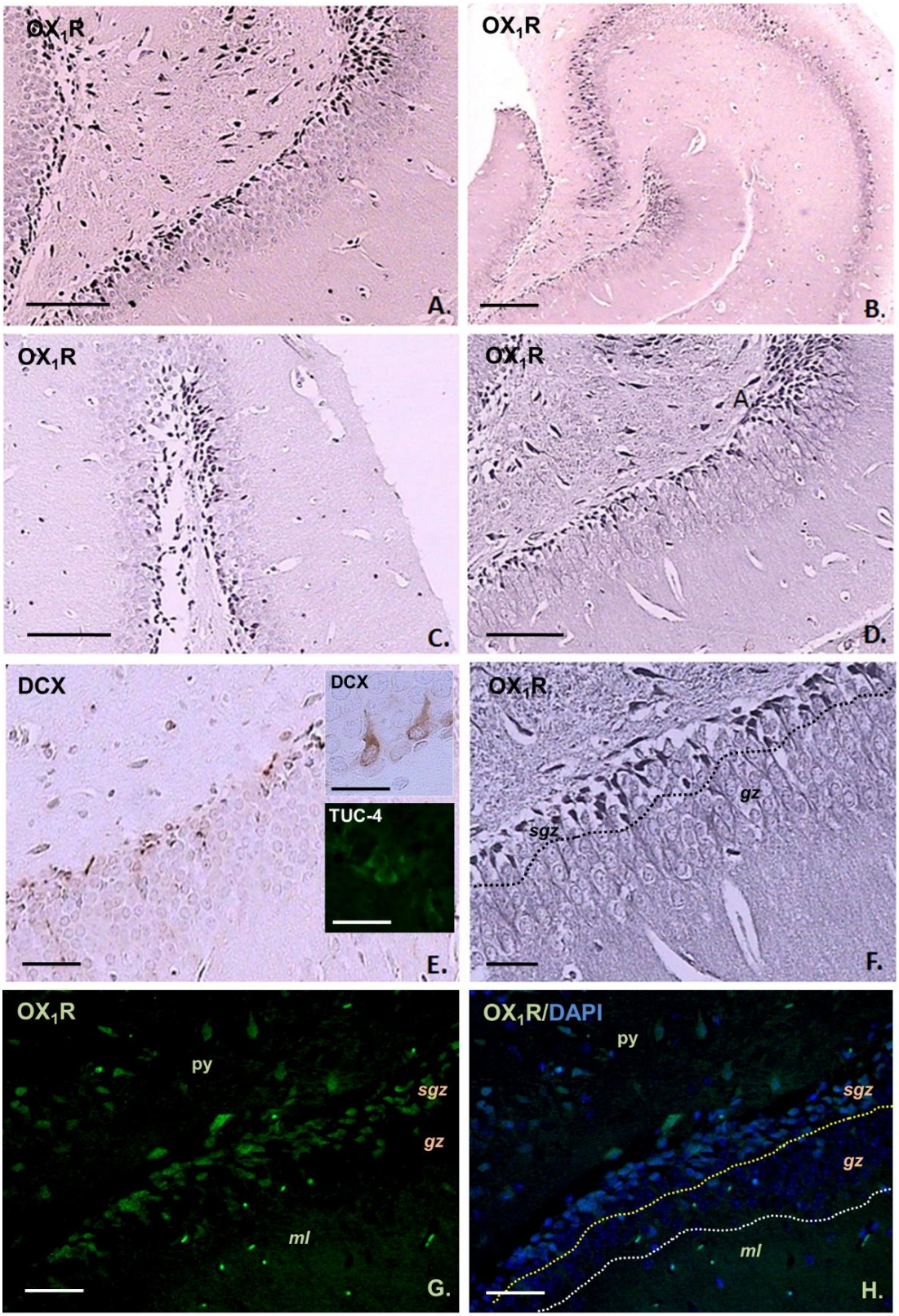

Fig. 1. Orexin receptor-1 (OX_1R)-expressing neurons in the hippocampus. Overview of neuroanatomical OX_1R immunodistribution in the mouse and rat Ammon's horn and dentate gyrus. Immunoperoxidase reaction with DAB staining in mouse hippocampus (A–D, F). Scale bars: 100 μm (A–D), 25 μm (F). Expression of adult neurogenesis markers doublecortin (DCX) and TUC-4 in the rat subventricular zone (E). Scale bars: 50 μm (E), 25 μm (insets). Immunofluorescence for OX_1R in the rat dentate gyrus (G–H). Scale bar: 50 μm. gz – granular zone; ml – molecular layer; py – pyramidal layer; sgz – subgranular zone.

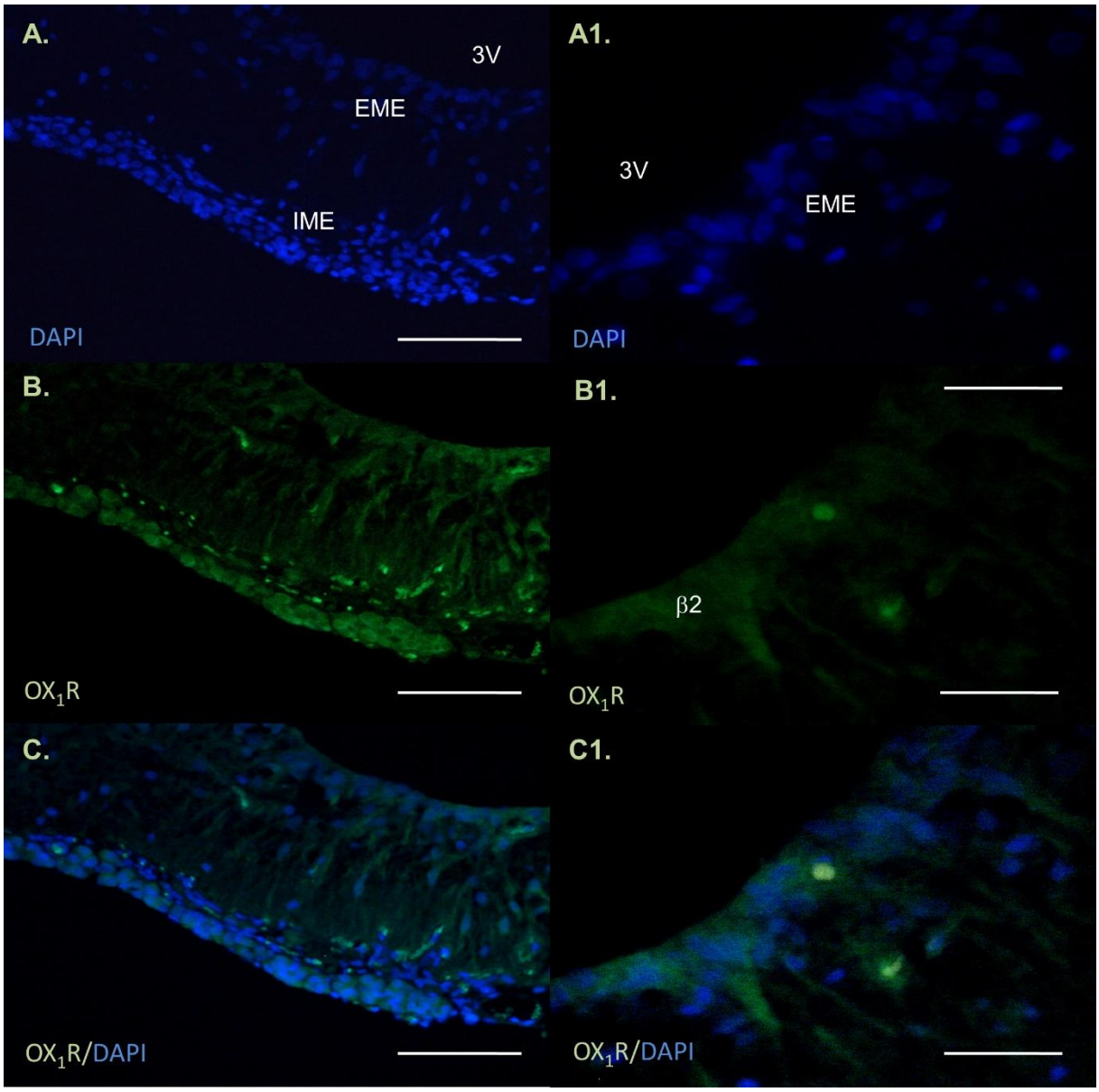

Fig. 2. Orexin receptor-1 (OX_1R)-immunopositive cells in the rat median eminence. Scale bars: 250 μm (A–C), 50 μm (A1–C1). EME – external medial eminence; IME – internal medial eminence; 3V – third ventricle.

DISCUSSION

Our study reveals a region-specific expression of OX_1R, in the SGZ of the dentate gyrus of the hippocampus in both rats and mice. For the first time, it reports strong OX_1R immunoreactivity in the majority of β2 tanycytes within the median eminence of the hypothalamus.

Accumulating evidence suggests that the multidirectional nature of orexin signaling in the brain contributes to a wide range of autonomic and affective processes, including food intake, sleep-wake regulation, stress responses, reward and addiction mechanisms, and the pathogenesis of various neuropsychiatric disorders [24,25,26,27,28,29]. The hippocampus is a well-established target of the orexinergic system, receiving dense projections from the lateral hypothalamus. Orexin receptors – OX_1R and OX_2R – are expressed in complementary patterns across the hippocampal subregions: OX_1R is found in CA1, CA2, and the dentate gyrus, while OX_2R is in the dentate gyrus and CA3 [21,22,30]. These receptors are implicated in diverse hippocampal functions, including reward processing, learning, memory [27,31,32,33], spatial cognition [34], stress response [35,36], and, notably, antinociception [37,38].

Orexin-A in particular has been shown to enhance hippocampal neurogenesis, potentially contributing to cognitive performance. However, whether adult neurogenesis influences the population of orexin--producing neurons remains uncertain [39,40]. For instance, local perfusion of orexin-A into the dentate gyrus promotes structural and functional plasticity [41], while transgenic mice lacking orexin neurons exhibit reduced hippocampal plasticity [42]. Intracerebroventricular orexin-A administration increases cellular proliferation in the dentate gyrus and alleviates depression-like symptoms [43,44].

Similarly, in penthylenetetrazol (PTZ)-kindled rat models of epilepsy, orexin-A boosts proliferation and promotes differentiation of neural precursors in the dentate gyrus [45]. The PTZ-induced kindling model is currently widely used in epileptogenic drug testing. As PTZ induces seizures via glutamatergic excitation and GABAergic inhibition [46], these findings suggest that orexin-A may counteract seizure-induced cognitive deficits through OX_1R-mediated neurogenesis. Reduced orexin-A levels following seizures may partly underlie such impairments [45].

Orexins also stimulate neurogenesis in the SVZ, although its functional relevance remains unclear [23]. It is still debated whether orexin signaling is essential for hippocampal neurogenesis and whether orexinergic neurons themselves can be replenished via adult neurogenesis [39,40].

Some evidence suggests that a limited population of newly generated hypothalamic neurons may express orexin [47]. In this brain region, adult neurogenesis is believed to support adaptive responses to dietary changes [48,49]. Tanycytes play a critical role, as they can sense hormonal and nutritional cues and can differentiate into orexigenic or anorexigenic neurons. However, the identity of tanycyte subtypes serving as true neural stem cells remains controversial. Notably, in seasonally breeding species, hypothalamic neurogenesis is modulated by day length, with increased levels being observed in the short photoperiod in sheep [50]. Similar changes in cell proliferation and tanycyte function align with feeding behavior and seasonal cues in hamsters [51,52].

Our study found that β2 tanycytes in the inner layer of the median eminence displayed consistent OX_1R immunoreactivity in both their columnar somata and vascular-directed processes. Importantly, β2 tanycytes are the most mitotically active tanycyte subtype [53]; they are especially neurogenic in younger animals [54]. These cells express high levels of Hes1 and Hes2 – markers of neural progenitors – and all newly generated neurons remain within the median eminence [54,55]. This local neurogenesis may support a stable population of sensory neurons responsible for monitoring CSF composition.

In addition, OX_1R-immunoreactive cells in dentate gyri displayed a variety of shapes. This intriguing diverse shape pattern is challenging to interpret and may reflect as yet unidentified interspecies differences in cellular morphology. Additionally, we cannot rule out the possibility that certain cells exhibit an irregular immunostaining pattern, potentially confined to the perikarya, thereby rendering some cellular processes undetectable.

It is important to acknowledge the limitations of our preliminary, predominantly qualitative morphological analysis. Future studies should aim to expand upon these findings by incorporating co-expression analyses of OX_1R with established markers of adult neurogenesis. While adult neurogenesis remains a prominent and debated topic in contemporary neuroscience, robust evidence supporting sustained, long-term neurogenesis in the adult human brain remains limited. Moreover, clinical approaches such as stem cell transplantation for neurodegenerative conditions, including Alzheimer's and Parkinson's diseases or ischemic brain injuries, have thus far yielded disappointing therapeutic outcomes [56]. In contrast, numerous animal studies continue to provide valuable insights into the mechanisms of adult neurogenesis, advancing our understanding of brain structure and function.

CONCLUSIONS

Our findings revealed a distinct expression pattern of OX_1R in the dentate gyrus of both rats and mice, specifically confined to the subgranular zone. Moreover, we demonstrated for the first time that the majority of β2 tanycytes within the median eminence exhibit robust OX_1R immunoreactivity. These observations cautiously point to a previously underexplored link between orexin signaling and adult neurogenesis in both the classic hypothalamic neurogenic regions. Nonetheless, further research is necessary to elucidate the functional significance of these potential regulatory interactions.

Compliance with Ethical Standards

Ethical approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Conflict of interest

The authors declare no conflict of interest.

Authors' contribution

Study design – A. Pinna, A. Pałasz
Data collection – A. Pinna
Data interpretation – A. Pinna, A. Pałasz
Manuscript preparation – A. Pinna, A. Pałasz
Literature research – A. Pinna

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OPIS PRZYPADKU
CASE REPORT

Should we exclude hemato-oncological patients from obesity treatment with semaglutide? – A case report

Czy powinniśmy wykluczyć pacjentów hematoonkologicznych z leczenia otyłości semaglutydem? – opis przypadku

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ABSTRACT

Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), is now widely used in the treatment of diabetes and obesity. However, there are still insufficient safety data for the use of GLP-1RAs in oncological and hemato--oncological patients, as they have not been included in clinical trials. The potential prooncogenic activity of GLP-1RAs in patients with thyroid cancer has been reported, raising concerns about the safety of semaglutide in oncological and hemato-oncological patients. We present a case of a 57-year-old man, who suffered from class III obesity (BMI: 40.4 kg/m^2), type 2 diabetes, and chronic lymphocytic leukemia (CLL; RAI stage I and Binet A stage). The patient started therapy with semaglutide to manage obesity and diabetes; he had already begun systemic therapy for CLL with obinutuzumab and venetoclax, which was continued after its complete remission. More than 3 years of semaglutide therapy improved the patients' metabolic control of diabetes and resulted in significant weight loss (16% of the initial body mass), with no reported adverse drug reactions and without compromising hematologic stability. Our case report suggests that hemato-oncological patients should not be categorically excluded from treatment with semaglutide, as long as close hematological and clinical monitoring is ensured. However, as this observation is based on a single case report, no definitive general recommendations regarding the safety of semaglutide in hemato-oncological patients can be made at this time.

KEYWORDS

obesity, cancer, case report, type 2 diabetes, oncogenesis, semaglutide

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STRESZCZENIE

Semaglutyd, będący agonistą receptora glukagonopodobnego peptydu 1 (*glucagon-like peptide-1 receptor agonist* – GLP-1RA), znajduje szerokie zastosowanie w terapii cukrzycy oraz leczeniu otyłości. Mimo to wciąż brakuje wystarczających danych dotyczących stosowania GLP-1RAs u pacjentów onkologicznych i hematoonkologicznych, ponieważ nie zostali oni uwzględnieni w badaniach klinicznych. Pojawiające się doniesienia o korelacji stosowania GLP-1RAs i nowotworzenia, szczególnie w przypadku nowotworów tarczycy, zrodziło dalsze obawy co do bezpieczeństwa stosowania semaglutydu u pacjentów onkologicznych i hematoonkologicznych. W pracy przedstawiono przypadek 57-letniego pacjenta, chorującego na otyłość III stopnia (BMI: 40,4 kg/m^2), cukrzycę typu 2 oraz przewlekłą białaczkę limfocytową (*chronic lymphocytic leukemia* – CLL; RAI I, Binet A). W celu leczenie otyłości i cukrzycy pacjent rozpoczął terapię semaglutydem, następnie włączono leczenie systemowe CLL obejmujące obinutuzumab z wenetoklaksem; po uzyskaniu remisji CLL kontynuowano leczenie semaglutydem. Ponad 3-letnia terapia semaglutydem pozwoliła na optymalną kontrolę glikemii i spowodowała istotną utratę masy ciała (16% wyjściowej masy ciała pacjenta), podczas leczenia nie odnotowano żadnych działań niepożądanych ani negatywnego wpływu na parametry hematologiczne oraz uzyskaną remisję. Opisany przypadek sugeruje, że pacjentów hematoonkologicznych nie należy kategorycznie wykluczać z leczenia semaglutydem, pod warunkiem zapewnienia właściwego monitorowania parametrów hematologicznych oraz stanu klinicznego. Ponieważ jednak obserwacja opiera się na pojedynczym opisie przypadku, nie można obecnie sformułować jednoznacznych, ogólnych zaleceń dotyczących bezpieczeństwa stosowania semaglutydu w tej grupie pacjentów.

SŁOWA KLUCZOWE

otyłość, nowotwór, opis przypadku, cukrzyca typu 2, onkogeneza, semaglutyd

INTRODUCTION

Obesity and type 2 diabetes (T2D) are among the most significant factors that promote neoplasia. The primary mechanism contributing to this process is hyperinsulinemia, which compensates for insulin resistance [1,2]. Hyperinsulinemia activates the mitogen-activated protein kinase (MAPK) and the PI3K/Akt signaling pathways, which are involved in the regulation of cell division and differentiation, thereby promoting oncogenesis [1]. Obesity, through the accumulation of adipocytes in the bone marrow, leads to the formation of so-called "fat marrow," which affects hematopoietic functioning and promotes the formation of abnormal blood cells. Harmful adipocytes in the bone marrow promote the secretion of proinflammatory cytokines, such as IL-6, IL-1β, and TNF-α, which may contribute to the development of hematological malignancies [3].

Incretin drugs, such as glucagon-like peptide 1 receptor agonists (GLP-1RAs), are among the modern therapeutic options for both T2D and obesity. They act centrally, reducing appetite and decreasing gastrointestinal motility, in turn resulting in significant weight reduction [4]. However, the use of such therapy in patients with cancer is a controversial issue due to the potential activation of the pathways involved in carcinogenesis [5,6,7]. Nevertheless, there is no conclusive evidence of increased cancer risk among those treated with liraglutide or semaglutide [8]. When the study was published, the authors emphasized the need for closer monitoring of the potential link between GLP-1RAs and thyroid malignancies, as conclusive evidence was lacking [9].

Meanwhile, the body weight reduction and beneficial effects for T2D therapy and cardiovascular complications remains a debatable issue in cancer patients. In the case study, we describe a 57-year-old male patient diagnosed with chronic lymphocytic leukemia (CLL), obesity, and T2D, who benefited from treatment with semaglutide.

METHODS

The patient gave informed consent to review and publish his anonymized medical history, diagnosis, and disease management. The confidentiality and security of personal data have been maintained. Our observations and conclusions are based on medical history, laboratory results, and diagnostic imaging obtained during the 4-year follow-up. Furthermore, a literature review and analysis were carried out and are presented.

CASE REPORT

A 57-year-old patient with obesity and related T2D was diagnosed with asymptomatic RAI stage I, Binet A stage CLL in 2019. At that time, the patient did not meet the criteria for the initiation of systemic therapy for CLL. Additionally, the man suffered from comorbidities, including benign prostatic hyperplasia, arterial hypertension, and mild chronic kidney disease. Initially, the treatment of T2D consisted of metformin, followed by metformin and sitagliptin, with good glycemic control. During the COVID-19 pandemic, the patient gained weight and the control over T2D

deteriorated. As of June 2021, at a body mass index (BMI) of 40.4 kg/m^2 – which indicates class III obesity – therapy was modified, adding subcutaneous semaglutide in increasing dosages, from 0.25 mg to the final dosage of 1 mg per week. Significant improvements in glycemic control and weight reduction were achieved. By September 2021, a decrease in BMI to 35.8 kg/m^2 had already been noted, signifying a change in obesity classification from class III to class II within four months.

In April 2022, due to rapidly increasing lymphocytosis, symptomatic spleen and lymph node enlargement, and thrombocytopenia with neutropenia, the patient was qualified for systemic therapy with obinutuzumab and venetoclax. These medications may mutually exacerbate the risk of infection, severe neutropenia, and tumor lysis syndrome (TLS). The patient was closely supervised, especially during the initial phase of treatment. The assessments included regular hematological examinations (Table I) and monitoring of kidney and liver function and electrolyte levels. The treatment consisted of six administrations of obinutuzumab and 12 cycles of venetoclax. During treatment, the patient's BMI was further reduced to 33.9 kg/m^2 by November 2022, bringing his obesity level down from class II to class I. In March 2023, lab tests showed minor leukopenia and thrombocytopenia, and a follow-up computed tomography scan revealed no lymphadenopathy or splenomegaly. A complete remission was achieved with a partial hematologic recovery (CRh).

Upon completion of CLL therapy, the patient's BMI was 33.9 kg/m^2, which equates to a loss of 20 kilograms, and 16% of the patient's initial body weight. No adverse drug reactions (ADRs) or interactions between the administration of semaglutide and CLL therapy were reported. The patient maintained moderate physical activity both before and during treatment. His diet was not restricted and he reported no use of cigarettes or alcohol.

In August 2023, the patient was hospitalized due to a lower respiratory tract infection followed by acute respiratory failure. Echocardiography and coronary angiography revealed significant coronary artery disease, and a CABG was performed. After the surgical intervention, the patient remained stable. A computed tomography scan carried out in April 2024 confirmed no lymphadenopathy or splenomegaly, maintaining complete remission of CLL. The patient is under close oncological supervision and is currently being evaluated for thrombocytopenia. Chronic conditions are being actively managed, including diabetes, which is treated with metformin and preprandial insulin boluses based on glycemic levels.

Interestingly, the improvement in metabolic parameters occurred independently of hematologic disease progression, suggesting that semaglutide therapy was not only safe, but also effective in managing obesity without interfering with oncological treatment.

Table I. Laboratory data

Parameter	Reference range	April 1, 2022	March 6, 2023	April 5, 2024	March 14, 2025
WBC [×10^3/µl]	4–10	194.17↑	3.85	14.64↑	8.15
RBC [×10^6/µl]	4–5.8	4.99	3.83↓	4.79	4.56
HGB [g/dl]	11.2–15.8	13.3	13.8	15.7	13.2
HCT [%]	35–45	43.1	39.7	46.3↑	42.5
MCV [fL]	82–98	86.4	103.7↑	96.7	93.2
PLT [10^3/µl]	130–400	207.0	86.0↓	20↓	6↓
Neutrophils [×10^3/µl]	1.6–6	9.07↑	1.55↓	8.00↑	2.96
Lymphocytes [×10^3/µl]	1–3.3	–	1.28	3.19	2.25
Monocytes [×10^3/µl]	0.15–0.6	–	0.81↑	2.46↑	2.34↑
Eosinophils [×10^3/µl]	0.2–0.5	0.32	0.00↓	0.13↓	0.53↑
Basophils [×10^3/µl]	0–0.1	0.11↑	0.01↓	0.06↓	0.02↓
Reticulocytes [%]	0.5–2	1.89	1.52	5.25↑	4.13↑
Glucose [mmol/L]	3.9–5.5	9.91↑	5.12	6.74↑	7.00↑

WBC – white blood cell count; RBC – red blood cell count; HGB – hemoglobin; HCT – hematocrit; MCV – mean corpuscular volume; PLT – platelet count

DISCUSSION

Obesity is an important and modifiable risk factor for the development of T2D and cardiovascular diseases such as hypertension and atherosclerosis [10]. Additionally, numerous studies have demonstrated the association between being overweight and the occurrence of malignancies such as cancers of the breast, endometrium, ovary, prostate, colon, gallbladder, esophagus (adenocarcinoma), liver, kidney, and thyroid, as well as some leukemias and non-Hodgkin lymphoma [11,12].

Despite the knowledge of obesity, it is a significant and growing health problem. However, in cancer patients, weight loss is particularly complex, since they may develop cachexia [13]. Intentional weight loss may improve prognosis and reduce cardiovascular risk, but is recommended only for selected cancer patients. In advanced diseases, it may lead to cachexia and reduced treatment response [14].

The literature on weight loss during cancer treatment is inconclusive. The American Society of Clinical Oncology's 2022 guidelines recommend lifestyle changes to maintain healthy weight. Physical activity helps reduce ADRs associated with oncological therapy. Additionally, the importance of dietary changes is emphasized, but evidence regarding specific diets and their impact on treatment is limited [15].

An "obesity paradox" is described in the literature, suggesting that an elevated BMI may promote better treatment outcomes compared to a normal BMI [16]. Possible explanations for this phenomenon are being investigated, including deliberations on the methodology of the relevant studies and the immunological and hormonal mechanisms associated with excess body fat accumulation. In addition, some studies have reported a better response to immunotherapy in obese patients, especially to anti-PDL1/PD-1 palliative therapy [17]. The obesity paradox applies to cases of solid tumors, such as colorectal, prostate, breast, and lung cancers, as well as certain hematologic malignancies. Despite this phenomenon, there is a preponderance of scientific evidence and meta-analyses indicating a correlation between obesity and cancer and stating that excessive body weight harms cancer patients.

Cardiometabolic complications of obesity, necessitating coronary revascularization, also occurred in our patient, despite the complete remission of CLL. This cannot be interpreted as a failure of semaglutide treatment, while cardiovascular benefits can only be estimated from clinical trials in non-cancer patients [18].

Non-pharmacological methods (such as lifestyle or dietary changes or surgical treatment) and pharmacological methods are currently used to treat obesity. Current pharmacotherapy options mostly use naltrexone with bupropion, GLP-1RAs (liraglutide or semaglutide), or recently, the combination of a gastric inhibitory polypeptide (GIP) analog and a GLP-1RA (tirzepatide). Results show the high efficacy of semaglutide therapy, in which a patient can achieve a reduction of up to 7% from the baseline body weight within 68 weeks through treatment at a dosage of 1 mg per week and of 9.6% at a dosage of 2.4 mg [19]. In 2021, it was approved by the US Food and Drug Administration and a year later by the European Medicines Agency for the treatment of obesity. This drug's growing popularity has shed new light on its ADRs and potential involvement in carcinogenesis [1,20]. A correlation between treatment with liraglutide and the incidence of medullary thyroid cancer was highlighted, as liraglutide therapy has been shown in animal models to activate GLP-1 receptors on thyroid C cells and thereby increase the incidence of cancers originating from them [1,2,20]. Having reviewed evidence from the literature on the subject, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) concluded on October 27, 2023 that there is no confirmed correlation between GLP-1RAs and thyroid cancer (not only medullary cancer) [21]. Moreover, in 2024, a meta-analysis of randomized controlled trials (RCTs) involving 14,550 patients showed an incidence of thyroid cancer among participants treated with semaglutide of less than 1%, suggesting no significant risk [22]. Similar results were also obtained in another study summarizing RCTs, where actual studies of patients receiving semaglutide in the intervention group showed no increased risk of any cancer [23].

Ashruf et al. [24] and co-authors conducted a retrospective cohort study on patients with T2D who had been prescribed GLP-1RAs, insulin, or metformin. The study showed that the usage of GLP-1RAs was associated with a significant reduction in the risk of hematological malignancies, including leukemia, lymphoma, and myelodysplastic and myeloproliferative syndromes, compared with metformin and insulin.

An ongoing study led by Sørum et al. [25] is investigating the impact of semaglutide on the severity of gastrointestinal mucositis in patients diagnosed with lymphoma undergoing high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (auto-HSCT). This is expected to be a life-saving strategy for patients, as it reduces the

toxic effects of chemotherapy on the gastrointestinal mucosal barrier.

T2D and CLL are becoming increasingly common diseases in society. We can identify risk factors and mechanisms common to both diseases, for example, the presence of hyperinsulinemia. An analysis of data on drugs for glycemic control, including GLP-1RAs, can provide valuable information on treatment and prevention strategies for hematological malignancies [26].

Although it is still necessary to monitor patient safety during therapy with GLP-1RAs, it is also worth remembering that patients suffering from obesity and hemato-oncological malignancies may benefit from improving metabolic conditions and reducing cardiovascular mortality.

PATIENT PERSPECTIVE

Semaglutide has numerous ADRs, most of which are mild, including dizziness, headache, fatigue, and gastrointestinal issues [9]. The experience of patients suffering from cancer and being treated with semaglutide can vary. Oncological disease and its treatment can worsen patients' well-being, leading to an increase in concerning symptoms. There is also a possibility that the side effects of semaglutide and cancer therapy may overlap and become more noticeable. The patient we described did not report any ADRs during the therapy, and achieved clinically significant weight reduction and CLL remission, as presented in Figures 1, 2 and 3.

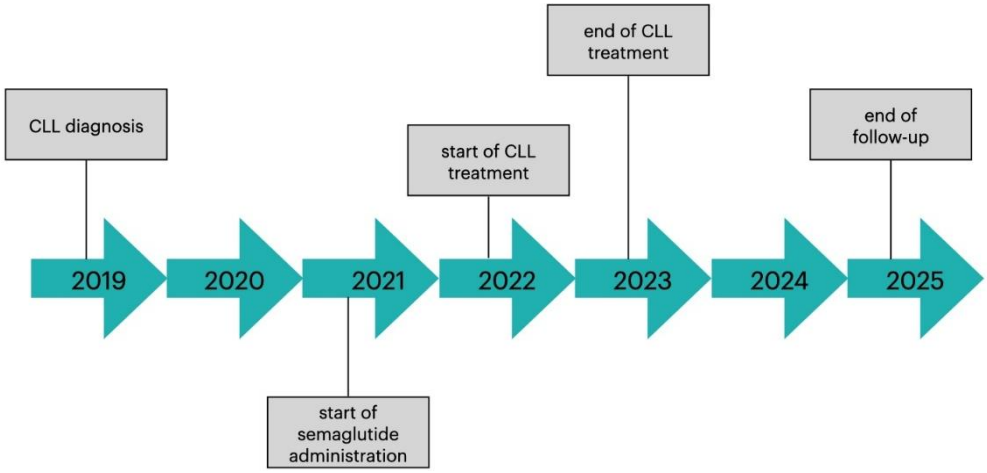

Fig. 1. Treatment timeline. CLL – chronic lymphocytic leukemia.

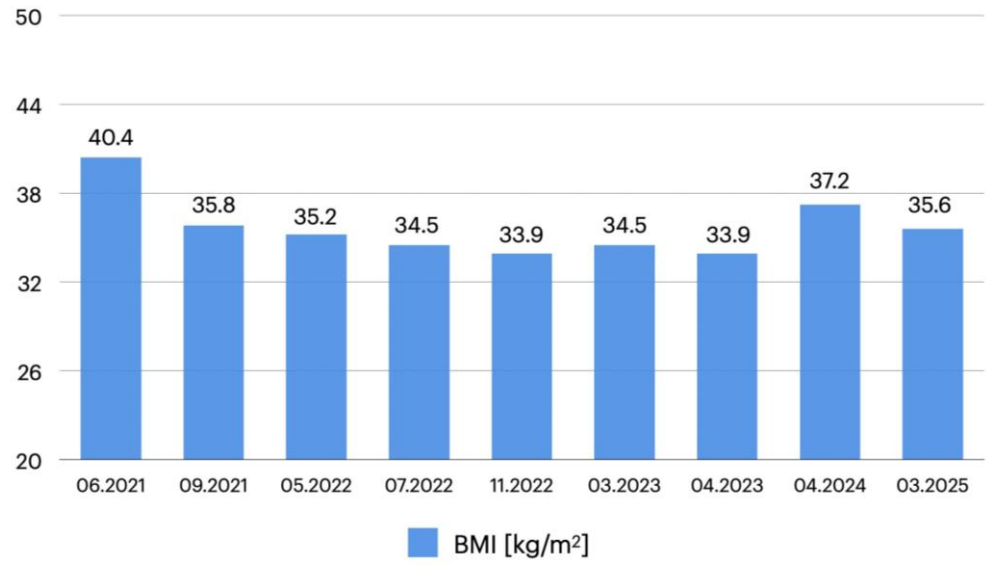

Fig. 2. Patient's body mass index (BMI).

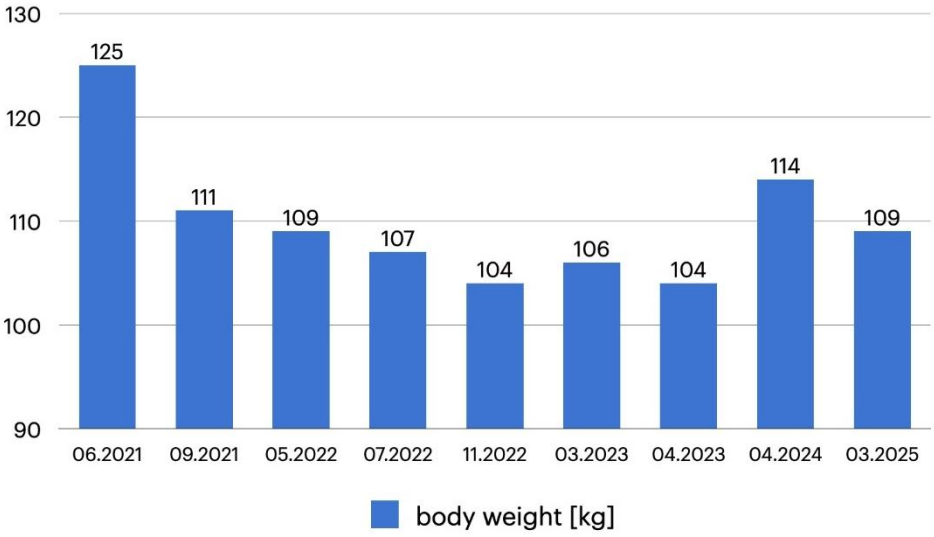

Fig. 3. Patient's body weight.

CONCLUSIONS

In this case report of a patient who suffered from asymptomatic RAI stage I, Binet A CLL with concomitant obesity, semaglutide treatment resulted in significant weight loss without compromising hematologic stability. Throughout the course of CLL treatment, the medication was well tolerated and no ADRs were reported, which suggests its potential safety in this specific group of patients.

These findings suggest that hematological patients should not be categorically excluded from obesity treatment with semaglutide, as long as close hematological and clinical monitoring is ensured. However, as this statement is based on a single case report, no definitive general recommendations regarding the safety of semaglutide in hemato--oncological patients can be made at this time.

In light of the intricacy inherent in the treatment of obesity in individuals with malignancies, as well as the insufficient evidence on the use of semaglutide in such cases, further research is required. As the opportunities for performing clinical trials on oncological and hemato-oncological patients are scarce, there is a need to collect real-life data to evaluate the long-term safety and therapeutic efficacy of GLP-1RAs in these patients in order to establish their safety.

Authors' contribution

Study design – J. Chudek
Data collection – J. Dobrowolska, K. Kozak, A. Morawa, L. Peisert, K. Wdowiak
Manuscript preparation – J. Dobrowolska, K. Kozak, A. Morawa, L. Peisert
Literature research – J. Dobrowolska, K. Kozak, A. Morawa, L. Peisert
Final approval of the version to be published – J. Chudek, K. Wdowiak

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Unrecognized diabetes mellitus among acute coronary syndrome patients in Basra, Iraq – A cross-sectional study

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ABSTRACT

INTRODUCTION: Diabetes mellitus (DM) is one of the most prevalent modifiable risk factors for acute coronary syndrome (ACS). Patients with DM constitute approximately 25%–30% of those admitted with ACS. However, data on the prevalence of unrecognized DM among patients with ACS in Iraq is generally limited.
MATERIAL AND METHODS: This cross-sectional study was conducted on patients admitted with ACS to Al Sadir Teaching Hospital, Basra Teaching Hospital, and Basra Specialized Cardiac Center in Basra. Patients with known diabetes or conditions affecting glucose or hemoglobin A1c (HbA1c) levels were excluded. This was a consecutive sampling of eligible patients. All patients admitted during the study period who met the inclusion criteria were approached and invited to participate. Those who consented were enrolled until the desired sample size was achieved. Data were collected through direct interviews and a structured questionnaire, with anthropometric measurements and laboratory investigations, including fasting blood sugar (FBS), random blood sugar (RBS), HbA1c, and lipid profile. Patients were classified as normal, prediabetes, or newly diagnosed diabetes.
RESULTS: A total of 275 ACS patients were included (mean age: 56.6 ± 12.5 years; 72% male). Screening revealed that 15.3% had unrecognized diabetes and 11.6% had prediabetes. Newly diagnosed diabetes was significantly associated with younger age (P = 0.007), smoking (P = 0.013), higher BMI (P = 0.01), dyslipidemia (P = 0.001), family history of diabetes (P < 0.001), and STEMI presentation (P = 0.047).
CONCLUSIONS: Unrecognized DM causes a significant burden among ACS patients. Effective screening for DM would aid in early detection and proper management, particularly among younger ACS patients, those with a family history of DM, smokers, and obese patients.

KEYWORDS

diabetes mellitus, screening, prediabetic state, acute coronary syndrome, cardiovascular risk factors, Iraq

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INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death worldwide. It is estimated that more than 75% of deaths related to CVDs mainly occur in low- and middle-income countries [1]. Acute coronary syndrome (ACS) is a group of clinical conditions characterized by reduced blood flow to the coronary myocardium that includes ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (non-STEMI), and unstable angina [2].

Community-based studies regarding the prevalence of ACS among the Iraqi population are limited. However, a study conducted in Kurdistan revealed that nearly 31% of patients who were undergoing coronary angiography were diagnosed with premature coronary artery disease before the age of 45 years. This indicates that there is a high burden of early-onset cardiovascular risk [3].

Diabetes mellitus (DM) is a chronic metabolic disease with a complex pathogenesis. It is characterized by hyperglycemia, or high blood glucose levels, which results from abnormal insulin secretion, insulin action, or both [4]. The prevalence of type 2 DM has been increasing globally over the last 40 years, especially in Asia, the Middle East, and North Africa. This could be explained by the sedentary lifestyle and the high prevalence of overweight and obesity [5].

Nearly 1.4 million Iraqis have diabetes and the prevalence of type 2 DM in Iraq ranges from 8.5% to 13.9% [6]. A study conducted in 2014 in Basra reported an age-adjusted prevalence of 19.7% among individuals aged 19 to 94 years [7].

In 2021, the global prevalence of undiagnosed DM reached 44.7% of all diabetic patients [8]. To identify patients with unrecognized or undiagnosed DM, a screening test must be conducted. The American Diabetes Association (ADA) has listed criteria for screening among asymptomatic adults. This includes screening for adults aged 45 and over, those with prediabetes, and women with prior gestational diabetes. For overweight or obese adults, screening is recommended if additional risk factors such as family history, hypertension, and polycystic ovary syndrome are present [9].

Patients with DM have significantly higher risks of cardiovascular events, including acute myocardial infarction, with a prevalence 3 to 5 times higher than that observed in the general population [10]. Moreover, patients with DM constitute a substantial portion of those admitted with ACS, approximately 25%–30% [11]. Diabetes is associated with a 2- to 4-fold increase in the risk of death from a CVD. More than 70% of diabetic patients over the age of 65 years will die from causes related to heart disease or stroke [12]. Despite advancements in treatment, mortality rates from coronary artery disease in patients with DM remain relatively high compared to non-diabetics, who have shown remarkable improvement in their mortality rates [13].

Thus, unrecognized DM is common and may adversely affect outcomes if left undetected. Identifying the prevalence and associated factors of unrecognized DM in ACS patients can help in early diagnosis and targeted management. To address this gap, we conducted a hospital-based screening of ACS patients in Basra to determine the prevalence of unrecognized DM and its association with demographic and clinical characteristics, providing locally relevant evidence for prevention and care.

The aim of this study was to estimate the prevalence of unrecognized DM among patients with ACS and to estimate its association among this population with demographic and clinical characteristics such as age, sex, body mass index (BMI), family history of DM, smoking status, hypertension, and dyslipidemia.

MATERIAL AND METHODS

This cross-sectional, observational study was conducted on patients admitted with ACS from January 1 to June 15, 2024 to coronary care units (CCUs) in three centers in Basra, Iraq: Al Sadir Teaching Hospital, Al Basra Teaching Hospital, and Basra Specialized Cardiac Center. The study was approved by the scientific council of the Arab Board of Health Specializations, the Ministry of Health and Environment, and the Basra Health Directorate.

The sample size estimation was based on a previous cross-sectional study conducted in Qatar by Abdullatef et al. [14], in which the prevalence of unrecognized DM among patients with ACS was 21.1%. The minimum sample size was determined according to the formula $n = (Z^2 \times p \times (1 - p)) / d^2$, where n is the sample size, Z is 1.96 at a 95% confidence interval, and the desired margin of error d is 0.05. The total number of participants was 275 patients, thus exceeding the minimal calculated sample size of 254 participants.

In this study, consecutive sampling of eligible patients was performed. All patients diagnosed with ACS, based on history, clinical examination, and assays (electrocardiogram and cardiac biomarkers), were subjected to the inclusion and exclusion criteria specific to this study. All patients admitted during the study period who met the inclusion criteria were approached and invited to participate. Those who consented were enrolled until the desired sample size was achieved. The inclusion criteria called for patients admitted to a CCU who were diagnosed with ACS during the study period who had given informed consent to participate. Known cases of DM and patients with conditions that could affect hemoglobin A1c

(HbA1c) or blood sugar readings – such as hemoglobinopathies, hemolytic anemia, pregnancy, chronic kidney disease, chronic liver disease, thyroid dysfunction, or steroid use – were excluded (Figure 1).

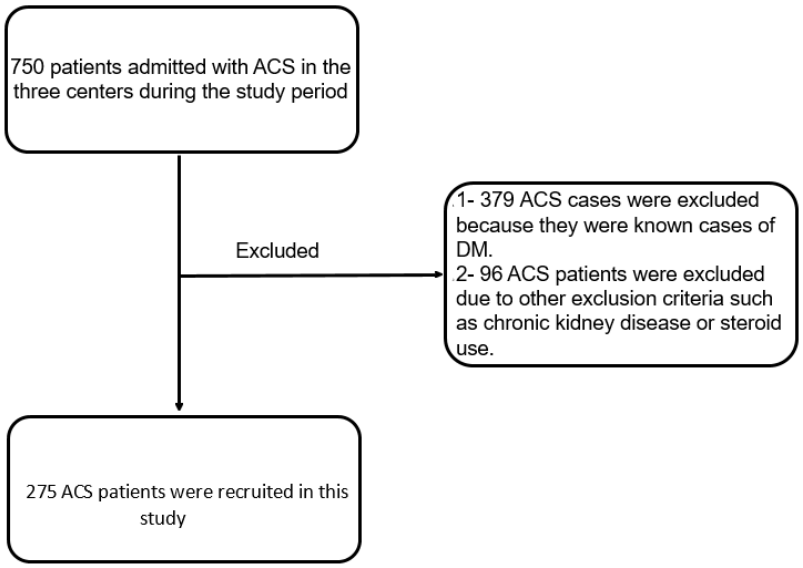

Fig. 1. Flowchart of the study. ACS – acute coronary syndrome; DM – diabetes mellitus.

The data was collected by direct interviews with the patients using a questionnaire. The questionnaire used in this study was developed by the research team based on a thorough review of the relevant literature and clinical guidelines related to ACS and DM screening. To ensure validity and clarity, the questionnaire was reviewed by experts in cardiology and endocrinology. A pilot study was conducted with a small group of patients to test its reliability. The questionnaire consisted of sections covering demographic information (age, sex, education level, and residence), clinical history (smoking status and family history of diabetes, hypertension, and dyslipidemia), and details relevant to ACS and diabetes risk factors.

Anthropometric measurements were taken using standardized methods: weight was measured with a calibrated digital scale, and height was measured using a stadiometer. Patients were measured without shoes and wearing light clothing to ensure accuracy. This was followed by calculating the BMI, which was categorized into four groups according to the World Health Organization (WHO) classification criteria (underweight: < 18.5; normal: 18.5–24.9; overweight: 25–29.9; and obese: ≥ 30 kg/m²) [15].

The investigations included DM screening using fasting blood sugar (FBS), random blood sugar (RBS), HbA1c, and lipid profile testing. Dyslipidemia was defined as abnormalities in any of the lipid profile parameters. Based on the results of the diabetes screening, the patients were classified into three categories using the ADA criteria for diagnosis (normal: both FBS and HbA1c were within normal ranges; prediabetes [pre-DM]: either FBS of 100––125 mg/dL or HbA1c of 5.7%–6.4%; newly diagnosed DM [new-DM]: either FBS ≥ 126 mg/dL or HbA1c ≥ 6.5%) [9]. The reference ranges for laboratory tests were based on the American Board of Internal Medicine laboratory test reference ranges published in January 2024.

The statistical analysis was conducted using Statistical Package for the Social Sciences version 26. Descriptive statistics, including frequency and percentage, were used for categorical variables. For quantitative data, the means and standard deviation were reported. The chi-square test was used to describe the association between categorical variables. A one-way ANOVA test was performed to compare the means of quantitative data of more than two sets. The Shapiro–Wilk test was used to test the normality of distribution. Statistical significance was defined as a P-value of less than 0.05.

RESULTS

In this study, 275 patients with ACS who fulfilled the inclusion and exclusion criteria specified for this study were recruited. The study population had a mean age of 56.60 ± 12.48 years. The majority of participants were male (72.0%). Regarding the education levels, the highest percentages had a primary (25.1%) or secondary (25.8%) education. Nearly 59% were active smokers. The mean weight of the patients was 84.78 ± 13.58 kg, and the mean height was 170.38 ± 7.86 cm. The mean BMI was 29.26 ± 4.33, ranging from 18.51

to 43.90. Among the study population, only 41 (14.9%) fell into the normal BMI category; 112 participants (40.7%) were overweight and 122 (44.4%) were obese. Hypertension was observed in 54.9% (n = 151) of the participants. Regarding lipid profiles, 128 subjects (46.5%) were identified as having dyslipidemia. Among the participants, 129 (46.9%) reported a positive family history of DM among their first-degree relatives.

STEMI was the most common subtype of ACS, occurring in 141 patients (51.3%). Non-STEMI was found in 88 participants (32.0%), while unstable angina was present in 46 participants (16.7%), as presented in Table I.

The screening indicates that 15.3% of the 275 individuals surveyed were newly diagnosed with DM, which represents the prevalence of unrecognized DM among ACS patients admitted to a CCU in the three centers in Basra. Normal results were found in 201 participants (73.1%), while 32 (11.6%) were identified with prediabetes (Figure 2).

There was a statistically significant difference in the mean age between the three groups (P = 0.007). Prediabetic patients and those who were newly diagnosed with DM were significantly younger than the non-diabetics.

Table I. Sociodemographic and clinical characteristics of the study group

Variable	Categories	Frequency	Percentage (%)
Age (years)	Mean ± SD	56.60 ± 12.48	–
Sex	Male	198	72.0
	Female	77	28.0
Education	Illiterate	23	8.4
	Literate	16	5.8
	Primary	69	25.1
	Intermediate	59	21.5
	Secondary	71	25.8
	Higher	37	13.4
Smoking	Smoker	163	59.3
	Non-smoker	96	34.9
	Ex-smoker	16	5.8
BMI	Normal	41	14.9
	Overweight	112	40.7
	Obese	122	44.4
Hypertension	Hypertensive	151	54.9
	Non-hypertensive	124	45.1
Lipid profile	Dyslipidemia	128	46.5
	Normal	147	53.5
Family history of DM	Positive	129	46.9
	Negative	146	53.1
ACS type	STEMI	141	51.3
	Non-STEMI	88	32.0
	Unstable angina	46	16.7
Total		**275**	**100.0%**

BMI – body mass index; DM – diabetes mellitus; ACS – acute coronary syndrome; STEMI – ST-segment elevation myocardial infarction.

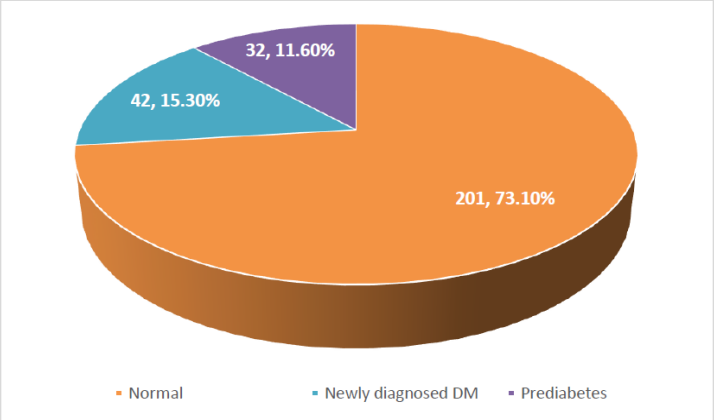

Fig. 2. Distribution of the study group according to diabetes mellitus (DM) screening results.

A significant association was found between smoking and DM (P = 0.013). Nearly two thirds of the newly diagnosed diabetic patients were active smokers. The mean BMI was significantly higher among new-DM and pre-DM patients compared to those with normal screening results (P = 0.01).

Moreover, the new-DM and pre-DM groups were more likely to be overweight or obese (P = 0.024). Dyslipidemia was significantly more prevalent among these groups as well (P = 0.001). A family history of DM was more likely among the pre-DM patients and to a lesser extent among the new-DM ones (P < 0.001).

A significant association between DM screening and ACS subtype was found (P = 0.047). The new-DM group had a higher percentage of STEMI (71.4%) compared to the pre-DM and normal groups (46.9% and 47.8%, respectively).

There was no statistically significant association between DM screening results and sex, educational level, place of residence, or hypertension (P > 0.05), as seen in Table II.

Table II. Comparison of the sociodemographic and clinical characteristics across the diabetes mellitus (DM) screening groups

Variable	Categories	Normal (n = 201)	New-DM (n = 42)	Pre-DM (n = 32)	P-value
Age (years)	Mean ± SD	57.90 ± 13.40	54.69 ± 8.43	50.94 ± 8.61	**0.007****
Sex	Male	149 (74.1%)	29 (69.0%)	20 (62.5%)	0.356*
	Female	52 (25.9%)	13 (31.0%)	12 (37.5%)	
Education	Illiterate	17 (8.5%)	2 (4.8%)	4 (12.5%)	0.201*
	Literate	13 (6.5%)	2 (4.8%)	1 (3.1%)	
	Primary	48 (23.9%)	9 (21.4%)	12 (37.5%)	
	Intermediate	34 (16.9%)	17 (40.5%)	8 (25.0%)	
	Secondary	54 (26.9%)	10 (23.8%)	7 (21.9%)	
	Higher	35 (17.4%)	2 (4.8%)	0 (0.0%)	
Smoking	Smoker	121 (60.2%)	28 (66.7%)	14 (43.8%)	**0.013***
	Non-smoker	69 (34.3%)	9 (21.4%)	18 (56.3%)	
	Ex-smoker	11 (5.5%)	5 (11.9%)	0 (0.0%)	
BMI	Mean ± SD	28.78 ± 4.35	30.71 ± 4.05	30.34 ± 4.05	**0.010****
	Normal	36 (17.9%)	3 (7.1%)	2 (6.3%)	**0.024***
	Overweight	87 (43.3%)	13 (31.0%)	12 (37.5%)	
	Obese	78 (38.8%)	26 (61.9%)	18 (56.3%)	
Hypertension	Hypertensive	112 (55.7%)	23 (54.8%)	16 (50.0%)	0.833*
	Non-hypertensive	89 (44.3%)	19 (45.2%)	16 (50.0%)	
Lipid profile	Dyslipidemia	80 (39.8%)	26 (61.9%)	22 (68.8%)	**0.001***
	Normal	121 (60.2%)	16 (38.1%)	10 (31.3%)	
Family history of DM	Positive	79 (39.3%)	24 (57.1%)	26 (81.3%)	**0.000***
	Negative	122 (60.7%)	18 (42.9%)	6 (18.8%)	
ACS subtype	STEMI	96 (47.8%)	30 (71.4%)	15 (46.9%)	**0.047***
	Non-STEMI	66 (32.8%)	10 (23.8%)	12 (37.5%)	
	Unstable Angina	39 (19.4%)	2 (4.8%)	5 (15.6%)	

*Chi-square test was used; **One-way ANOVA test was used; new-DM – newly diagnosed diabetes mellitus; pre-DM – prediabetes mellitus; BMI – body mass index; ACS – acute coronary syndrome; STEMI – ST-segment elevation myocardial infarction.

DISCUSSION

DM is recognized as a global public health concern. The WHO has ranked DM as the eighth leading cause of death in 2021, based on the global projections of causes of death [16]. The Middle East and North Africa region comes second among the International Diabetes Federation regions, with a prevalence of DM of 9.2% [17].

In a pooled analysis to measure the worldwide trends of DM, it is estimated that the prevalence of DM in Iraq in 2014 was approximately 17.5% [18]. Data from a population-based study conducted in Basra in 2014 found that 11% of individuals screened for DM were identified to have undiagnosed DM and 29.1% were found to have prediabetes [7].

In this study, the prevalence of unrecognized DM among ACS patients during the study period was 15.3%. This finding was comparable to that of a study conducted in India by Ashraf et al. [19], in which 14.7% of ACS patients were newly diagnosed with diabetes. Notably, this group had a mortality rate that was double that of the normal and pre-diabetic groups.

Across countries, the prevalence rates of undiagnosed DM in ACS patients were highly variable. Starting as low as 5.3% in Macedonia [20] or 7.4% in Pakistan [21], they reach up to 21.1% in Qatar [15], 22% in India [22], and as high as 24.5% in Egypt [23]. The relatively lower prevalence in our study compared to other

countries might reflect the widespread accessibility to healthcare services in Iraq as well as the screening programs established in primary health center settings [6]. Furthermore, this variation between different studies is also linked to the demographic and geographic characteristics of the populations, the diagnostic criteria applied, the choice of laboratory tests (HbA1c, FBS, RBS, and oral glucose tolerance test), and the methodologies used [24].

The study revealed that 11.6% of patients were found to be prediabetic. This was slightly lower than in studies by Kumar et al. [22] and Abdullatef et al. [14], where pre-DM patients represented 14% of ACS patients.

In the current study, the mean age of the patients with newly diagnosed DM was 54.69 ± 8.43 years, which was significantly lower than the mean age of the non--diabetic group (57.90 ± 13.40 years). This was in line with a study conducted in Pakistan in 2024 by Khan et al. [25], which found that both undiagnosed DM and pre-DM groups were significantly younger than the non-diabetic group. The accelerated atherosclerosis, oxidative stress, and increased inflammation caused by DM can promote the progression of atherosclerotic changes at earlier ages compared to non-diabetic individuals [26].

In the study, ACS patients who had newly diagnosed DM and pre-DM had significantly higher BMI and dyslipidemia rates compared to the non-diabetic patients. Dyslipidemia was prevalent among nearly 62% of the newly diagnosed DM patients. This was comparable to two studies, by Filisa-Kaphamtengo et al. [27] in Malawi and by Yadegar et al. [28] in Iran. Both studies found that approximately 70% of DM patients had dyslipidemia and that it acts as a predictor of the risk of atherosclerotic cardiovascular diseases.

Filisa-Kaphamtengo et al. [27] also revealed that dyslipidemia among diabetic patients was associated with being overweight and obese. Both obesity and dyslipidemia are associated with reduced levels of serum adiponectin, a hormone that is integral to glucose regulation and lipid metabolism. Obesity among patients with DM is also associated with elevated levels of leptin, a hormone that plays a role in appetite regulation. Elevated leptin levels contribute to endothelial dysfunction, a key mechanism in the pathogenesis of atherosclerotic cardiovascular diseases [29].

In the current study, newly diagnosed DM patients had a mean BMI of 30.71 ± 4.05, which was significantly higher than the BMI among the normoglycemic group (28.78 ± 4.35). This was in line with a study by Mansour et al. [7] in Basra, who found that diabetic patients had significantly higher BMI than non-diabetics (28.3 ± 5.6 and 26.8 ± 6.6, respectively).

The current study revealed that 81.3% of pre-DM patients and 57.1% of new-DM ones had a family history of DM. Likewise, a study in Pakistan found a similar association, where 45% of newly diagnosed DM patients had a family history of DM [21]. A family history of DM among first-degree relatives results in a 3-fold higher risk of developing DM [30].

In this study, approximately 67% of the newly diagnosed DM patients were active smokers, which was higher than a study in China, which reported that 50.8% of ACS male patients with undiagnosed DM were smokers [31]. According to the European Society of Cardiology, smoking increases the risk of type 2 diabetes, cardiovascular disease, and premature death [32].

The study found no association between DM screening results and hypertension. More than half of patients with newly diagnosed DM were also hypertensive. This disagrees with the findings of Mansour et al. [7] in a study from Basra in which hypertension rates were significantly higher among DM and pre-DM individuals.

In the study, patients with unrecognized DM had a significantly higher frequency of STEMI (71.4%) compared to the pre-DM (46.9%) and non-diabetic groups (47.8%). The prevalence of STEMI was higher than that reported in Pakastani studies by Kazim et al. [21] and Khan et al. [25], in which STEMI was seen in 50% and 37% of undiagnosed DM patients, respectively, and no significant association was revealed. In contrast to our results, a study by Zhou et al. [31] in China found significantly higher rates of both non-STEMI and unstable angina among ACS cases with DM. The variation in these results is likely due to differences in study design and sample size, inclusion criteria, and diagnostic methods. Undiagnosed diabetes affects the development of ACS through various mechanisms, such as endothelial dysfunction, inflammation, hypercoagulability, and accelerated atherosclerosis. The presence of hyperglycemia causes an increase in oxidative stress and impairment of endothelial function. This leads to a greater risk of plaque destabilization and rupture, which are key factors in ACS [24].

This study is limited by its hospital-based sample, which may restrict the generalizability of the findings to the broader population. Patients in hospital settings may differ from those in the community or primary care settings in terms of disease severity, access to healthcare, and other factors. Additionally, the cross--sectional design estimates the prevalence at a specific point in time. Future research should consider including patients from diverse healthcare settings to improve external validity and ensure a more comprehensive understanding of the findings.

CONCLUSIONS

This study demonstrates a substantial burden of unrecognized DM among ACS patients and it is strongly associated with cardiovascular risk factors such as smoking, high BMI, dyslipidemia, family history of DM, and younger age at presentation, as well as higher rates of STEMI. These findings highlight the need for routine diabetes screening in all ACS patients, with particular focus on high-risk individuals. Integrating targeted interventions, including smoking cessation programs, weight management, dyslipidemia control, and public health education on healthy lifestyles at both primary healthcare centers and through media campaigns should be prioritized in order to reduce the impact of diabetes and cardiovascular disease in this population.

Authors' contribution

Study design – M.Q.M. Ali, N.R. Shiaa
Data collection – Z.Q.M. Ali
Data interpretation – A.A. Al-Rubaye
Statistical analysis – A.A. Al-Rubaye
Manuscript preparation – Z.Q.M. Ali, A.A. Al-Rubaye
Literature research – Z.Q.M. Ali, M.Q.M. Ali, N.R. Shiaa, A.A. Al-Rubaye

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PRACA ORYGINALNA
ORIGINAL PAPER

The situation of inmates in Poland between 2002 and 2023, considering healthcare, health-promoting behavior, and well-being maintenance

Sytuacja więźniów w Polsce w latach 2002–2023 z uwzględnieniem opieki zdrowotnej, zachowań prozdrowotnych oraz utrzymania dobrostanu więźniów

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ABSTRACT

INTRODUCTION: Protecting health is a priority for every modern democratic country. No one should be discriminated against in any sphere of life, obligating the national authorities to protect all citizens. The aim of the study is to assess the health condition and healthcare needs of prison inmates in light of the costs of prisoners' maintenance (including expenses for healthcare) over the course of 20 years, from 2002 to 2023.
MATERIAL AND METHODS: The methods were analysis and synthesis of source material obtained from Statistics Poland, the central statistics authority. The results are presented with descriptive and comparative methods of statistical analysis.
RESULTS: We observed increases in the number of natural deaths, reported addictions (to medications and alcohol), psychiatric consultations (resulting in fewer acts of self-aggression), and declarations of addiction (resulting in more prisoners being identified and treated).
CONCLUSIONS: We concluded that there is a need to improve medical care in prisons.

KEYWORDS

healthcare, well-being, prisoners, medical needs, health service

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STRESZCZENIE

WSTĘP: Zdrowie oraz jego ochrona są priorytetem w każdym demokratycznym kraju. Nikt nie może być dyskryminowany w jakiejkolwiek sferze życia, co nakłada na władze obowiązek, by chronić każdego obywatela. Celem pracy jest ocena stanu zdrowia oraz potrzeb leczniczych więźniów w korelacji z kosztami ich utrzymania (z uwzględnieniem wydatków na ochronę zdrowia) na przestrzeni 20 lat (2002–2023).
MATERIAŁ I METODY: Zastosowano metody analizy i syntezy materiału źródłowego otrzymanego z Głównego Urzędu Statystycznego w Polsce. Wyniki zaprezentowano z użyciem opisowych oraz porównawczych metod analizy statystycznej.
WYNIKI: Zaobserwowano wzrost liczby zgonów naturalnych, zgłaszanych uzależnień (od leków i alkoholu), konsultacji psychiatrycznych (co skutkowało zmniejszeniem liczby aktów autoagresji) i deklaracji uzależnienia (co skutkowało większą liczbą zidentyfikowanych i leczonych więźniów).
WNIOSKI: Opieka zdrowotna w więzieniach wymaga poprawy.

SŁOWA KLUCZOWE

opieka zdrowotna, dobrostan, więźniowie, potrzeby lecznicze

INTRODUCTION

The protection of health is a priority for every modern democratic country [1]. Winston Churchill once said that a society is measured by the treatment of its prisoners [2].

The Constitution of the Republic of Poland, ratified on April 2, 1997, is the supreme law in Poland [3]. It is written there that no one shall be discriminated against in any sphere of life; this imposes an obligation on the national authorities to protect all citizens. Undoubtedly, being imprisoned violates personal dignity and may cause a sense of abasement [2]. Moreover, the role of the authorities is to provide special care for the inmates. This includes protecting their health, as guaranteed in Article 68(1) of the Constitution [3]. The obligation of the government in terms of the life and health of the prisoners is a result of health being treated as a public good as well as a personal one [4]. It can be said that protecting the health of inmates is a part of their future social rehabilitation [5]. Prisoners have a constitutional right to medical care [4]. Healthcare for prisoners is regulated by medical law, penitentiary law, and the Penal Enforcement Code [1]. According to Article 115 of the Penal Enforcement Code, free medical care, medications, and sanitary articles are guaranteed to the inmates. If a lack of any additional articles – such as dentures or orthopedic remedies – make it impossible to serve a sentence, the prisoner should receive such article. Inmates do not have the right to choose their nurse or doctor in either ambulatory or primary healthcare. They cannot choose the provider of basic outpatient procedures, dentists, or hospitals. Medical care for prisoners is primarily provided by the assigned medical institutions [6].

The rules, range, and mode of providing health services are regulated by the Regulation of the Minister of Justice published on June 14, 2012. The Prison Health Service is obliged to provide medical procedures regarding prophylaxis, diagnostics, nursing, psychological care, dental care, and medical care. Special care is guaranteed for inmates who are disabled, pregnant, or in labor and for newborn children [7].

It is strictly described in the law when medical procedures for inmates can be provided by the public healthcare system. Those special situations are when immediate medical aid is necessary due to a life- or health-threatening condition or when there is a need for specialist examination, specialistic treatment, or rehabilitation. If any of these conditions occurs, appropriate transport is provided to the prisoner. Prisoners who are granted a day off from prison can be treated by all the specialists mentioned above [6,7].

There is a schedule of medical examinations that includes preliminary, periodic, and medical check-ups. Preliminary examinations must be conducted within 3 days of the inmate's admission. During first 14 days, a prophylactic x-ray of the thorax and a dental examination must be conducted. A medical doctor or dentist may recommend additional examinations. The first x-ray of the thorax may not be taken if the inmate provides one taken no later than 6 months before admission to the prison or if the prisoner is pregnant. Subsequent x-rays of the thorax must be taken no less often than every 24 months. It can only be omitted if the x-ray was taken due to another reason or because of pregnancy. Medical check-ups are performed if the prisoner is transferred to another penitentiary or before the prisoner is released from prison [7].

The Prison Service is an institution that strictly follows the rules and directions described in the Executive Penal Code, the European Prison Code, and the Standard Minimum Rules for the Treatment of Prisoners. The Prison Service, a uniformed and armed apolitical formation with its own structural organization, is directly responsible to the Minister of Justice. According to the legal act on the Prison Service, published on April 9, 2010, it is responsible for organizing activities that promote the acquisition of professional qualifications; teaching, cultural, and educational activities; and physical culture and sport. The Prison Service must respect the rights of the prisoners, especially regarding their living conditions,

respect of their dignity, healthcare, and religious care [8].

The international community claims that the health of prisoners should be treated as a public health issue [4,9,10]. The harmfulness of imprisonment has been confirmed [11]. Two very important, international documents were created in order to improve the conditions in penitentiaries. The first of them is the European Prison Code, which was adopted on January 11, 2006 and is the recommendation of the Committee of Ministers of the European Union. On its basis, the healthcare of prisoners became unified with the public healthcare system. Each prisoner has a right to be treated by a primary care physician, surgeon, psychiatrist, ophthalmologist, or dentist. The Prison Service should provide medical care in case of any emergency. If treatment cannot take place in the penitentiary, a sick prisoner should be transported to a specialist healthcare unit [12].

The United Nations' Standard Minimum Rules for the Treatment of Prisoners – also known as the Nelson Mandela Rules – were adopted by the United Nations Assembly on December 12, 2015. Nelson Mandela, a South African activist who served 27 years in prison, said, "It is said that no one truly knows a nation until one has been inside its jails" [13]. The standards described in that document require that each prison should have a qualified, interdisciplinary medical staff and that their decisions cannot be ignored by the Prison Service. The healthcare service should be tasked with promoting, protecting, and improving the physical and mental health of prisoners, paying particular attention to those with special healthcare needs. The healthcare service is obliged to prepare an accurate, up-to-date, and confidential individual medical history. All prisoners should be ensured prompt access to medical aid in any urgent cases. All prisons should offer appropriate psychological, psychiatric, and dental care. Prisoners who require specialized treatment or surgical treatment should have access to specialist or general hospitals [12].

Both documents similarly describe the medical procedures that are required when a prisoner is admitted to prison. The examination on admission is necessary not only to diagnose any physical disability, but also to learn whether any psychological problems regarding imprisonment may occur. Those procedures are intended to limit acts of self-aggression, including suicide attempts and withdrawal symptoms. If any symptom of torture or inhumane or humiliating treatment is observed, it should be immediately noted and reported. It is very important to avoid the spread of any infectious disease by treating it and immediately isolating infected prisoners. It is the responsibility of the physician to inform the prison authorities if any signs of deterioration in the prisoners' health is observed. Any medical experiments that can cause the deterioration of prisoners' health are also forbidden. Additionally, the Rules recommend getting the opinion of a physician in terms of the prisoners' diet, hygiene, and accommodation [12].

The aim of this article is to assess the well-being, health status, and healthcare needs of inmates over the course of 20 years, from 2002 to 2023.

MATERIAL AND METHODS

The methods were analysis and synthesis of source material obtained from the Prison Service, Statistics Poland, the Institute of Labour and Social Studies, and the Office of the Director General of the Prison Service. The results are presented with the descriptive and comparative methods of statistical analysis. Before the appropriate material was extracted, the research thesis was formulated. The research thesis and appropriate statistical methods enabled the aim of the study to be realized [14,15,16,17,18,19,20,21,22,23,24,25,26].

The research examined the following:

- acts of self-aggression, suicide attempts, suicides, and deaths
- addictions compared with self-aggression, psychiatric consultations, and deaths
- interventions of the Emergency Medical Service with regard to psychiatric consultations, acts of self-aggression, and suicide attempts
- types of medical aid provided in penitentiaries and outside them
- long-term trends in dental consultations for Polish inmates

Statistical analysis

In this analysis, the significance threshold was set at $\alpha = 0.05$. The normality of numerical variables was assessed using the Shapiro–Wilk test. For variables that did not follow a normal distribution, the association between them was examined using Spearman's rho correlation coefficient. The p-values were determined through an asymptotic approximation based on the t-test. In the case of multiple comparisons, the p-value was additionally adjusted (p_{adj}) using the Holm method. Furthermore, the growth rate of the time series data was quantified using the compound annual growth rate (CAGR) according to the formula:

$$\mathbf{CAGR} = \left(\frac{\mathbf{EV}}{\mathbf{BV}}\right)^{\frac{\mathbf{1}}{\mathbf{n}}} - \mathbf{1}$$

where *EV* is the value of the parameter under study in the last year, *BV* is the initial value in the first year, and *n* is the number of years under observation. The analysis was conducted using the R Statistical language (version 4.3.1) [27] on Windows 10 Pro 64-bit (build 19045), using the packages *sjPlot*

(version 2.8.15) [28], *report* (version 0.5.7) [29], *ggstatsplot* (version 0.12.1) [30], and *ggplot2* (version 3.4.4) [31].

RESULTS

Analysis of incidents of self-aggression, suicide attempts, and mortality rates in Polish prisons, 2002–2023

The data provided in Table I show that in 2009 the number of self-aggression acts was the highest. Between 2020–2023, the number of natural deaths was the highest, which correlates with the increase in prisoners' age. The data spanning from 2002 to 2023 on self-aggression, suicide attempts, and mortality in prisons reveal several key trends and insights into the changing landscape of inmate behavior and institutional management (Figure 1).

The analysis of mortality rates presents a more complex scenario. There was an increasing trend in general deaths, escalating from 96 (0.12%) in 2002 to a peak of 192 (0.26%) in 2022, before slightly decreasing to 188 (0.25%) in 2023 (CAGR = 3.5%). This increase might be attributed to an aging prison population and possibly deteriorating health status over time. The deaths specifically caused by self-aggression decreased overall, from 40 (0.05%) in 2002 to 19 (0.02%) in 2023 (CAGR = -2.9%), aligning with the decreases seen in self-aggression and suicide attempts. Natural deaths showed a significant rise, from 56 (0.07%) in 2002 to 168 (0.22%) in 2023 (CAGR = 5.2%). This substantial growth could reflect an aging inmate demographic, as well as potential challenges in providing healthcare within the prison system.

Table I. Number of self-aggression incidents, suicide attempts, and deaths in prisons in particular years (the proportion of the overall number of prisoners is given in parentheses)

Year	Self-aggression overall	Suicide attempts	Deaths overall	Deaths caused by self-aggression	Natural deaths	Others
2002	948 (1.16%)	172 (0.21%)	96 (0.12%)	40 (0.05%)	56 (0.07%)	0
2003	664 (0.82%)	130 (0.16%)	127 (0.16%)	37 (0.05%)	86 (0.11%)	4 (0.005%)
2004	730 (0.91%)	135 (0.17%)	107 (0.13%)	30 (0.04%)	67 (0.08%)	10 (0.012%)
2005	773 (0.93%)	187 (0.23%)	122 (0.15%)	32 (0.04%)	84 (0.10%)	6 (0.007%)
2006	795 (0.91%)	188 (0.22%)	154 (0.18%)	42 (0.05%)	112 (0.13%)	0
2007	633 (0.70%)	174 (0.19%)	145 (0.16%)	41 (0.05%)	95 (0.11%)	11 (0.012%)
2008	715 (0.83%)	191 (0.22%)	135 (0.16%)	39 (0.05%)	93 (0.11%)	3 (0.003%)
2009	818 (0.96%)	211 (0.25%)	125 (0.15%)	41 (0.05%)	84 (0.10%)	0
2010	622 (0.75%)	147 (0.18%)	135 (0.16%)	34 (0.04%)	91 (0.11%)	10 (0.012%)
2011	433 (0.52%)	191 (0.23%)	105 (0.13%)	22 (0.03%)	102 (0.12%)	3 (0.004%)
2012	281 (0.33%)	150 (0.18%)	107 (0.13%)	18 (0.02%)	89 (0.11%)	0
2013	266 (0.32%)	188 (0.22%)	109 (0.13%)	19 (0.02%)	80 (0.10%)	10 (0.012%)
2014	217 (0.27%)	175 (0.22%)	107 (0.14%)	26 (0.04%)	75 (0.09%)	6 (0.008%)
2015	215 (0.29%)	173 (0.23%)	105 (0.14%)	23 (0.03%)	79 (0.11%)	3 (0.004%)
2016	220 (0.31%)	197 (0.28%)	123 (0.17%)	24 (0.03%)	93 (0.13%)	6 (0.008%)
2017	244 (0.33%)	223 (0.30%)	153 (0.21%)	27 (0.04%)	124 (0.17%)	2 (0.003%)
2018	223 (0.30%)	208 (0.28%)	170 (0.23%)	26 (0.04%)	135 (0.18%)	9 (0.012%)
2019	215 (0.29%)	198 (0.27%)	159 (0.21%)	24 (0.03%)	129 (0.17%)	6 (0.008%)
2020	142 (0.20%)	119 (0.17%)	174 (0.25%)	27 (0.04%)	145 (0.21%)	2 (0.003%)
2021	174 (0.24%)	145 (0.20%)	188 (0.26%)	27 (0.04%)	155 (0.22%)	6 (0.008%)
2022	130 (0.18%)	117 (0.16%)	192 (0.26%)	15 (0.02%)	166 (0.23%)	11 (0.015%)
2023	141 (0.18%)	120 (0.16%)	188 (0.25%)	19 (0.02%)	168 (0.22%)	1 (0.001%)

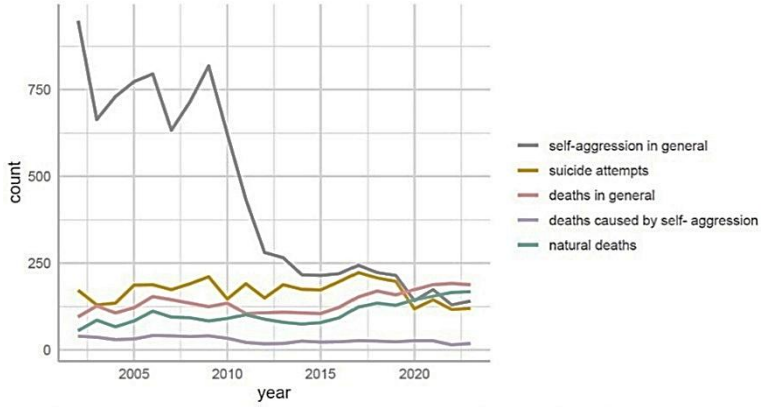

Fig. 1. Twenty-year trends in self-aggression, suicide attempts, and mortality in Polish prisons (2002–2023).

Analysis of prison population dynamics: trends in self-aggression, mortality, and substance dependence, 2002–2023

Looking at the data from 2002 to 2023, several key trends and dynamics emerge regarding addiction to intoxicants or psychotropic drugs, alcohol addiction, self-aggression, general deaths, and psychiatric counseling within the prison setting. Addiction rates, for both intoxicants/psychotropic drugs and alcohol, generally exhibit an increasing trend over the years. Starting from lower figures in 2002, with 347 (0.43%) for intoxicants and 420 (0.52%) for alcohol, these numbers had risen significantly by 2023, to 1,170 (1.53%) for intoxicants and 2,103 (2.76%) for alcohol. The rise in addiction could reflect broader trends in substance availability, changes in population demographics, or possibly evolving patterns of reporting and diagnosis. The number of psychiatric consultations started at 54,925 (67.48%) in 2002 and rose substantially to 76,421 (more than 1 per prisoner) by 2023. The correlation between self-aggression, mortality, substance dependence, and psychiatric counseling is depicted in Figure 2.

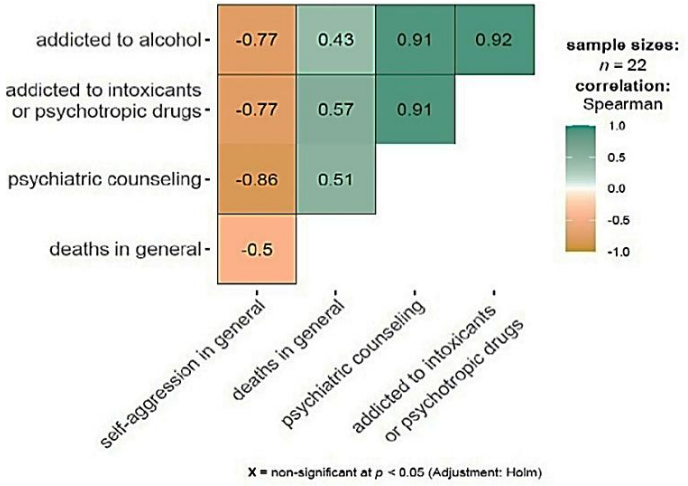

Fig. 2. Correlation matrix of the relationships between self-aggression, mortality, psychiatric counseling, and substance dependence.

Firstly, the negative correlation between self-aggression and mortality (*rho* = -0.50; p_{adj} = 0.042) suggests that as self-aggressive incidents decreased, mortality rates tended to increase. This counterintuitive relationship might indicate that while direct self-harm is being reduced – possibly due to effective interventions – other factors leading to mortality may be on the rise, potentially as a consequence of untreated or inadequately addressed underlying issues. There was a more pronounced negative correlation between self-aggression and psychiatric counseling (*rho* = -0.86; p_{adj} < 0.001), indicating a strong inverse relationship where more counseling was associated with fewer instances of self-aggression. This suggests that psychiatric interventions effectively mitigate self-aggressive behaviors, underscoring the importance

of such services in managing behavioral issues within the prison population. In contrast, a positive correlation between mortality and psychiatric counseling was observed (*rho* = 0.51; p_{adj} = 0.043), implying that as psychiatric counseling increases, mortality rates also tend to rise. This could reflect more severe cases being identified and treated as counseling services expand, or it might indicate a lag effect where the benefits of counseling on reducing mortality are delayed.

In terms of substance dependence, both intoxicants and alcohol showed strong positive correlations with psychiatric counseling (*rho* = 0.91, p_{adj} < 0.001 for intoxicants; *rho* = 0.91, *p* = 0.001 for alcohol). These high correlations indicate that increases in counseling were closely linked with the higher reported rates of substance dependence. This relationship may suggest that as more individuals receive psychiatric attention, more cases of substance dependence are identified and treated. Furthermore, substance dependence (both intoxicants and alcohol) was negatively correlated with self-aggression (*rho* = -0.77; p_{adj} < 0.001 for both substances), demonstrating that increased addiction was associated with a decrease in self-aggression. This could be interpreted as substance use serving as a maladaptive coping mechanism that reduces outward aggression. There was a notable positive correlation between deaths and substance dependence (*rho* = 0.57, p_{adj} = 0.021 for intoxicants; *rho* = 0.43, p_{adj} = 0.046 for alcohol), indicating that the higher dependency rates were associated with increased mortality. This relationship underscores the lethal risk associated with substance abuse, which may contribute directly to mortality through overdose or indirectly through health complications. Lastly, the interdependency between addiction to intoxicants and alcohol (*rho* = 0.92; p_{adj} < 0.001) was the strongest observed correlation, suggesting a significant overlap in these addiction patterns. This could reflect a common vulnerability or shared risk factors in the population, where individuals susceptible to one form of substance dependence are also likely to be dependent on the other.

Analysis of emergency service interventions and their correlation with self-aggression, psychiatric counseling, and suicide attempts in Polish prisons, 2008–2023

Table II shows that the number of emergency service interventions in Polish prisons between 2008 and 2023 was stable, taking values between 6,223 and 8,564. The data provided details on the number of emergency service interventions in detention wards (DT) and penitentiaries (P) during this period, with earlier years missing from the record. Over this 16-year period, the trends and fluctuations in the number of interventions offer significant insight into the evolving dynamics of emergency healthcare demands within these facilities (Figure 3).

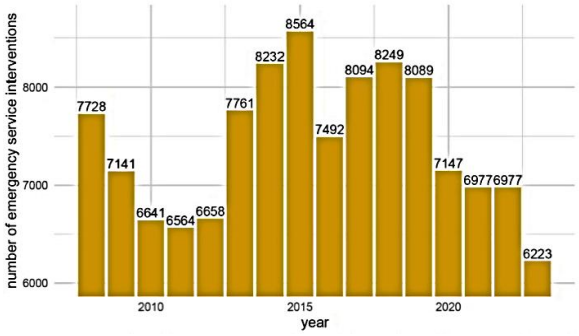

Fig. 3. Annual trends in emergency service interventions in Polish detention wards and penitentiaries (2008–2023).

Table II. Number of emergency service interventions in Polish prisons in particular years

Year	Number of emergency service interventions
2008	7,728
2009	7,141
2010	6,641
2011	6,564
2012	6,658
2013	7,761
2014	8,232
2015	8,564
2016	7,492
2017	8,094
2018	8,249
2019	8,089
2020	7,147
2021	6,977
2022	6,977
2023	6,223

Initially, the data shows relatively fewer interventions in 2008, with 7,728 (8.99%). This number initially decreases until 2010, suggesting an improvement in either the health conditions within the facilities or the effectiveness of preventive healthcare measures. However, the trend reverses from 2011 onwards, with a noticeable increase that peaks in 2015 at 8,564 (11.45%) interventions.

The year 2020 shows a more pronounced drop in interventions, to 7,147 (10.11%), which might reflect the impact of the COVID-19 pandemic. From 2021 onwards, the number stabilizes somewhat, with a slight decrease continuing into 2023, when a record low of 6,223 (8.16%) interventions was recorded. This continued decrease could be indicative of sustained improvements in healthcare provision within these settings, or possibly a decrease in the overall detention and penitentiary populations.

The correlations presented in Table III between emergency service interventions and various parameters in detention wards and penitentiaries over the period 2008–2023 reveal several nuanced insights about the relationships between these variables.

Table III. Correlations between emergency service interventions and self-aggression, psychiatric counseling, suicide attempts, and the number of prisoners, 2008–2023

Parameter	rho	p
Acts of self-aggression	-0.04	0.875
Psychiatric counseling	0.19	0.488
Suicide attempts	0.49	0.055
Number of prisoners	-0.15	0.587

Note: The number of pairs (n_{pairs}) was 16.

Comprehensive analysis of medical consultations for Polish inmates, 2002–2023

The comprehensive data from 2002 to 2023 concerning medical consultations for inmates at both penitentiaries and public health centers across various medical specializations provides a rich field for analysis. Overall, the annual mean number of consultations in penitentiaries during 2002–2023 significantly surpassed that recorded at public health centers, with 1,492,077 consultations at penitentiaries compared to just 26,198 at public health centers (Figure 4). This stark contrast underscores the central role that penitentiaries play in providing healthcare to inmates.

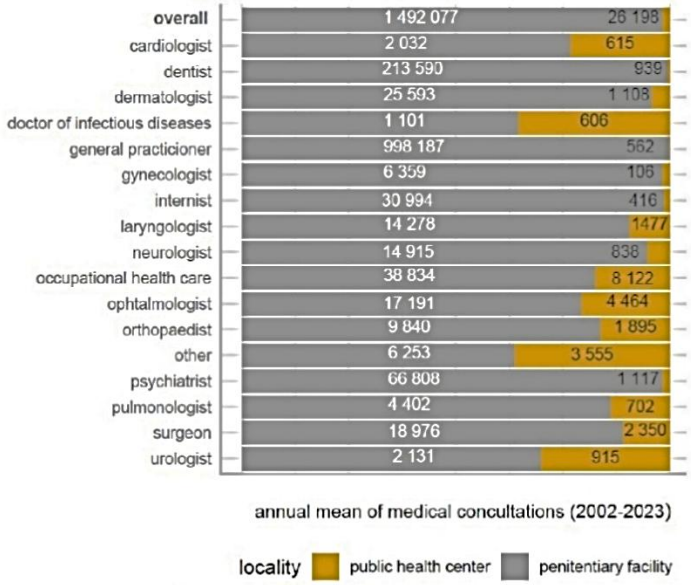

Fig. 4. Average number of medical consultations given by type of medical unit, 2002–2023.

The most frequent consultations at penitentiaries were with general practitioners (998,187), which reflects the general medical needs that are typically the first point of contact in the healthcare system. This is followed by a notably high number of consultations with psychiatrists (66,808), which could indicate a significant demand for mental health services among the inmate population. Dental consultations also showed a substantial count (213,590), highlighting the importance of dental health in the overall healthcare provided in these facilities.

Other specializations – such as dermatology, neurology, and ophthalmology – also showed considerable numbers, suggesting a broad spectrum of health needs among inmates that are being addressed within the facilities. The lower but still significant numbers in specializations such as surgery, cardiology, and orthopedics further reflect comprehensive healthcare that extends beyond basic medical care.

In general, the data illustrate a robust in-house healthcare system at penitentiaries, primarily driven by high numbers of consultations with general practitioners and psychiatrists, indicating a focus on both physical and mental healthcare. The comparatively lower numbers at public health centers suggest their more supplementary role in inmate healthcare, possibly used for services which are not readily available at penitentiaries.

Long-term trends in dental consultations for Polish inmates, 2002–2023

Over the period 2002–2023, the trend in dental consultations for Polish inmates exhibited a long-term decline in both penitentiaries and public health centers,

although the scale and implications differed significantly between these two settings (Figure 5, Table IV). Starting with penitentiaries, there was a clear, steady decline from a high of 306,172 consultations (more than 3 per prisoner) in 2002 to 131,641 (more than one per prisoner) in 2023 (CAGR = -2.75%). This reduction was not abrupt but gradual, indicating a systemic decrease in dental consultations. The most drastic reduction seems to have occurred after 2019, when the numbers dropped from 162,168 (more than 2 per prisoner) to 124,440 (more than 1 per prisoner) in 2020; this trend continued to decline, reaching a low in 2023.

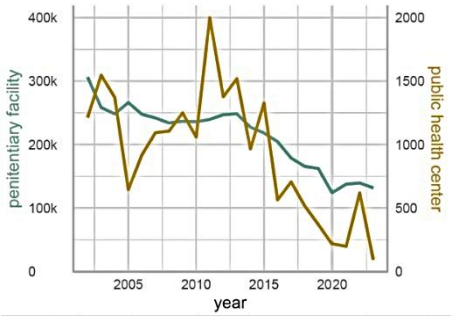

Fig. 5. Trends in dental consultations for Polish inmates in penitentiaries vs public health centers, 2002–2023.

Public health centers, on the other hand, started with much fewer consultations in 2002, totaling 1,213 (1.49%), and fluctuated over the period. Despite a peak of 1,998 consultations (2.42%) in 2011, the trend generally followed a decline, with particularly low numbers after 2019. By 2023, the consultations plummeted to just 91 (0.12%), marking a significant reduction (CAGR = -14.67%).

The statistical analysis also reveals a significant correlation with the correlation coefficient (*rho* = 0.77; $p < 0.001$). This strong positive correlation suggests that trends in dental consultations at penitentiaries closely aligned with those in public health centers over the study period. This linkage might indicate several underlying factors affecting both settings simultaneously, such as changes in national health policies or the allocation of funding.

Capacity and number of prisoners, 2002–2023

It can be observed that the number of prisoners increased from 2002 to a peak in 2009 (Table V). At the same time, the capacity of penitentiaries was also increasing. In 2009, this trend reversed until 2023. Starting in 2010, the capacity was greater than the number of prisoners until 2023, when the observed difference was 9,825.

Table IV. Number of dental consultations in Polish prisons in particular years

Year	Number of dental consultations
2002	306,172
2003	258,336
2004	248,346
2005	266,097
2006	247,677
2007	241,825
2008	233,882
2009	236,705
2010	235,831
2011	239,573
2012	247,005
2013	248,343
2014	227,320
2015	218,130
2016	204,476
2017	178,654
2018	165,521
2019	162,168
2020	124,440
2021	137,505
2022	139,336
2023	131,641

Table V. Comparison between the capacity of Polish prisons and the number of prisoners, 2002–2023

Year	Capacity of penitentiaries	Number of prisoners
2002	69,083	81,391
2003	69,469	81,321
2004	69,616	80,239
2005	70,186	82,761
2006	75,550	87,370
2007	79,213	89,995
2008	83,124	85,920
2009	84,490	85,384
2010	85,295	82,863
2011	86,123	82,558
2012	86,906	84,399
2013	87,311	83,898
2014	87,742	78,987
2015	87,395	74,814
2016	87,409	71,456
2017	86,868	73,807
2018	84,171	74,077
2019	84,021	74,564
2020	84,328	70,716
2021	84,966	71,209
2022	85,768	72,513
2023	86,109	76,284

DISCUSSION

The analysis of the mortality indices is much more complicated. There was a tendency for the overall number of deaths to rise, reaching 192 in 2022 before a slight decrease to 188 in 2023. This trend might be the result of the prison population aging and their general health worsening. The number of deaths as a result of self-aggression decreased, reaching 19 in 2023, which is in line with the data on acts of self-aggression and suicide attempts. The number of natural deaths increased from 56 in 2002 to 168 in 2023. That significant increase might be the result of population aging and it may indicate the need to improve penitentiary healthcare. There was a negative correlation between self-aggression and mortality, which might indicate that although acts of self-aggression were less frequent, other factors leading to higher mortality worsening (inadequately treated general health problems). However, it can also be observed that the higher number of psychiatric consultations could have led to the falling number of acts of self-aggression. In order to limit acts of self-aggression, the authorities should also consider changing diagnostic practices, prison administration polices, or staff training and engaging the inmates in additional activities (unpaid) [32,33,34].

Imprisonment is associated with suicide risk [35]. However, the data indicate significant improvements in managing self-aggression and suicide attempts. It highlights an urgent need to address the healthcare needs of an apparently aging inmate population. Old age is a special stage in a person's life, one that involves numerous changes in functioning [36]. That is extremely important to bear in mind when talking about prisoners, who are recognized as vulnerable to poor health and lifestyle choices, as well as accelerated aging [10]. Longer sentences imply a rise in the average age of prisoners [9]. Additionally, the persistent variability in suicide attempts suggests that prison environments remain complex, with varying degrees of psychological stressors impacting inmate behavior. Studies have shown that inadequate coping stress skills are related to an increased likelihood of both mental disorders and suicidal behavior [37]. Mental health problems such as major depressive symptoms, psychosis, anxiety, and drug misuse disorders have been identified as factors associated with, and potentially precipitating, near-lethal suicide attempts in prisoners [35].

The data reveal a pronounced decline in self-aggression incidents, decreasing from 948 in 2002 to 141 in 2023. This trend suggests effective interventions and improved management within prisons, potentially incorporating enhanced surveillance, better inmate support systems, and proactive mental health services. Therefore, prisoners need positive feedback, acceptance, and respect (i.e., emotional support) from prison staff and other inmates [35]. The substantial 85% reduction over the 21-year period (CAGR = -12.5%) underscores significant improvements in inmate conditions and, possibly, changes in reporting practices. The trend in suicide attempts mirrors that for self-aggression, albeit with less steepness, which may suggest a need to investigate high-risk behaviors in the prisons where these incidents take place [34]. Starting at 172 in 2002 and falling to 120 in 2023, there was an evident decrease (CAGR = -1.7%), although the data shows fluctuations throughout the years. The peaks at around 2017–2018 suggest periods of heightened risk, necessitating continuous evaluation of mental health and preventive measures. However, the relatively modest decrease compared to the reduction in self-aggression incidents suggests ongoing challenges in addressing extreme cases of distress among inmates. Relations with the prison staff are also important: if the staff are supportive and generally positive, prisoners' well-being is more likely to be high [35].

There was a more pronounced negative correlation between self-aggression and psychiatric counseling, indicating a strong inverse relationship where more counseling was associated with fewer instances of self-aggression. This suggests that psychiatric interventions effectively mitigate self-aggressive behaviors, underscoring the importance of such services in managing behavioral issues within the prison population. Some authors suggest that when working with prisoners, it is essential to devote attention to individuals who show depressive symptoms. They should be the first to receive the support they need, because depressive traits are a significant negative determinant of an important component of prisoners' health and is closely linked suicide risk [35]. In contrast, a positive correlation between mortality and psychiatric counseling was observed: as psychiatric counseling increased, mortality rates also tended to rise. This could reflect more severe cases being identified and treated as counseling services expanded, or it might indicate a lag effect, where the benefits of counseling to reduce mortality are delayed. On average, prisoners have a higher morbidity rate, which implies greater healthcare needs than in the overall population [10]. The indices of addiction to intoxicating substances and alcohol showed an increasing tendency: in 2002, there were 347 people addicted to intoxicating substances and 420 to alcohol, while in 2023 there were 1,170 addicted to intoxicating substances and 2,103 to alcohol. The observed increase may indicate more availability to those substances. This is confirmed by research conducted by Sierosławski [38] in 2007, in which prisoners indicated which illegal substances they were able to acquire while imprisoned. Alcoholic

beverages that the majority stated were the easiest to obtain were moonshine (indicated by 22% of the prisoners), vodka (12%), wine (5.7%), and beer (4.5%). Similarly, the inmates said that they can just as easily obtain illegal narcotics such as tranquilizing agents (39.6%), amphetamine (31.6%), cannabis (29.5%), steroids (23.9%), LSD (16.4%), cocaine (10.2%), heroin (9.9%) or crack cocaine (6.9%). This most likely stems from the fact that narcotics are easier to smuggle. The usage rate of narcotics inside penitentiaries has been established at 20.3% [5]. This contradicts the number of prisoners that have been directed to therapeutic departments, where convicts addicted to alcohol form the majority. This may be due to the fact that inmates seem to take advantage of the sporadic availability of substances supplied through "the underground" [39]. Additionally, it has been evidenced that 2% of convicted people started using illegal substances in a correctional institution or holding cell [38]. In other studies, alcohol dependence was diagnosed at a penitentiary in 6.8% and 4.5% of cases [39]. It should be emphasized that the scale of the problem in both cases is significant. The usage of narcotics can cause or exacerbate many health issues and can make it difficult to perform quick, adequate aid in a life-threatening situation [5].

The rate of addiction was strongly connected with the number of psychiatric consultations: 54,925 in 2002 and 76,421 in 2023. The peak of interventions in 2015 could potentially be attributed to several factors, including an aging inmate population or a change in reporting practices or in the threshold for what constitutes an emergency intervention. The reasons for seeking emergency care vary, although the presence of psychopathologies also leads to increased use of hospital emergency services [33]. After 2015, there was a general decline in the number of interventions, though the figures remain relatively high compared to the earliest years for which data is available. As was noted, higher expenditure on medical staff is associated with more primary care visits and fewer emergency room visits [9]. Interestingly, the year 2020 showed a more pronounced drop in interventions (to 7,147), which might reflect the impact of the COVID-19 pandemic. The pandemic could have led to stricter lockdown measures within facilities, reduced the incidence of communicable diseases other than COVID-19 by limiting contact, or possibly even impacted the reporting and response mechanisms due to a shift in healthcare priorities.

The most telling relationship was between suicide attempts and emergency interventions. This relationship was the most pronounced among the examined factors and could reflect the fact that suicide attempts inherently demand an immediate medical response, thus directly impacting the frequency of emergency interventions (Table I). The loss of privacy and increase in stress from overcrowding could also worsen mental health and induce violent and self-harming behavior [9]. Research conducted in Spain shows that trauma is the most prevalent problem requiring emergency care among inmates [33]. The other parameters, while associated, do not show strong enough correlations to draw definitive conclusions about their impact on emergency service interventions.

Comparatively, while public health centers also provide a range of services, they see much fewer consultations, with the highest numbers in general practice and dentistry (562 and 939, respectively). The average yearly number of medical consultations in 2002–2023 was much higher than noted in the public healthcare system. That visible contrast underscores the role that penitentiaries play in providing healthcare to the inmates. Most of the consultations were with general practitioners. It should be acknowledged that many of the available studies show that some convicts may use their health as leverage to gain advantages and services [5]. This can lead to the unnecessary overuse of the prison's healthcare system. Inmates feigning symptoms has been noted by 92.71% of doctors working inside of penitentiaries. However, a high number of psychiatric consultations was also noted, which may represent the needs of inmates in terms of psychiatric healthcare. This could very well be due to the fact that prison isolation has been proven to cause many adverse and often irreversible changes in one's mental health and thus leads to changes in one's social situation [5].

A significant number of dental consultations was also observed, suggesting that oral health is of greater importance and confirming that dental offices are found in prisons. It must be mentioned that other specialist consultations also took place (dermatology, neurology, and ophthalmology). All those appointments were provided at penitentiaries, so it can be concluded that the prisoners were provided with a wide range of specialists. This could suggest that these services are less accessible or they could be provided within the penitentiaries themselves. The relatively lower numbers in specializations such as cardiology and neurology at public health centers could suggest that inmates with serious conditions were more likely to be treated within the penitentiary system, possibly due to logistical, security, or policy reasons. Research conducted in 2005 measured the frequency of prison doctors diagnosing various illnesses: neurosis (37.94%), allergies (29.89%), diseases of the stomach and duodenum (29.89%), vision and hearing problems (29.71%), cardiovascular diseases (26.44%), respiratory diseases (25.29%), mental illnesses (24.14%), cancer (13.8%), dermatological diseases (13.8%), diseases of the musculoskeletal system (13.8%), and diseases of the liver (8.5%) [5]. The percentage of inmates unaffected by any kind of disease

has been estimated by doctors to be 8.05%, although none of the participants considered themselves to be completely healthy [5]. It should be clarified that the above results do not add up to 100%, since it is possible to indicate a few diseases in a single patient. The same author continued the research in 2011 and 2012. Visible differences were found in the frequency of diseases among the inmates: diseases of the digestive system (37.04%), dermatological diseases (22.23%), and neurosis and sleep disorders (29.63%) [5].

Many prisoners present with multiple health conditions that have been neglected, and prison provides their first healthcare experience in a long time [9]. The significant difference in mean consultation numbers between penitentiaries and public health centers may also highlight a potential gap in the accessibility of specialized medical services in the public system for inmates or possibly a structured policy that prioritizes in-house healthcare in order to manage inmate health effectively within the security framework of penitentiaries.

The reduction of dental consultations for Polish inmates was not abrupt but gradual, indicating a systemic decrease in dental consultations over the years. The initial numbers could suggest a high demand or an extensive backlog of dental issues among inmates that gradually got addressed or deprioritized. The most drastic reduction seems to have occurred in 2019–2020; this trend continued to decline, reaching a low in 2023. This recent sharp decline could have been influenced by external factors such as budgetary constraints, changes in prison policies regarding healthcare, or possibly the impact of pandemic-related restrictions and reallocation of health services.

The variable nature and dramatic fall in the numbers might reflect more about the accessibility and policy changes impacting how inmates interact with public healthcare services outside of penitentiary settings, possibly indicating a shift towards providing most care within the confines of penitentiaries. There was a strong, positive correlation suggesting that trends in dental consultations within penitentiaries closely aligned with those in public health centers over the study period. This linkage might indicate several underlying factors affecting both settings simultaneously, such as changes in national health policies or allocation of funding. Overall, the long-term decline in dental consultations, particularly the sharp decline in recent years, suggests that there is a need to assess the adequacy of dental care for inmates, consider the potential health effects of reduced dental services, and re-evaluate the allocation of resources to ensure that healthcare needs are adequately met within the inmate population. While considering this problem in our previous work, we decided to estimate the need for dental healthcare in prison [40,41].

Study limitations

Undoubtedly, our study faced a few limitations. The possibility of analyzing the inmates' medical history could provide a benefit from more detailed, complex data on their general and mental health status. It could indicate the particular problems that ultimately led to the suicide attempts. With the data we obtained, we were unable to assess whether a particular prisoner had one or more suicide attempts or to determine the frequency of a single prisoner's specialist visits; we can only refer to the whole population. Definitely, studying the prisoners and distributing a questionnaire could provide more detailed data.

CONCLUSIONS

In 2002–2023, the following observations were noted.

1. The number of deaths increased until 2022 (due to the aging population of prisoners and the worsening of their health); this was followed by a decrease in 2023.
2. There were fewer deaths caused by self-aggression and fewer acts of self-aggression or suicide attempts.
3. The increase in the number of natural deaths was likely due to the aging of the population and may indicate the need to improve medical care in prisons.
4. There was an increase in the reported number of addictions (to medications and alcohol), probably as a result of their easier availability.
5. The number of psychiatric consultations increased, probably due to addictions.
6. There was a negative correlation between self--aggression and mortality; despite the decrease in acts of self-aggression, the mortality rate rose (probably due to untreated general health problems).
7. The higher number of psychiatric consultations resulted in fewer acts of self-aggression.
8. There was a strong correlation between addiction to intoxicants and alcohol, probably due to fact that those addicted to one are more prone to also be addicted to the other.
9. The number of external medical interventions fluctuated: there was an increase which peaked in 2015, in 2020, a decrease was observed, probably caused by the COVID-19 pandemic; in 2021, the number stabilized; and again it decreased until 2023, probably due to improved penitentiary healthcare.
10. The number of medical consultations was higher than those in the general healthcare system – the role that the penitentiary system played in

providing healthcare increased between 2002 and 2023.

11. The most frequent medical consultations were with general practitioners and psychiatrists.
12. There was a high number of dental consultations, suggesting a sufficient number of dental offices in the penitentiary system.

Authors' contribution

Study design – R. Korkosz, M. Tanasiewicz, M. Rahnama
Data collection – R. Korkosz
Data interpretation – R. Korkosz
Statistical analysis – R. Korkosz
Manuscript preparation – R. Korkosz, A. Trzcionka, M. Tanasiewicz
Literature research – M. Kiełbratowski, A. Kuśka-Kiełbratowska

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PRACA POGLĄDOWA
REVIEW

Takotsubo syndrome – A review of recent reports

Zespół takotsubo – przegląd najnowszych doniesień

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ABSTRACT

Takotsubo syndrome is a poorly understood but increasingly diagnosed condition, especially in postmenopausal women. It affects patients of all ages. It is divided into two types according to its triggering factor. In the primary type, chronic stress is the main cause, while in the secondary type the trigger is physical – iatrogenic. The name of the disease comes from the Japanese word for a octopus trap with a narrow neck and wide base. In imaging studies, this cardiomyopathy resembles such a device. The aim of the study is to comprehensively analyze the available literature in scholarly databases such as PubMed, Google Scholar, and ScienceDirect. The work examines historical background, possible risk factors, clinical course, classification of the disease, preventive measures, and treatment strategies. The current lack of consensus regarding the definition used by prestigious cardiology societies has been highlighted in the context of recent scientific research. Further research is necessary to better understand the pathomechanism of the disease, in order to choose the best pharmacological treatment and improve the quality of life of patients with this condition.

KEYWORDS

takotsubo syndrome, cardiomyopathy, acute coronary syndrome, myocardial structural disorder, catecholamines, beta-blockers, prevention, pharmacological treatment

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STRESZCZENIE

Zespół takotsubo jest jednostką chorobową słabo poznaną, lecz coraz częściej diagnozowaną, zwłaszcza w grupie kobiet po menopauzie. Dotyczy pacjentów w każdym wieku. Ze względu na czynnik wyzwalający wyróżnia się dwa typy choroby – pierwotny oraz wtórny. W typie pierwotnym główną przyczyną jest przewlekły stres, natomiast w typie wtórnym czynnik fizyczny – jatrogenny. Nazwa choroby pochodzi od japońskiego słowa oznaczającego naczynie rybackie z wąską szyjką i szerokim dnem, używane do chwytania ośmiornic. W badaniu obrazowym kardiomiopatia ta przypomina kształtem owo naczynie. Celem pracy jest kompleksowa analiza dostępnej literatury w bazach danych takich jak PubMed, Google Scholar i ScienceDirect. W pracy uwzględniono rys historyczny, możliwe czynniki ryzyka, przebieg kliniczny oraz klasyfikację schorzenia. Omówiono także postępowanie profilaktyczne i strategie leczenia. Obecny brak jednomyślności w definicji stosowanej przez prestiżowe towarzystwa kardiologiczne został uwidoczniony w kontekście najnowszych badań naukowych. Konieczne są dalsze badania w celu lepszego zrozumienia patomechanizmu choroby, aby dobrać jak najlepsze leczenie farmakologiczne i poprawić jakość życia pacjentów z tym schorzeniem.

SŁOWA KLUCZOWE

zespół takotsubo, kardiomiopatia, ostry zespół wieńcowy, zaburzenie budowy mięśnia sercowego, katecholaminy, beta-blokery, profilaktyka, leczenie farmakologiczne

Introduction

Takotsubo syndrome (TTS) is recognized as a stress--induced cardiomyopathy and as a form of cardiomyopathy with paraclinical and clinical symptoms similar to acute myocardial infarction (AMI) [1]. The exact pathogenesis of the syndrome remains unclear. Typical presenting symptoms reported by patients are chest pain and dyspnea. On physical examination, an electrocardiogram may show transient ST elevation and a small rise in cardiac troponin T [2]. It progresses to an acute clinical state characterized by reversible systolic and diastolic dysfunction of the left ventricle. In this condition, one segment of the ventricle contracts very strongly, while another segment becomes dilated and ceases to function. The InterTAK registry distinguishes four TTS subtypes. The most prevalent type is apical [1]; it is associated with hypokinesis or akinesis of the mid and apical segments of the left ventricle. The disease is often preceded by a physical or emotional stressor that causes a sudden increase in catecholamines, leading to heart dysfunction [3,4]. Over the past few years, there has been a noticeable upward trend in the number of cases reported. Despite the growing awareness among physicians about TTS, the syndrome still represents a significant diagnostic challenge. A study published in 2019 indicated that the in-hospital mortality risk is similar to that in patients presenting with acute coronary syndrome. One group which is particularly often diagnosed with TTS is postmenopausal women who have experienced an episode of psychological stress [5].

The authors conducted a detailed analysis of the available scientific literature found in the databases PubMed, Google Scholar, and ScienceDirect. To refine the selection of relevant sources, narrow the results, and increase accuracy, the specific keywords in the search were "takotsubo syndrome," "management in takotsubo syndrome," "stress cardiomyopathy," "broken heart syndrome," and the Boolean operators AND and OR. The selection criteria included original research articles and reviews published in peer--reviewed journals in both Polish and English. Publications without full-text access and non-specialist articles lacking scientific evidence were excluded. The sources were also selected by publication date, as articles published within the last ten years were favored. Initially, 10,629 articles were identified based on the search strategy. After removing duplicates and reviewing titles and abstracts, 780 articles remained for further evaluation. Ultimately, after the full texts were analyzed and the inclusion and exclusion criteria were applied, 91 studies were selected for the study (Figure 1).

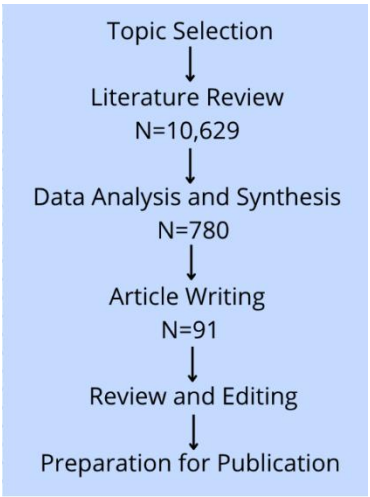

Fig. 1. Flowchart.

Historical background

The majority of newly classified disease entities undergo a name change over time as knowledge about them increases. This was also the case with the syndrome described in the 1990s by Japanese

cardiologist Hikaru Sato, especially in the first few years following his description [6]. Initially, the term "takotsubo cardiomyopathy" was commonly used in the literature on the subject, but over the years, the following names were used to define the disease: "takotsubo cardiomyopathy," "left ventricular ballooning syndrome," "broken heart syndrome," and "stress cardiomyopathy" (Figure 2). Due to the different nomenclature, various abbreviations of these names have appeared in the literature. In the past few years, most experts have agreed that the abbreviation for takotsubo syndrome should be "TS" or "TTS" [7,8]. These abbreviations inform the reader that only the left ventricle of the heart is affected by transient regional systolic dysfunction, dilation, and swelling.

There is also controversy over the classification of the disease as cardiomyopathy, which is defined by persistent structural and functional abnormalities of the heart muscle. The syndrome does not have a genetic basis and is not a primary cardiomyopathy; individuals with cardiomyopathy cannot spontaneously recover. Furthermore, this term cannot be used when abnormalities in the functioning or morphology of the coronary arteries lead to acute myocardial ischemia and are responsible for systolic dysfunction in the left ventricle. Considering the transient nature of this phenomenon, the guidelines for cardiomyopathy published in 2023 by the European Society of Cardiology do not recommend classifying TTS as cardiomyopathy; however, most scientific reports still do so [9,10,11].

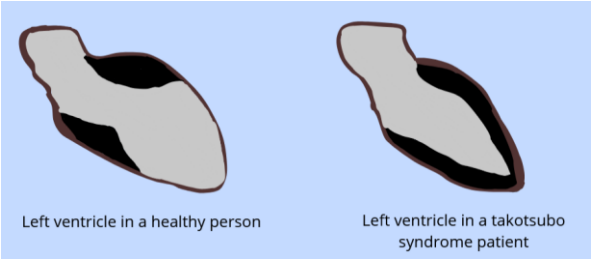

Fig. 2. Comparison of the appearance of the left ventricle (based on [1]).

Epidemiology

A precise determination of its incidence rate is not currently possible, due to the lack of sufficient knowledge among medical professionals and its similarity to acute coronary syndrome (ACS), resulting in the possibility that many cases may be missed and undocumented [12,13]. Continued medical advances, increasing awareness of the symptoms of this disease, and widespread access to invasive coronary angiography are increasing the percentage of accurate diagnoses. Clinical diagnoses are increasingly being reported on all continents, but are relatively rarely detected among Latin American and African-American populations [14,15]. According to the currently available information, the prevalence in the population is less than 2%. These data may be misleading due to an undersampled study group that is not representative of the entire population. In addition, studies conducted in one region may not be generalizable to other areas.

The vast majority of diagnoses, up to 90%, are in women aged 65–70. This syndrome is less frequently diagnosed in women below this age, as well as in men and children, including even premature babies. Few cases of TTS in men have been described in the literature, mainly associated with medical procedures such as bladder catheterization, gastroscopy, or knee joint arthroscopy. Men diagnosed with TTS are statistically younger than women, and in their case, physical triggers are more likely than in women, among whom emotional triggers are predominant. Cardiogenic shock and ventricular fibrillation occur more frequently in men, while chronic heart failure is most common in women. Japan is the only country where a higher percentage of the patients are men, although the reason for this finding has not been determined so far. Younger patients often have an atypical clinical picture characterized by the absence of comorbidities or neurological and psychiatric disorders; they are also less likely to develop complications. The occurrence in children was mainly related to mental illnesses, the use of psychoactive substances, and the development of sepsis. TTS described in the pediatric population presents a characteristic clinical profile, with a higher frequency of atypical symptoms and physical factors, as well as higher prevalence of cardiogenic shock and a similar mortality and recurrence rate to the adult population.

The frequency varies by gender as well as ethnicity, as it is less common in Latinos and African Americans, who more often experience complications such as respiratory failure or stroke, as opposed to Caucasians, in whom TTS is more commonly seen [13,16,17]. Increasing awareness among healthcare workers increases the number of accurate diagnoses in men, mainly residing in Japan, due to men's predisposition to physical rather than psychological stress [18,19].

In 2011, the Zurich Heart House, based in Switzerland, established the International Takotsubo Registry (ITR) to study clinical features, analyze study results, and determine the best options for treatment and prevention of this disease. Currently, it is studied at 26 research centers in Europe and the United States, including two in Poland: the 1st Department and Clinic of Cardiology of the Medical University of Gdańsk and the 1st Department and Clinic of Cardiology of the Medical University of Warsaw (MUW) [13,20]. Due to the limited availability of Polish patients, researchers from the center at MUW created a Polish registry of people diagnosed with TTS under the patronage of the Polish Cardiology Society's Heart Failure Association and the Interventional Cardiology Association of the

Polish Cardiology Society. The aim of the registry is to analyze the clinical profile of hospitalized patients in Poland. Data are provided by all hemodynamic laboratories affiliated with the Interventional Cardiology Association. The main facility is the Independent Public Central Clinical Hospital in Warsaw, which is the University Clinical Center MUW, while the coordinating center is the aforementioned 1st Department and Clinic of Cardiology at MUW, which described the first case of TTS in Poland in 2006 [21,22,23].

Etiology

In nearly one third of patients diagnosed with TTS, the triggering factor cannot be determined. Possible stress--related factors can be categorized as psychological or physical. The former may include strong emotions such as those connected with financial losses, arguments, domestic violence, or speaking before a large audience. Physical stressors classified as iatrogenic triggers include a fear of undergoing numerous medical procedures, which may be accompanied by unpleasant sensations such as varying levels of pain and merely staying in a medical facility [24,25]. Most stress factors are associated with discomfort, but not all. Positive stress (eustress) mobilizes and motivates the human body. This additional, albeit short-term, energy boosts activity. This interesting type of TTS is called the "happy heart syndrome," but unfortunately, it is not often described in the literature [26,27]. Gender also plays a role in the potential occurrence of this condition. Men react more strongly to physical events than women, who are naturally more sensitive and less resistant to situations causing a lot of emotions [28].

Pathophysiology

The syndrome was identified and classified 35 years ago by a cardiologist in Japan, but its exact pathophysiological mechanism is still unknown. It is suspected to be related to catecholamine cardiotoxicity, coronary artery spasm, microvascular dysfunction, and estrogen deficiency. A potential triggering system may also be excessive stimulation of the nervous system, changes in its functioning and structure, and changes in the balance and distribution of adrenergic receptors, including adrenaline and noradrenaline [29,30,31]. The most commonly discussed mechanism is the release of catecholamines due to stress and activation of the sympathetic autonomic part of the nervous system, which is responsible for preparing the body for defense or evacuation in case of danger. Endogenous catecholamines released by the body have a detrimental effect on the heart muscle, causing transient myocardial hypokinesis with local wall motion abnormalities [32].

Classification

Various types of stress-induced cardiomyopathies have been described in the specialist literature (Figure 3). We can divide them into primary TTS and secondary TTS. In the first case, the cause of psychological stress or the absence of such stress can be determined, so most people seek specialized medical help when they experience acute chest pain. The secondary form occurs much more frequently and is triggered by physical factors, such as an existing illness, past trauma, or current medical procedure. In these individuals, sudden activation of the sympathetic nervous system or a sudden increase in catecholamines may be the triggering factor [13].

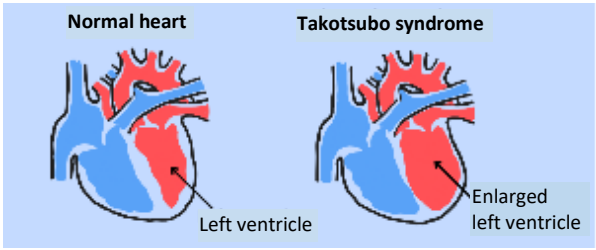

Fig. 3. Left ventricle (based on [34,37]).

Due to differences in anatomical presentation, we can distinguish four subtypes of typical and atypical cases, based on abnormalities seen in the angiogram of the left ventricle or echocardiographic deviations. Typical cases include the most common (81.7%) apical ballooning, also known as TTS, characterized by hypokinesis or dyskinesis of the apical and mid segments of the anterior, septal, inferior, and lateral walls of the left ventricle and associated with hyperkinesis of the basal segments. Atypical subtypes entail mid-ventricular, basal, and focal abnormalities. The mid-ventricular subtype (14.6%) is recognized when there is a ring-like hypokinesis or dyskinesis of the mid-ventricular segments, with normokinesis or hyperkinesis of the basal and apical segments. Patients with the basal subtype (2.2%) have hypokinesis or dyskinesis of the basal segments and normokinesis or hyperkinesis of the mid-ventricular and apical segments, resulting in left ventricular motion abnormalities outside the perfusion area of the coronary artery. The least common variant is the focal subtype (1.5%), which is diagnosed only in cases of focal hypokinesis or dyskinesis of any segment of the left ventricle according to laboratory, electrocardiographic, and clinical criteria [15,33,34].

Reversed takotsubo cardiomyopathy (rTTC) is also distinguished in the literature. It is one of the rarest types of stress-induced cardiomyopathies, characterized by hypokinesis of the basal and mid-ventricular

segments. It has similar pathophysiological causes but affects a different group of patients, as it is diagnosed in young people with reduced hemodynamic compromises. Patients with the reversed type of the syndrome present with chest pain, which may be accompanied by dyspnea and additional symptoms such as indigestion, abdominal pain, and syncope. There may also be moderate heart failure due to reduced ejection fraction and hypotension due to obstructive outflow. Treatment involves beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). Proper identification of this type is important due to the potential negative health consequences [30,35,36,37,38].

Diagnostic criteria

Differential diagnosis is recommended with symptoms that are also present in ACS in populations at high risk of an episode. It is most commonly detected in postmenopausal women experiencing acute chest pain and respiratory symptoms, often associated with emotional stress and an abnormal electrocardiogram. However, such symptoms occurring in men should not be underestimated. Various laboratory, electrocardiographic, and imaging studies are used in the diagnosis. Coronarography is most commonly used to exclude coronary artery disease (CAD). Ventriculography can be used to assess left ventricular function (left ventricular apical dilatation is seen in TTS). In contrast, transesophageal echocardiography with longitudinal strain assessment and acoustic marker tracking allows a detailed assessment of myocardial function, including the degree of left ventricular dysfunction [2,39].

One of the most commonly used diagnostic criteria is the one proposed by the Mayo Clinic in 2004 and updated in 2008. The updated criteria include the four key symptoms reported by patients with suspected TTS: transient hypokinesis, akinesis, or dyskinesis of the mid-segments of the left ventricle with or without involvement of the apex; local abnormalities in contractility caused by a triggering factor; the absence of diagnosed CAD; and angiographic evidence of a myocardial infarction plaque rupture, new ECG abnormalities such as ST elevation or T wave inversion, and elevated troponin levels, with no evidence of a thrombus or myocarditis [40,41] (Table I).

The most up-to-date diagnostic criteria are those published by the European Society of Cardiology in 2018, which incorporate the latest medical findings based on a consensus between conflicting information. The International Takotsubo Diagnostic Criteria, known as the InterTAK diagnostic criteria, include the following eight points: transient left ventricular dysfunction with possible contractility abnormalities, a psychological or physical triggering factor, neurological disturbances, new ECG changes, elevated troponin and creatine kinase levels, elevated B-type natriuretic peptide, absence of infectious myocarditis, and menopause. Additionally, the coexistence of CAD is not an obstacle to diagnosing the syndrome [27,42]. Typically, patients present with textbook symptoms, but there is a group of patients in whom the ECG may be normal or their young age may raise doubts about the presence of this disease. These are challenges faced by clinicians on a daily basis.

Table I. InterTAK Diagnostic Score (based on [41])

Criteria	Points
Female sex	25
Emotional trigger	24
Physical trigger	13
Absence of ST-segment depression	12
Psychiatric disorders	11
Neurologic disorders	9
QTc prolongation	6
> 70 points – high probability of TTS	
≤ 70 points – probability of TTS	

TTS – takotsubo syndrome.

Differential diagnosis

TTS is a medical condition that is difficult to correctly identify due to its similarities in course and symptoms to many other cardiac diseases. Despite its resemblance to ACS, as mentioned above, it also shows similarities to various types of cardiomyopathy [43,44]. Dilated cardiomyopathy (DCM) is characterized by a progressive increase in the volume of the heart chamber with impaired contractility, causing symptoms that appear suddenly, such as ventricular arrhythmias or sudden death of the myocardium [45]. The opposite of DCM is non-dilated left ventricular cardiomyopathy (NDLVC), which does not meet all diagnostic criteria because the left ventricle has only subtle systolic dysfunction and its walls are not enlarged [46]. One of the diseases that should be differentiated from TTS is hypertrophic cardiomyopathy (HCM), which manifests as an asymmetrically thicker left ventricular wall (hypertrophy) and interventricular septum; in about 30% of people, there is also obstructed outflow of blood from the left ventricle, resulting in myocardial ischemia and rhythm disturbances. It is the most common cause of sudden cardiac death in people under 35 years of age living in the United States [47]. Another condition that can be confused with TTS is genetically determined arrhythmogenic cardiomyopathy, usually of the right ventricle, but the disorder can also affect the left ventricle, leading to arrhythmias and heart failure [48]. Restrictive cardiomyopathy (RCM) involves severe diastolic dysfunction with a limited ability to fill with blood. RCM can involve the left, right, or both ventricles, with typically normal to slightly increased

ventricular thickness, but atrial enlargement is characteristic due to the increased pressure in them [49]. The symptoms in each of these dysfunctions include heart failure, chest pain, and rhythm disturbances. Nevertheless, a detailed medical interview can facilitate the correct differentiation of the above-mentioned cardiomyopathies due to differences in imaging diagnostics and different clinical courses, leading to the correct diagnosis for a patient presenting with this condition.

Symptoms

In most patients, the clinical picture is indistinguishable from ACS due to the similar symptoms. Most patients report an initial symptom of shortness of breath or gradually increasing chest pain of a squeezing nature during rest, often accompanied by shortness of breath. The occurrence of chest pain resembling that in ACS is reported by about 70% of all patients. The presence of ST-segment deviations on the electrocardiogram and abnormal cardiac biomarkers should be indications for conducting a differential diagnosis of TTS. Currently, cardiac catheterization is the only method that can distinguish TTS from ACS and myocardial infarction with nonobstructive coronary arteries (MINOCA). Other reported symptoms include dizziness, syncope, or circulatory arrest. There is also a group of patients in whom such symptoms are not observed. The varying intensity of individual symptoms depending on the type of syndrome is intriguing. In patients with primary TTS, chest pain with associated vegetative symptoms – such as heart palpitations, rapid heart rate, and a feeling of tightness in the chest – is more frequently observed than syncope, cardiogenic shock, and palpitations, which are more commonly seen in patients representing the secondary type [21,50,51,52,53].

Risk factors

The main risk factor is often intensely stressful situations, divided into negative and positive events. Negative life events, such as the death of a loved one, divorce, or diagnosis of a serious illness (e.g., asthma, chronic obstructive pulmonary disease, or pancreatitis) are widely recognized factors. Positive strong emotions modulate the autonomic nervous system in a similar way to negative ones. Further research on the impact of positive emotions can lead to a paradigm shift in how we understand TTS [54,55]. Gender is an undeniable risk factor, as the majority of those affected are postmenopausal women; hormonal changes due to the lack of estrogen can significantly increase the likelihood of developing the disease. Currently, there are not enough reports related to genetic factors, but five cases of familial occurrence of this disease are well described. Two of them were mother-daughter relationships, while the other three involved sisters. The coexistence of neurological and psychiatric disorders can also predispose one to this syndrome [13]. Detailed descriptions of newly diagnosed patients show the possible multi-faceted nature of the disease, thus expanding the spectrum of factors that may predispose one to it.

Clinical course

The majority of patients have a transient nature of the disease, but they are still at risk of developing serious complications. In most patients, the disease is transient, but there is still a risk of serious complications from hospitalization, cardiac arrest, heart failure, cardiogenic shock, or the effects of comorbidities such as renal failure or stroke. In some patients, the disease may have an acute course, characterized by severe symptoms and cardiac dysfunction. In the acute phase, patients experience chest pain similar to that of a heart attack, difficulty breathing, and pulmonary edema. Relapse and long-lasting functional consequences such as depression and fatigue are also possible. The next phase is the recovery phase, in which symptoms gradually subside, and the left ventricular contractility returns to normal [24,56].

Prevention

To prevent a subsequent episode of TTS, it is essential to focus on the triggering factors. Lifestyle modifications and targeted interventions can play a crucial role in mitigating the risk. The primary emphasis should be on reducing exposure to chronic stress and incorporating relaxation techniques such as yoga and meditation, which have proven effective. Emotional stress can negatively impact the circadian rhythm, leading to difficulties in falling asleep, waking up at night, and making poor dietary choices. It is important to choose foods rich in unsaturated fatty acids, whole grains, and a variety of vegetables and fruits in order to create diverse and well-balanced meals, tailored to individual nutritional needs. The foundation of prevention should include balanced physical activity that is preferred and enjoyed, and avoiding any substances like alcohol or cigarettes.

Educating patients and their loved ones about the disease, its course, food-drug interactions, possible implications, and the importance of monitoring their body is crucial to achieving optimal outcomes and preventing future incidents. Likewise, a strategic approach should aim to optimize an individualized, coordinated treatment plan and minimize any adverse effects, such as controlling symptoms, ensuring quality of life, slowing progression, and preventing life-threatening complications like arrhythmias. Ethical considerations must guide the decision-making process, ensuring informed consent and respecting patient autonomy in therapeutic choices, especially

considering the unpredictable and uncharted effects of this disease in later years.

We should focus on previous comorbidities – monitoring test results and the body's response to medications and maintaining regular specialist visits – as they can exacerbate the disease's course. Nevertheless, regular screenings play a significant role in prevention, allowing for the early detection of abnormalities in the body. Appropriate coordination of healthcare plays a key role in minimizing risks and improving patient safety.

Treatment

In the treatment of TTS, medications commonly used for ACS are initially administered, but only after a proper differential diagnosis is symptomatic treatment introduced. It is also important to remember that CAD and TTS can often coexist, which should be considered when choosing pharmacotherapy. Various drug groups can reduce the likelihood of the disease recurring [34]. Diuretics and vasodilators are used in treatment. To reduce myocardial overload and control blood pressure, ACE inhibitors and ARBs are used. Intravenous administration of diuretics is associated with an increased mortality rate within 30 days, in contrast to ACE inhibitors, which were associated with reduced long-term mortality. ACE inhibitors should not be used in individuals with normal cardiac output, as this can result in impaired peripheral nervous system function related to low peripheral vascular resistance.

Given the likely mechanism related to catecholamine hyperstimulation, it is justified to use beta-blockers, which can improve blood flow through the heart, thus preventing patient death. In the analysis of an Italian registry of individuals diagnosed with TTS (the Takotsubo Italian Network), it was found that the use of beta-blockers was associated with a lower risk of death from all causes, including non-vascular diseases, though the probability of recurrence was comparable with or without beta-blockers. It should be noted that these drugs do not prevent the development of the disease, as more than 30% of people were regularly taking therapeutic doses due to other diseases [57,58,59]. ARBs and beta-blockers did not statistically correlate with patient mortality [60].

In patients with large areas of hypokinesis of the heart or reduced left ventricular contractility, anticoagulant therapy should be initiated. Aspirin acts both as an anticoagulant and an anti-inflammatory agent, inhibiting the production of prostaglandins and thromboxane, and reducing the concentration of inflammatory proteins in plasma. It was administered to 1,533 individuals out of 1,750 in the InterTAK registry. Comparing these patient groups led to the conclusion that the use of aspirin was not associated with a reduced risk of cardiovascular events after 30 days or after 5 years of patient observation. Additionally, the use of statins did not affect the short- or long-term possibility of serious complications and was not associated with lower mortality among the group using these drugs [61,62,63,64].

According to data and recommendations from a Swedish research registry, the majority of patients were treated with beta-blockers (77.8% orally and 8.3% intravenously) and antiplatelet drugs such as aspirin (66.7%). Less frequently, oral anticoagulants (11.3%), ACE inhibitors (55.5%), ARBs (15.3%), statins (55.1%), and diuretics (19.5% orally and 17.2% intravenously) were administered [15,60,65,66] (Table II).

Table II. Medications used in takotsubo syndrome management (based on [35,58,63])

Medication	Indication
Loop diuretics	Elimination of excess fluids
ACE inhibitors	Reduction of blood pressure
ARBs	Heart failure
Beta-blockers	Reduction of heart rate

ACE – angiotensin-converting enzyme; ARBs – angiotensin receptor blockers.

Currently, there are no established treatment guidelines due to the relatively rare occurrence, which significantly limits the possibility of large clinical trials, as well as the complexity of the pathophysiology, including the lack of a defined etiology of disease episodes. All actions taken to alleviate the course of the disease are based on the consensus of cardiology experts through a detailed analysis of previously described patients. The main goal of the therapy is to reduce serious brain and blood vessel damage, which can result in significant hemodynamic complications such as stroke and AMI.

In patients with TTS and comorbidities, the prevention and treatment of coexisting diseases should be continued until the patient is admitted to the hospital and treated for TTS. The condition for such therapy is an absence of adverse clinical reactions in the patient to whom it was administered. Therefore, it is necessary to continue administering medications for hypertension, heart failure, arrhythmias, diabetes, and hyperlipidemia, although their dosages can be adjusted according to the patient's current condition.

An episode of cardiomyopathy requires appropriate care from healthcare professionals. Such a patient should be hospitalized in a cardiology department equipped with the necessary facilities, and after discharge should be under cardiological observation, including preventive echocardiography to assess the degree of recovery and detect any complications of the disease. We cannot predict long-term effects. In many people, the heart returns to its normal function within a month, and routine ECGs only confirm this.

There is a possibility of TTS recurring in the same person. About 5% of patients experience a recurrence, most commonly within 3 months to 3 years of the first disease episode. A recurrence can occur at any age, in both women and men, even if it was first diagnosed in early childhood. A different triggering factor may be involved, which may also be a different anatomical type visible on imaging [40,58,67].

The prognosis is favorable, as left ventricular contractility returns to normal within 30 days of an episode and recovery soon follows. However, unavoidable complications may occur after the disease. The most commonly observed complications are arrhythmias, valve abnormalities, clot formation, pulmonary edema, and hypotension, which can lead to tissue hypoxia [68,69].

Invasive treatment of complications

ACS is the most serious complication of TTS and CAD. It is differentiated into ACS with ST-segment elevation (STEMI) and without ST-segment elevation (NSTEMI) on a 12-lead electrocardiogram. Unstable angina, where clinical symptoms suggest a heart attack but without biochemical evidence, is also included in ACS. Globally, STEMI currently accounts for 30% of all ACS cases, while NSTEMI accounts for 70%. The latter has a worse prognosis. STEMI poses an immediate life-threatening condition and requires the fastest possible intervention in the catheterization laboratory. Percutaneous reperfusion of the coronary artery within 120 minutes of symptom onset reduces mortality from 9% to 7%. In percutaneous coronary intervention (PCI), the use of drug-eluting stents or bare-metal stents is recommended for STEMI. Adjunctive pharmacotherapy is also very important. The European Society of Cardiology guidelines recommend the use of acetylsalicylic acid in the form of oral or chewable tablets at a dose of 150–300 mg and a strong P2Y12 inhibitor – mainly prasugrel or ticagrelor, possibly clopidogrel, in the case of primary PCI. Antiplatelet therapy should be accompanied by anticoagulant therapy. A class I recommendation drug is unfractionated heparin, and bivalirudin in patients with low platelet count. The patient's age, body weight, and comorbidities, such as stroke, should be considered so as to exclude possible adverse effects from individual drugs. Anticoagulant therapy should be continued for 12 months after the procedure. High-sensitivity troponin measurement is the preferred test for diagnosing NSTEMI. In high-risk patients, coronary angiography is recommended and percutaneous or surgical revascularization of the closed coronary artery should be performed within 24 to 48 hours to confirm the diagnosis. The surgical procedure is aortocoronary bypass (CABG), which involves creating a connection between the main artery – the aorta – and the remaining coronary arteries, bypassing the narrowing site. However, it is associated with a higher risk of stroke than PCI [70,71,72,73, 74,75,76,77] (Figure 4).

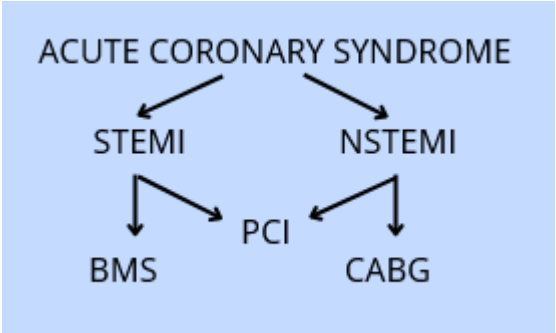

Fig. 4. Types of acute coronary syndrome (based on [73,74,75,77]). STEMI – ST-segment elevation myocardial infarction; NSTEMI – non-ST-segment elevation myocardial infarction; BMS – bare metal stent; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting.

Ventricular arrhythmias, such as ventricular tachycardia – including torsades de pointes – are common electrophysiological disturbances that can be caused by TTS. Torsades de pointes is a type of ventricular tachycardia with a multifactorial etiology. It is characterized by electrolyte disturbances – hypokalemia and hypomagnesemia. The primary treatment for this disturbance is intravenous administration of magnesium, regardless of whether its level is reduced in the blood. In cases resistant to treatment, it is recommended to shorten the repolarization period by increasing the heart rate with isoproterenol. Stopping the heart's action or severe hypotension should be managed with electrical cardioversion. To improve outcomes in patients who have experienced an episode of ventricular arrhythmia, an implantable cardioverter-defibrillator (ICD) should be implanted. The device does not completely eliminate episodes of arrhythmia, but it often proves to be a life-saving therapy [78,79,80] (Figure 5).

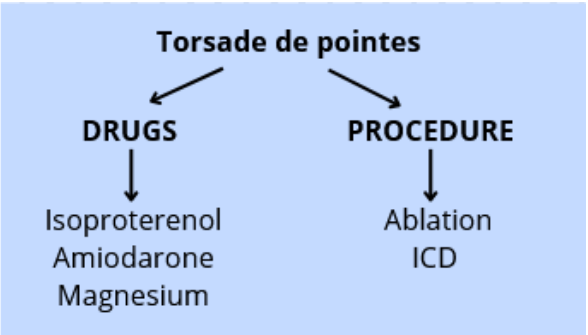

Fig. 5. Management of torsade de pointes (based on [80,81,82,83]). ICD – implantable cardioverter-defibrillator.

Treatment of ventricular arrhythmia initially involves the use of antiarrhythmic drugs, such as amiodarone,

which is considered the most effective antiarrhythmic in ventricular tachycardia pharmacotherapy. In the case of recurrent arrhythmia resistant to antiarrhythmic drugs, ablation therapy is the treatment of choice. It was once performed on an open heart, but there is now a safe, effective percutaneous method for treating rhythm disturbances. The procedure is performed in the electrophysiology laboratory and begins with electroanatomic mapping to detect the structure initiating the rhythm disturbance. The doctor then creates lesions with an ablation catheter inserted via the femoral artery that uses electrical current or low temperature. This disrupts conduction through the structure causing the rhythm disturbance, thereby eliminating the disturbance [81,82,83].

Clinical trials

There is a visible deficit of adequate scientific research on TTS treatment methods. Currently, two significant phase IV clinical trials are being conducted in Europe, studying the side effects caused over time by a new treatment method after its approval and introduction on the market. Due to the large scale of these studies, it is possible to detect the rarest side effects. Long-term side effects are monitored in different patient groups to assess their effectiveness in various clinical aspects. Both studies aim to evaluate the effectiveness of different pharmacological treatment methods and their impact on heart function and patient survival. The first study, named BROKEN-SWEDEHEART, or officially "Optimized Pharmacological Treatment of Broken Heart Syndrome (Takotsubo)," is being conducted in three Scandinavian countries: Denmark, Sweden, and Norway. It assesses left ventricular ejection fraction after 48–96 hours, the frequency of thromboembolic incidents and heart thrombosis, the need for heart-supporting devices within 30 days of a disease episode, and detailed patient examination results. The study focuses on the effects of adenosine, an antiarrhythmic drug, and dipyridamole, an antiplatelet drug. The second study is titled "Beta-blockers in Takotsubo Syndrome: A Randomized Clinical Trial (β-TAKO)" and is being conducted by hospitals in Spain. It concerns the effects of beta-blockers with alpha activity or nitric-oxide-releasing properties, which may improve left ventricular function. It assesses changes in left ventricular activity using the left ventricular ejection fraction method and global longitudinal strain. The systolic function of the left ventricle is analyzed using the echocardiogram wall motion score index over a period of 7 days. The results of these studies will provide valuable information on TTS management by comparing different therapeutic strategies and their impact on heart function and patient survival [84,85].

Conclusions

This review has presented the latest cardiological findings on TTS. In further research, it is important to not only to establish the exact pathophysiology of the disease and its long-term health effects after an episode, but also to determine why the disease primarily affects women. It is suspected that this may be due to the hormonal changes occurring after menopause. Ongoing research in this area is essential. By adjusting the pharmacotherapy, the risk of potential complications that reduce quality of life can be minimized. Another important element is to disseminate knowledge about this disease among specialists from various fields in order to enable proper diagnosis. Collaboration between a family doctor, cardiologist, gynecologist, and endocrinologist at the early stages of TTS can significantly improve prognosis and enhance the prospects of maintaining good quality of life in these patients.

Important limitations in the available studies were noted, such as the lack of long-term data, the limited number of studies involving men, and the small number of clinical trials. The paucity of data on long-term effects makes it difficult to assess the potential implications of the results in a broader clinical context. In addition, the dominance of studies on female populations leads to a gap in the knowledge regarding the effects of specific factors on men's health and limits the possibility of generalizing conclusions for both sexes. The small number of clinical trials further hinders the verification of the efficacy and safety of proposed solutions, which may limit their practical application.

Authors' contribution

Study design – W. Ficoń, M. Dobosz
Data collection – W. Ficoń, M. Dobosz
Manuscript preparation – W. Ficoń, M. Dobosz
Literature research – W. Ficoń, M. Dobosz
Final approval of the version to be published – W. Ficoń, M. Dobosz

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OPIS PRZYPADKU
CASE REPORT

Visual field defects in the course of bipolar affective disorder in a teenager

Ubytki pola widzenia w przebiegu choroby afektywnej dwubiegunowej u nastolatki

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ABSTRACT

Visual field defects are associated with diseases of visual and central nervous systems or pituitary gland, such as retinopathies, optic nerve disorders and visual pathway pathologies or proliferative conditions. A 17-year-old girl with multiple endocrine illnesses – hyperprolactinemia, hypothyroidism, hyperinsulinemia, obesity and bipolar affective disorder – reported visual field disturbances, which were confirmed in kinetic and static visual field examination. Magnetic resonance imaging of the head did not reveal any significant pathologies. Fundus examination showed no abnormalities. The severity of visual field defects changed over time. There were periods of deterioration, when the field of vision narrowed into a tunnel vision, and periods of improvement. A thorough history taking and analysis of psychiatric documentation indicated that episodes of visual field disturbances depended on the phase of bipolar disorder. During mania, the field of vision improved, and during depression, it worsened. This case report shows that not only somatic diseases can lead to visual field defects. After excluding proliferative conditions, central nervous systems or retinal degeneration, it is necessary to expand the differential diagnosis to include a thorough medical history including psychiatric diseases in the family, as well as a psychiatric examination of the patient. The exclusion of optic neuropathy and structural brain changes in the presented patient suggest that the symptoms are caused by bipolar affective disorder.

KEYWORDS

visual field defects, bipolar affective disorder, mania, depression, ophthalmology

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STRESZCZENIE

Zaburzenia pola widzenia są związane z chorobami narządu wzroku, ośrodkowego układu nerwowego lub przysadki mózgowej, takimi jak retinopatie, zaburzenia nerwu wzrokowego, patologie dróg wzrokowych czy stany rozrostowe. Dziewczynka, lat 17, z wieloma chorobami endokrynologicznymi – hiperprolaktynemia, niedoczynność tarczycy, hiperinsulinemia, otyłość i choroba afektywna dwubiegunowa – zgłaszała zaburzenia pola widzenia, które zostały potwierdzone w kinetycznym i statycznym badaniu pola widzenia. Rezonans magnetyczny głowy nie wykazał istotnych patologii. Badanie dna oka również nie wykazało nieprawidłowości. Nasilenie zaburzeń w obrębie pola widzenia zmieniało się z biegiem czasu. Występowały okresy pogorszenia, kiedy pole widzenia zawężało się do widzenia tunelowego, a także okresy poprawy. Dokładny wywiad oraz analiza dokumentacji psychiatrycznej wykazały, że epizody zaburzeń pola widzenia zależą od fazy choroby afektywnej dwubiegunowej. W manii pole widzenia poprawiało się, w depresji ulegało zawężeniu. Opisany przypadek pokazuje, że nie tylko choroby somatyczne mogą prowadzić do wad pola widzenia. Po wykluczeniu organicznych chorób rozrostowych, chorób ośrodkowego układu nerwowego czy zwyrodnienia siatkówki konieczne jest poszerzenie diagnostyki różnicowej o dokładny wywiad lekarski, obejmujący choroby psychiatryczne w rodzinie, a także badanie psychiatryczne samego pacjenta. Wykluczenie neuropatii wzrokowej i zmian strukturalnych mózgu u prezentowanej pacjentki sugeruje, że przyczyną objawów jest choroba afektywna dwubiegunowa.

SŁOWA KLUCZOWE

defekty pola widzenia, zaburzenie afektywne dwubiegunowe, mania, depresja, okulistyka

INTRODUCTION

Bipolar affective disorder (BPAD) is a mental disorder manifested by pathological mood changes such as manic, hypomanic and depressive episodes [1,2,3,4]. A depressive episode in BPAD resembles unipolar depression, but is distinguished with coexistence of psychotic symptoms, excessive sleepiness, frequent recurrence, early onset [2,4]. With the development of the disease, there is a growing memory deterioration, impairment of attentional processes and executive functions [4]. Somatic disorders like cardiovascular disease, endocrine disorders, metabolic syndrome are also observed in patients with BPAD [4,5]. Somatic problems may be side effects of the therapy used, noncompliance with medical recommendations [4]. Yet no case of visual field abnormalities in the course of BPAD has been described in the literature. However, a tubular visual field contraction is not a pathognomonic symptom in BPAD, it can have psychogenic and somatic origin. Visual field defects occur in ophthalmic, neurological, genetic and mental diseases. Differentiating dissociative visual field loss from somatic causes requires multispecialist cooperation and a thorough diagnostics [6]. The aim of this study is to present the case of a teenage female patient with lunette-type visual field loss in the course of BPAD.

CASE REPORT

A 15-year-old girl was admitted to the Department of Paediatric Endocrinology to extend the diagnosis of increasing serum prolactin values, which had been observed since early childhood, and newly emerging subjective visual field disturbance. Previous treatment of hyperprolactinemia included oral cabergoline (Dostinex 0.5 mg twice a week). The patient was treated for hypothyroidism due to autoimmune thyroiditis (Euthyrox 75 ug once daily). Additionally, the girl suffered from menstrual disorder (oral hormonotherapy), hyperinsulinemia, obesity, acne (isotretinoin 20 mg once daily) and BPAD (lithium 0.5 g once daily, olanzapine 20 mg once daily). She underwent magnetic resonance imaging (MRI) of the head and pituitary gland with intravenous administration of contrast agent, which did not reveal any abnormalities in these structures. The patient was referred to the Outpatient Ophthalmology Clinic for the further diagnosis of visual field disturbance. During the examination, the best corrected distance visual acuity (BCDVA) and the best corrected near visual acuity (BCNVA) were determined, which were 0.9 and 0.5 for the right eye (RE), respectively and for the left eye (LE) 1.0 and 0.5. Standard Snellen and near vision-Jaeger charts were used to assess visual acuity. The intraocular pressure in both eyes was within normal limits. Slit lamp examination of the anterior and posterior segments of the eye revealed no abnormalities. She suffered from periodic peripheral visual field disturbance. Kinetic perimetry examination (Figure 1) showed a 10° narrowing of the visual field in both eyes in all quadrants; static perimetry examination showed visual field defects of a similar extent (Figure 2).

Based on imaging and neurological tests as well as on the exclusion of ophthalmological grounds for the reported symptoms, follow-up perimetry tests were planned within 3 months, but the patient did not attend the examination. Another diagnostic stay at the Department of Paediatric Endocrinology took place 1.5 years later. During this time, the patient reported significant deterioration of distance vision, periodic

disturbances of the peripheral visual field and headaches in the parietal area. The repeated MRI scans showed enlargement of the pituitary gland, with the dominant lobe compressing and modeling the neural part. Additionally, the anterior part of the glandular lobe was convex above the sellar diaphragm into the suprasellar cistern and cavernous sinuses. Nevertheless, the enlarged pituitary gland did not cause pressure on the visual pathway, neither individual optic nerves nor optic chiasm were impaired. BCDVA for both eyes was 0.4 whereas BCNVA for both eyes was 0.75. Re-examination of kinetic perimetry narrowed the field of view to 10° from the fixation point in all quadrants of both eyes – a tunnel visual field contraction. Visual evoked potential (VEP) examination (Figure 3) and examination of the anterior and posterior segments of both eyes revealed no abnormalities.

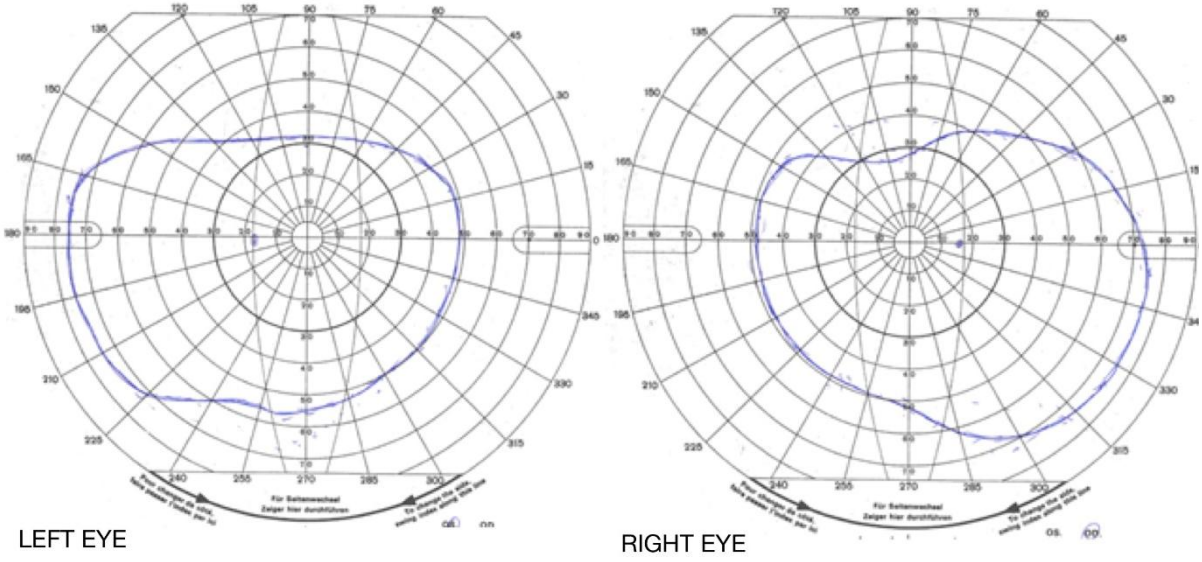

Fig. 1. Kinetic perimetry examination.

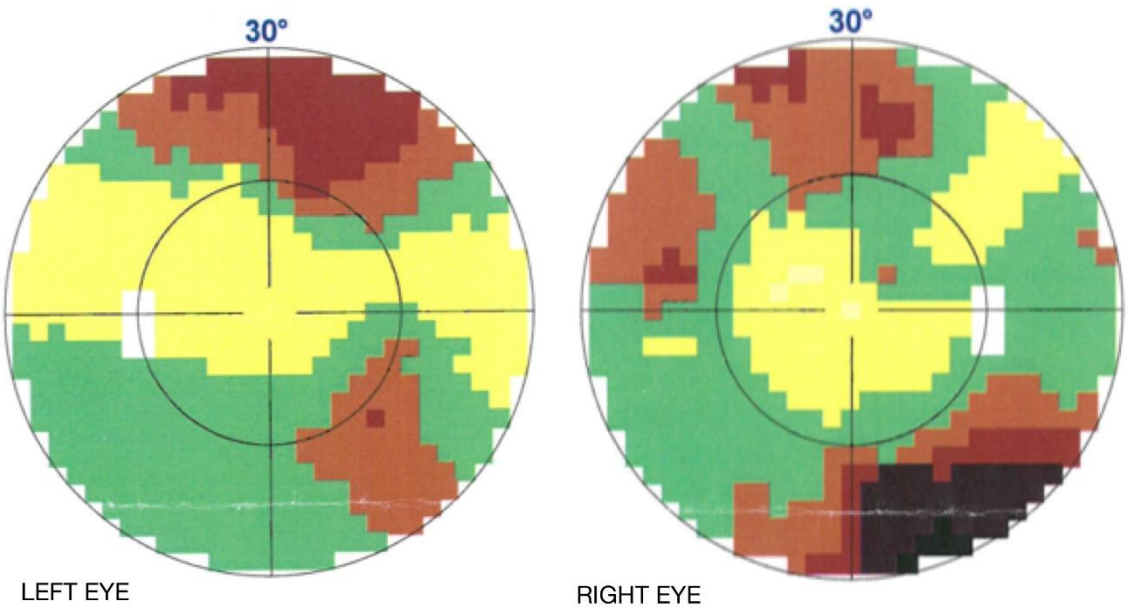

Fig. 2. Static perimetry examination.

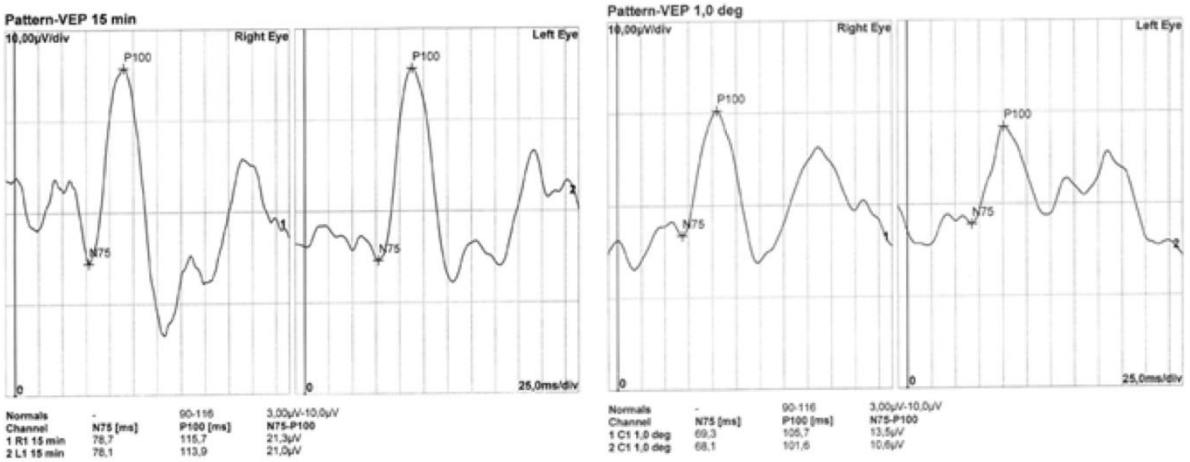

Fig. 3. Visual evoked potential (VEP) examination.

The diagnostics were extended to include RETeval® examination, optical coherence tomography (OCT) of the optic nerve and the thickness of the ganglion cell complex, the results of which were in normal range in every follow-up-examination and allowed the exclusion of glaucomatous neuropathy. A thorough history-taking and in-depth analysis of psychiatric documentation showed that the occurrence of narrowing in the visual field was related to the phase of BPAD. During the last ophthalmological examination, when a decrease in visual acuity and a tubular vision were observed (Figure 4), she was apathetic, uncooperative, showed no interest in tests, and was reluctant to cooperate – which reflected the phase of depression.

Disturbances in the visual field occurred both during an episode of increased and depressed mood, but during an episode of depressed mood they were more severe, resulting in a significant peripheral narrowing of the visual field and, additionally, in a significant deterioration of visual acuity. During periods of remission of BPAD, the patient did not report any visual field disturbances. The presented visual field tests of the patient are documented examples of visual field disturbance in particular phases of the disease. We know from the history that between visits to the clinic she experienced similar episodes, but did not report for follow-up-examinations. Due to the demonstrated correlation, the patient was required to re-evaluate her mental health and modify treatment.

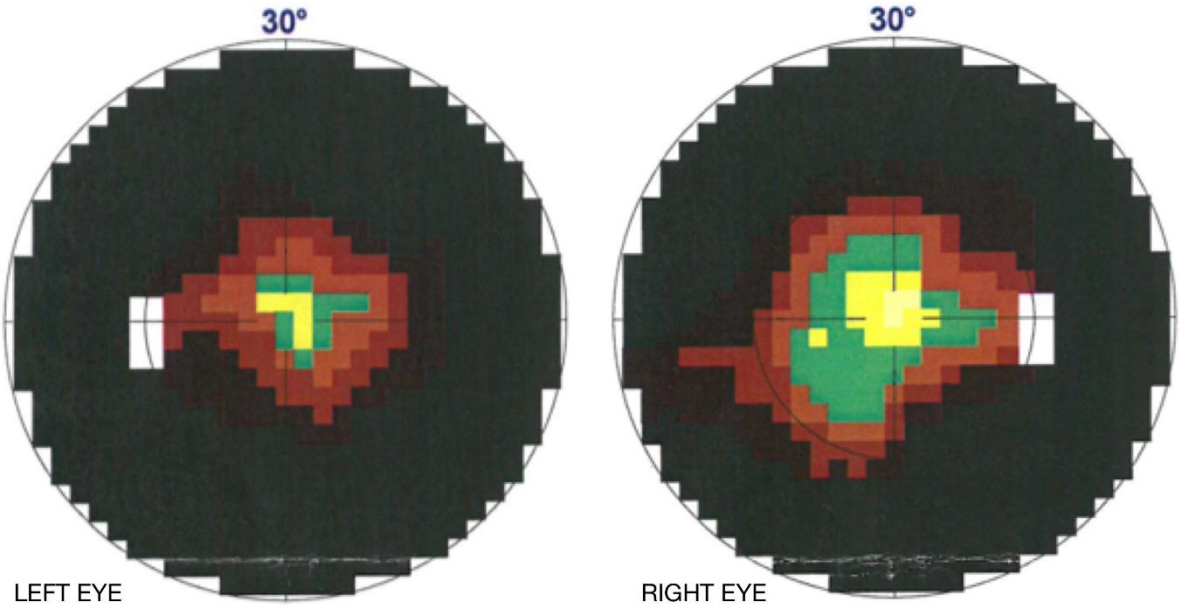

Fig. 4. Repeated static perimetry examination.

DISCUSSION

In many patients, including children, subjective visual disturbances have no identifiable organic cause. These symptoms may result from psychosomatic problems or be simulated [6,7,8,9]. Patients usually report loss of visual acuity, blurred vision, visual field disturbances [6,7]. In most cases of psychosomatic disorders, they are described by patients as tunnel vision [6]. Somers at al. [7] reported that in 50% of cases out of a group of 170 children with vision disorders the vision was of a non-organic visual loss (NOVL). Most cases of NOVL occurred in girls, which was significant in comparison to the population of patients suffering from visual impairment due to organic causes, where no gender differences were proven. Psychiatric examination showed a higher frequency of co-occurring disorders such as depression, anxiety and somatization in patients with NOVL [7]. Early diagnosis of NOVL is important in patients with psychiatric symptoms, as it allows quick consultation with a psychiatrist which improves the further prognosis [6,7,9].

BPAD affects over 1% of global population. The first symptoms usually appear at a young age [2,4,10]. Among children and adolescents with the onset of the disease in childhood, greater irritability, mood lability and a more frequent co-occurrence of attention deficit hyperactivity disorder (ADHD) were observed [11,12].

BPAD may be accompanied by various types of visual disturbances [13,14,15]. Fernandes et al. [13] assessed the color vision in patients with BPAD. The study showed that these patients had higher color discrimination thresholds. This visual function was also linearly correlated with the degree of mania [13]. Distance vision disorders and quality of life in schizophrenia, BPAD and severe depression were the subject of research in one of the psychiatric hospitals in Beijing. One-eighth of patients showed impaired distance vision and the associated reduced quality of life [14].

The coexistence of vision disorders, including color vision disorders and contrast sensitivity coexist with changes in the retinal layers examined using OCT in patients with BPAD [16,17,18]. In those with BPAD, whose color vision was poorer than in the general population, the Lanthony test showed significant thinning in the temporal areas of the retinal nerve fiber layer in two separate clinical studies [16,18]. In one of them, the full macular thickness, ganglion cell layer and internal plexiform layer were also reduced. A significant correlation has been demonstrated between reduced contrast sensitivity and thickness of the internal plexiform layer [16]. Vilades Palomar et al. [18] also tested contrast sensitivity and measured macular thickness, but did not show any significant changes.

It has been proven that people with severe depression have focal loss of the visual field. Patients also had retinal layer thickness measurements performed using OCT, which showed significant thinning of the ganglion cell inner plexiform layer. The severity of depression correlated with the severity of visual field loss and retinal ganglion cell thinning [19].

Medications can affect vision. Drug-induced toxic optic neuropathy manifests as disturbances in the visual field and may be caused by various types of drugs [20]. A case of optic disc edema has been reported during long-term use of lithium carbonate [21]. In a study on the side effects of lithium, there were non-significant trends towards visual field narrowing [22]. A normal VEP examination in the described patient, which showed no damage to the nerve fibers along their entire length, allows us to conclude that the drugs were not the cause of visual field disturbances.

CONCLUSIONS

Visual field defects, including tunnel vision, may be the result of organic diseases or have a psychosomatic cause. Vision disorders are also the subject of research in other psychiatric disorders. Both objective diagnostic tests and the patient's subjective feelings are important in the diagnosis of visual disorders. Extensive diagnosis, detailed history and cooperation of many specialists, including psychiatrists, are necessary.

Authors' contribution

Study design – A. Ziemba, E. Filipek

Manuscript preparation – A. Ziemba, A. Hitnarowicz, A. Jerzak, A. Tronina, E. Filipek

Literature research – A. Ziemba, A. Hitnarowicz, A. Jerzak

Final approval of the version to be published – E. Filipek

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PRACA POOGLĄDOWA
REVIEW

Management of anastomotic leak after esophagectomy – current standards of care

Leczenie nieszczelności zespolenia po resekcji przełyku – aktualne standardy postępowania

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ABSTRACT

Anastomotic leak (AL) is the most serious early complication after esophagectomy and significantly impacts treatment outcomes. The aim of this study is to review the current principles of diagnosis and management of AL using standardized definitions and classifications and the "step-up" approach. The key factors in diagnosis are a high index of clinical suspicion, computed tomography of the chest and abdomen with oral water contrast as the first-choice examination and early endoscopy, which combines a diagnostic role with the possibility of immediate therapy. The "step-up" approach involves rapid control of sepsis and source of infection (radiologic or surgical drainage), gastrointestinal decompression (*nil per os*), targeted antibiotic therapy and preferably enteral nutrition, with escalation to endoscopic treatment. Depending on the local findings, covered self-expanding metal stents or self-expanding plastic stents, endoscopic vacuum therapy (EVT), and – in selected situations – endoscopic internal drainage are used. In cases of extensive tissue damage, conduit necrosis, or failure of endoscopic therapy, surgical treatment may be required. Combined strategies (e.g. sequential EVT → stent) and hybrid solutions (stents with integrated vacuum systems) allow the therapy to be tailored to local conditions. Effective implementation of coordinated protocols in experienced centers, with the involvement of a multidisciplinary team, is associated with a decrease in mortality and improved short- and long-term outcomes.

KEYWORDS

esophageal cancer, esophagectomy, esophageal anastomosis, anastomotic leak, endoscopic vacuum therapy, stents, postoperative complications

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STRESZCZENIE

Nieszczelność zespolenia (*anastomotic leak* – AL) jest najpoważniejszym wczesnym powikłaniem po ezofagektomii i istotnie wpływa na wyniki leczenia. Celem pracy jest przegląd aktualnych zasad rozpoznawania i postępowania w AL z wykorzystaniem ujednoliconych definicji i klasyfikacji oraz podejścia „step-up". W diagnostyce kluczowe znaczenie mają: wysoka czujność kliniczna, tomografia komputerowa klatki piersiowej i jamy brzusznej z doustnym kontrastem wodnym jako badanie pierwszego wyboru oraz wczesna endoskopia, która łączy rolę diagnostyczną z możliwością natychmiastowej terapii. Postępowanie „step-up" obejmuje szybkie opanowanie sepsy i kontrolę źródła zakażenia (drenaż radiologiczny lub chirurgiczny), odciążenie przewodu pokarmowego (*nil per os*), antybiotykoterapię celowaną oraz preferencyjnie żywienie dojelitowe, z rozszerzeniem postępowania o leczenie endoskopowe. W zależności od obrazu miejscowego stosuje się pokryte samorozprężalne stenty metalowe lub plastikowe, endoskopową terapię podciśnieniową (*endoscopic vacuum therapy* – EVT) oraz – w wybranych sytuacjach – wewnętrzny drenaż endoskopowy. W przypadkach z rozległym uszkodzeniem tkanek, martwicą przeszczepu lub nieskutecznością leczenia endoskopowego konieczne bywa leczenie chirurgiczne. Strategie łączone (np. sekwencja EVT → stent) i rozwiązania hybrydowe (stent ze zintegrowanym podciśnieniem) pozwalają dostosować terapię do miejscowych warunków. Skuteczne wdrożenie skoordynowanych protokołów w doświadczonych ośrodkach, z udziałem wielodyscyplinarnego zespołu, wiąże się ze zmniejszeniem śmiertelności i poprawą wyników krótko- i długoterminowych.

SŁOWA KLUCZOWE

rak przełyku, ezofagektomia, zespolenie przełykowe, nieszczelność zespolenia, endoskopowa terapia podciśnieniowa, stenty, powikłania pooperacyjne

Introduction

Esophageal resection with restoration of gastrointestinal continuity remains the cornerstone of treatment for esophageal cancer. Its most serious early complication is anastomotic leak (AL), defined by the Esophagectomy Complications Consensus Group (ECCG) – as a full-thickness defect involving the esophagus, anastomosis, staple line, or graft, regardless of the method of detection [1]. The reported incidence of AL after esophagectomy ranges from about 5% to 30%, depending on factors, such as the anastomosis location and the definitions used [2,3].

AL significantly worsens the postoperative course, prolongs hospitalization, and increases morbidity and mortality (including negatively affecting long-term outcomes even after minimally invasive esophagectomy) [4]. In the international Oesophago-Gastric Anastomosis Audit (OGAA), the incidence of AL was 14.2%, and this complication was associated with significantly worse short-term outcomes [2]. Data from the TENTACLE-Esophagus study were used to develop a mortality risk model for the 90 days post-AL, emphasizing the importance of early diagnosis and coordinated management in experienced centers [5]. The aim of this article is to review the current principles of diagnosis and treatment of AL after esophagectomy in light of the latest literature and guidelines.

Definition and classification

The standard classification of AL severity is based on the invasiveness of the required treatment; this stratification was adopted by the ECCG consensus. Three grades are distinguished: I – a minor AL requiring conservative management, II – AL requiring a non-surgical intervention (endoscopic or radiological), III – AL requiring surgical treatment. The ECCG's uniform definition and classification have enabled comparison of outcomes and quality of reporting in AL management [1,3].

In recent years, high-volume centers with extensive endoscopic experience have proposed approaches that supplement the ECCG classification with an endoscopic morphological assessment of the anastomosis. One example is the classification of the Surgical Working Group on Endoscopy and Ultrasound (Chirurgische Arbeitsgemeinschaft für Endoskopie und Sonographie – CAES), in which the endoscopic assessment of AL (defect size, local conditions, necrosis) is directly linked to the choice of therapy [6]. The latest consensus of the Austrian Society of Surgical Oncology (ACO-ASSO) in 2025 takes endoscopic assessment into account in its treatment algorithm – each grade and endoscopic image is assigned a recommended treatment (for example, endoscopic techniques as first-line for most grade II leaks, reserving surgery for severe cases with necrosis/extensive dehiscence) [7].

In practice, a useful solution is to combine the ECCG grading with dynamic endoscopic assessment (e.g. CAES) and implement a staged "step-up" approach, in which escalation from conservative to endoscopic and – only if necessary – surgical therapy occurs in accordance with the severity and local AL results [1,6,7].

Diagnosis

The symptoms of AL are often nonspecific; early warning signs include tachycardia, fever, leukocytosis, dyspnea, or chest pain. Given the nonspecific clinical presentation, a high level of vigilance is necessary –

any abnormality in the postoperative course should raise suspicion of AL until it is ruled out. Data from the OGAA and TENTACLE-Esophagus studies emphasize the impact of rapid diagnosis and coordinated management on treatment outcomes (which is also significant for long-term results) [2,4,5].

The standard for confirming a leak is contrast-enhanced computed tomography (CT) of the chest and abdomen using an oral water-soluble contrast agent. CT can reveal extravasation of contrast outside the lumen, the presence of fluid or gas collections, and delineate the extent of infection in the mediastinum and pleural cavity. Current recommendations emphasize CT as the first-line modality [7]. Contrast esophagography using water-soluble (iodinated) contrast may be useful as a complementary examination – especially for evaluating small, clinically subtle leaks and monitoring healing. However, it should be remembered that it is less sensitive than CT and may miss AL; a negative esophagram does not exclude a leak, if clinical suspicion persists [7].

Early endoscopy (preferably within 24–48 hours of symptom onset) serves both diagnostic and therapeutic purposes: it allows direct visualization of the leak site (defect size, local conditions, necrosis) and immediate treatment in the same session (e.g. placement of a covered stent or initiation of endoscopic vacuum therapy [EVT]). This approach is in line with current guidelines and the modern "step-up" algorithm [7,8].

Principles of the "step-up" approach

The goal of the "step-up" approach is to bring sepsis under control quickly and to contain the infection spread [4]. The top priorities are to ensure effective drainage (radiological or surgical), keeping the patient *nil per os* (NPO; nothing by mouth), providing targeted antibiotic therapy, and nutritional support (preferably enteral nutrition) [7,8,9]. Treatment decisions are made dynamically based on the clinical picture and the morphology of the leak (ECCG/CAES classification) [1,3,6,7]. After a short period of clinical observation (24–48 hours, up to 72 hours maximum), if AL symptoms persist, treatment is then further escalated: first-line escalation is with endoscopic techniques (self-expanding metal stents – SEMS / self-expanding plastic stents – SEPS or EVT) [7,8,10,11, 12,13], and in cases with necrosis, extensive anastomotic dehiscence, or uncontrolled sepsis – surgical treatment is indicated [1,7]. This algorithm is consistent with the latest ACO-ASSO consensus and the European Society of Gastrointestinal Endoscopy (ESGE) guidelines [7,8,14].

Endoscopic treatment

Covered esophageal stents (SEMS or SEPS) are one of the fundamental methods for treating AL after esophagectomy [8,10]. Their mechanism of action is based on sealing the defect – a membrane-covered stent prevents further leakage of enteral contents into the mediastinum, effectively creating an internal "patch" over the leak site [8]. An additional benefit is the possibility of early resumption of oral or enteral feeding despite the presence of a leak, since the stent isolates the leak site from the enteric stream [15]. The clinical efficacy of stenting, defined as the rate of complete leak closure with this method, reaches approximately 70–80% in the latest studies [10]. Particularly high success rates are reported when periesophageal collections are simultaneously drained – which underscores the importance of combined therapy (stent + drainage) for the AL healing [16].

One of the main limitations of stent therapy is stent migration [8]. Self-expanding stensts, especially plastic stents, tends to shift from the implantation site once tissue edema subsides – this occurs in approximately 20–40% of cases, and in up to 60% for cervical anastomoses [17]. The risk of migration is greater for cervical leaks (short esophageal segment above the stent) and when there is no stricture at the leak site. To prevent migration, additional measures are sometimes used (e.g. percutaneous "anchoring" of the stent ends to the neck skin, endoscopic clips to fix the stent to the esophageal wall, or special anchoring systems) [18,19,20]. The second significant limitation is the lack of active drainage – while the stent closes the lumen of the defect, it does not remove infected contents from any already formed perianastomotic cavities (abscesses) [8,16]. Retention of the infected fluid beneath a stent creates a risk of infection progression or sepsis; therefore, when treating with a stent, parallel drainage must be ensured – either percutaneously under radiologic guidance or endoscopically (for example, leaving a transnasal drain into the perianastomotic cavity). Covered stents are typically left in place for about 6–8 weeks [8], then removed endoscopically. This dwell time minimizes the risk of stent ingrowth into the esophageal wall and later stricture at the leak site. Removing a stent before 6–8 weeks is associated with a higher rate of leak recurrence, whereas leaving a stent in longer increases the risk of complications such as difficult-to-treat anastomotic stricture. After AL healing, any anastomotic strictures that occur are usually managed with balloon dilations under fluoroscopic guidance, with high effectiveness over multiple sessions [21].

EVT involves placing a specialized sponge connected to a suction catheter into the perianastomotic cavity or within the anastomotic defect and attaching it to a continuous vacuum source [10,11,12,13]. Small polyurethane sponges are typically used; these are positioned endoscopically at the site of the leak or within the leak cavity, and continuous negative pressure of -100 to -125 mmHg is applied via

a vacuum pump [11,12,13,22]. This system acts as an internal suction drain: it provides continuous drainage of infected fluid, reduces the bacterial load in the wound, and stimulates granulation and healing by mechanically debriding the tissues (the so-called vacuum effect) [11,12,13]. The sponge is changed every 3–5 days during repeat endoscopies – with each exchange a new, usually smaller sponge is placed – until the defect is completely closed. The average duration of therapy is about 2–3 weeks, though it depends on the extent of the leak and the healing dynamics [11,12,13,23]. Over the past decade, EVT has gained great popularity in the treatment of esophageal anastomotic leaks, especially those accompanied by a perianastomotic abscess cavity [11,12,13]. Available meta-analyses and larger studies report complete healing rates of 85–95%, and comparisons with temporary covered stents show at least comparable and often superior efficacy of EVT [10,11,12,13,24]. For example, a meta-analysis by Scognamiglio et al. [10] demonstrated a 93% vs 71% success rate in favor of EVT. Consistent conclusions were also reported in a comparative study by Berlth et al. [24].

It should be noted that most data come from observational studies, and the choice of method often depended on the characteristics of the leak (larger, more contaminated cavities were more often managed with EVT) [10,11,12,13]. Overall, EVT is highly effective and safe, provided the necessary endoscopic therapy expertise is available [11,12,13].

The literature emphasizes that EVT is no less effective than stenting, and in cases of large infected cavities it is often the first-line method [7,11,12,13]. Limitations of EVT include the need for frequent anesthesia and endoscopy for sponge changes (approximately every 3–5 days), as well as patient discomfort related to the indwelling vacuum system. Patients are usually kept strictly NPO during therapy (with enteral or parenteral nutrition) for what may be several weeks. Nevertheless, EVT is well tolerated and complications are rare; the most commonly reported are minor local bleeding or mucosal injury during sponge placement/exchange [11,12,13,23].

In selected cases with a limited perianastomotic cavity, endoscopic internal drainage (EID) can also be used. Through-the-fistula placement of 1–2 double-pigtail plastic stents from the abscess cavity into the lumen of the gastrointestinal (GI) tract allows internal drainage of the purulent collection and offloading of the anastomosis. EID is considered when there is a confined cavity with a narrow connection; the method can enable early oral feeding in some patients, but it requires careful patient selection and does not replace EVT for large, contaminated cavities [25].

Combined strategies and new technologies

An increasing number of centers report benefits from combining endoscopic methods to optimize leak management. One example is the sequential EVT → stent strategy, which involves initial vacuum therapy to clean and reduce the leak cavity, followed by placement of a covered stent for more rapid sealing of the defect [7,12]. This approach may shorten the overall healing time – EVT quickly reduces the infection and prepares the wound bed, and the stent provides definitive closure of the leak [12]. EID can also be applied in combination (e.g. a covered stent provides intraluminal separation, while EID ensures internal drainage of abscess collections) in cases of limited cavities; for extensive, contaminated cavities, EVT remains the preferred modality [25]. It has been shown that deploying a stent after initial vacuum therapy can reduce the number of sponge exchanges and shorten hospitalization time [12]. Combined methods are especially recommended in cases with a large perianastomotic cavity, where stenting alone could be insufficient due to retention of infected material under the stent [7,12,24]. Clinical reports confirm the efficacy and safety of the sequential EVT + stent strategy, though randomized comparative studies are still lacking [12].

Another interesting innovation is the vaccum-assisted closure stent (VAC-stent) – a hybrid device combining a covered stent with an integrated vacuum system [26,27]. This device consists of a self-expanding covered stent equipped with a sponge structure attached to the outside of the stent and connected to a suction drain that is brought out through the nose [26,27,28]. The VAC-stent combines the advantages of both techniques: it simultaneously seals the defect (thanks to the stent) and provides active drainage (thanks to the vacuum sponge) [26,27,29]. The first clinical applications of VAC-stents are very promising – pilot studies have shown high rates of leak closure and no significant device-related complications [26, 27,28,29]. Lange et al. [26,27] described a series of patients treated with a VAC-stent in whom AL healing was achieved without reoperation. Currently, VAC--stents are still available only within studies or at select centers [26,27,29], but it is possible that they will become an important element in AL therapy in the future. Their cost and the greater technical complexity of placement compared to a standard stent or EVT are certain limitations [29]. Nevertheless, the development of such hybrid technologies illustrates the direction of improving AL treatment – the pursuit of methods that combine effective leak closure with simultaneous infection control. A summary comparison of endoscopic techniques, their indications, advantages, limitations and outcomes is presented in Table I.

Table I. Management of anastomotic leak after esophagectomy – comparison of endoscopic methods

Method	When to consider	Main advantages	Limitations	Typical treatment duration	Approximate closure rate
SEMS/SEPS	Small-moderate defect, no large cavity; external drainage in place	Rapid isolation of lumen; widely available; can bridge strictures	Stent migration; no active cavity drainage; risk of ulcers or granulation overgrowth	6–8 weeks (temporary stent)	70–85%
EVT	Presence of abscess cavity, unfavorable local conditions; need for active drainage and cleaning	Active drainage and debridement; promotes granulation; usually higher closure rate than stents (SEMS)	Requires sponge changes every 2–4 days; limited availability; patient discomfort	Usually 2–3 weeks (depending on cavity)	> 80–90% (in meta-analyses)
VAC-stent	Cases needing simultaneous intraluminal isolation and local negative pressure	Combines benefits of stent and EVT; potentially shorter treatment time	Early-stage technology; limited data; availability and cost	Depends on protocol (often shorter than standard EVT)	High rate in small series
EID	Limited cavity with narrow tract; external drainage in place and sepsis controlled	Internal drainage of abscess; often allows early oral feeding; technically simple	No active cleaning like EVT; patient selection is key	4–6 weeks (several weeks)	Success depends on selection; good results in studies

SEMS – self-expanding metal stents; SEPS – self-expanding plastic stents; EVT – endoscopic vacuum therapy; VAC-stent – vaccum-assisted closure stent; EID – endoscopic internal drainage.

Surgical treatment

Despite advances in minimally invasive methods, a subset of patients with an AL will require surgical treatment. Absolute indications for reoperation are: uncontrolled sepsis despite intensive conservative therapy and drainage, extensive anastomotic dehiscence (e.g. involving > 50% of the anastomotic circumference), necrosis of the anastomosis or conduit (for example, gastric conduit necrosis), and early complete anastomotic breakdown immediately post-surgery (the so-called "blow-out") [1,7]. Another indication is failure of endoscopic therapy – if despite stents or EVT the patient's condition is deteriorating or the leak is not healing, escalation to salvage surgery becomes necessary [7,8]. In clinical practice, the decision to reoperate can be difficult and should be made by an experienced team, considering the patient's overall condition (hemodynamic stability, severity of infection, comorbidities, expected quality of life) [2,7].

Possible surgical options are individualized depending on the local situation and the patient's condition. They include:

1. Limited surgical revision and drainage – indicated for a localized mediastinal abscess without massive anastomotic dehiscence. Surgical debridement and washout via a cervical approach or thoracotomy allows evacuation of pus, removal of necrotic tissue, and placement of drains. This approach can serve as a bridge, permitting subsequent continuation of endoscopic therapy (e.g. EVT) under improved conditions [7,10,11,12,13].
2. Anastomosis repair – if technically feasible, meaning the defect is not too large and the tissues of the anastomosis and graft are sufficiently well perfused. This involves re-suturing the dehiscence (usually after freshening the edges) and reinforcing the anastomosis – often an omental flap or a muscle flap (e.g. intercostal muscle) is used to buttress the repaired site [30]. A primary repair carries a risk of failure, especially if local conditions are unfavorable (infection, edema, friable tissues).
3. Temporary gastrointestinal continuity diversion – reserved for the most severe cases. This entails disconnecting the esophageal continuity (or removing a necrotic conduit) and creating a temporary stoma: most commonly a cervical esophagostomy to divert saliva, along with a decompressing gastrostomy (and/or a feeding jejunostomy) [30]. This approach controls the infection and offloads the leak site at the expense of a temporary loss of GI continuity. After a few months, once the patient's condition has improved, reconstruction can be performed – for example, using another conduit (such as a colonic interposition).

The choice of surgical strategy depends on the extent of the leak, the time elapsed since the initial surgery, the perfusion of the graft, and the patient's overall condition [7]. A staged approach is often used – first a limited life-saving operation (washout, drainage, diversion stomas), followed by a delayed reconstruction in a second stage after a few months [7,30,31]. Regardless of the extent of surgery, the overriding

goal is to control sepsis and save the patient's life, even at the cost of a temporary sacrifice (such as a stoma) [7]. The mortality of reoperation for AL is high and increases with AL severity and organ failure [2,4,5,32] – therefore the decision to operate is made after considering whether there is a chance to achieve healing of the leak by less invasive means. On the other hand, waiting too long to perform surgical intervention in the face of progressing sepsis worsens the prognosis [2,4,5]. Risk models (e.g. TENTACLE) indicate that the patient's overall condition and the severity of AL determine survival; brief, closely monitored trials of minimally invasive therapy are acceptable provided there is prompt escalation if no improvement is seen [5,7].

Conclusions

Management of an AL after esophagectomy should always be tailored to the individual patient's situation and the characteristics of the leak. Thanks to appropriate care and the development of endoscopic techniques, the results of AL treatment have improved in recent years [3,6,8,10,11,12,13,33]. Currently, a staged "step-up" strategy is preferred, in which treatment begins with conservative and endoscopic methods, with surgery reserved as a last resort [7,8]. Such approach minimizes the invasiveness of therapy and often allows control of the leak without graft resection or stoma creation [7,10,11,12,13]. However, early recognition of AL and management in specialized centers by an experienced multidisciplinary team is essential [4,6,7,14]. To ensure optimal care, close collaboration among the surgeon, endoscopic gastroenterologist, and interventional radiologist is necessary at all stages – from diagnosis to therapy [6,7]. This organized approach, supported by guidelines and protocols, has translated into a reduction of AL-associated mortality to low-teens percentages range in the best centers, which is a significant improvement over historical data [2,4,5]. Ongoing research into AL risk factors, refinement of minimally invasive treatment methods, and implementation of established standards on a wider population scale gives hope for further reduction of the adverse consequences of AL in the future [2,32].

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PRACA ORYGINALNA
ORIGINAL PAPER

Environmental study analyzing the knowledge of vaccinated patients about complications after vaccination against COVID-19: A preliminary report

Badanie środowiskowe analizujące wiedzę zaszczepionych pacjentów na temat powikłań po szczepieniu przeciwko COVID-19 – doniesienie wstępne

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ABSTRACT

INTRODUCTION: The aim of this study is to analyze the knowledge of vaccinated Poles about the side effects of COVID-19 vaccination in the light of misinformation about vaccines, their mechanism, and complications.
MATERIAL AND METHODS: The authors created an anonymous online survey. The study group consisted of 2,345 people and included 1,468 people vaccinated against COVID-19.
RESULTS: Vaccine leaflets, social media, and doctors were listed as the most frequent sources of information about vaccines. When asked about the possibility of developing COVID-19 as a result of vaccination, 55.18% of the respondents answered that it is not possible. Only 2.72% of the respondents claimed that complications will occur after each vaccine and booster dose. According to the respondents, the most common complication following the Comirnaty vaccine is muscle pain; after the Vaxzevria vaccine it is fever. In the case of the Moderna and Janssen vaccines, most did not know the answer.
CONCLUSIONS: The respondents knew the most about the side effects related to the Comirnaty vaccine and the least about the Janssen and Moderna ones. In the case of the Vaxzevria vaccine, the respondents pointed to thromboembolic events as one of the most common complications. The most common source of information was the vaccine leaflet. Fears about complications were declared by the highest number of people vaccinated with the Janssen vaccine.

KEYWORDS

SARS-CoV-2, COVID-19, vaccine

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STRESZCZENIE

WPROWADZENIE: Celem niniejszego badania jest analiza wiedzy zaszczepionych Polaków na temat powikłań po szczepieniu przeciwko COVID-19 w obliczu konieczności zwiększenia wiedzy na temat szczepionek, mechanizmu ich działania oraz powikłań.
MATERIAŁ I METODY: Autorzy stworzyli anonimową ankietę internetową. Badana populacja liczyła 2345 osób, w tym 1468 zaszczepionych przeciwko COVID-19.
WYNIKI: Jako najczęstsze źródła informacji o szczepionkach wskazywano ulotkę szczepionki, media społecznościowe oraz lekarza. Na pytanie o możliwość zachorowania na COVID-19 w wyniku szczepienia 55,18% respondentów odpowiedziało przecząco. Jedynie 2,72% ankietowanych twierdziło, iż po każdej dawce szczepionki wystąpią powikłania. Zdaniem ankietowanych najczęstszym powikłaniem po szczepionce Comirnaty jest ból mięśni, a po szczepionce Vaxzevria gorączka. W przypadku szczepionek Moderna i Janssen większość nie znała odpowiedzi.
WNIOSKI: Ankietowani wiedzieli najwięcej o powikłaniach mogących wystąpić po przyjęciu szczepionki Comirnaty, a najmniej o powikłaniach po szczepionkach Janssen i Moderna. W przypadku szczepionki Vaxzevria jako jedno z najczęstszych powikłań ankietowani wskazali incydenty zakrzepowo-zatorowe. Najczęstszym źródłem informacji o powikłaniach była ulotka dołączona do szczepionki. Obawy przed powikłaniami deklarowała największa liczba osób zaszczepionych szczepionką Janssen.

SŁOWA KLUCZOWE

SARS-CoV-2, COVID- 19, szczepionka

INTRODUCTION

In December 2019, the first cases of the severe acute respiratory disease COVID-19 caused by a new strain of coronavirus, SARS-CoV-2, were identified [1,2,3]. The first case in Poland was registered on March 4, 2020 [4]. On March 11, the World Health Organization (WHO) declared COVID-19 a pandemic [2,5].
Despite worldwide research programs aiming to find effective medication for COVID-19, there is still no standardized pharmacotherapy with high effectiveness proven by large-scale research [6,7]. Thus, vaccines play a significant role in decreasing COVID-19--related hospitalization and deaths [8,9,10,11].
In order to effectively fight the pandemic, most countries started the process of vaccinating their citizens [11,12,13]. The first country to launch a national vaccination program was the United Kingdom, on December 8, 2020 [14,15]. In Poland, the first person was vaccinated on December 27, 2020 [16]. As of March 29, 2022, 59.1% of Polish citizens were fully vaccinated [17]. In the European Union, Portugal has the highest vaccination rate, with 92.6% of its citizens having received two doses (as of March 29, 2022) [17]. Due to the acquired immunity against COVID-19 weakening over time, it is recommended to receive booster doses [18]. In Poland, the number of people who have received a booster dose exceeds 11 million citizens [19]. The National Vaccination Program was introduced to plan and control the process of voluntary vaccination among Polish citizens. It involves providing and distributing an adequate number of vaccines and controlling their safety and efficacy [20].
mRNA vaccines are currently available on the European market, including the Comirnaty vaccine (BioNTech/Pfizer) and the mRNA vaccine (Moderna). They work by delivering synthetic mRNA to the cytoplasm of the host cell, where the encoded SARS--CoV-2 antigen is translated, which is most often the S protein. This allows the antigen to be properly presented to the immune system and to induce an effective immune response [21,22,23]. In addition, viral vector vaccines are also available: Vaxzevria (AstraZeneca) and Janssen (Johnson & Johnson). These vaccines contain inactivated adenovirus, which acts as a vector carrying the genetic information necessary to synthesize the SARS-CoV-2 protein [21,22,24]. It is an antigen that induces an immune response based on cross-immunity [25]. The latest commercially available vaccine is the recombinant vaccine Nuvaxovid from Novavax, which contains purified SARS-CoV-2 S protein – or a fragment thereof – prepared using genetic recombination techniques [24,26]. The Sputnik V viral vector vaccine, Sinovac's inactivated Vero Cell vaccine, and the Vidprevtyn and Valneva vaccines are under phase review [26].
Despite the proven efficacy of all currently available COVID-19 vaccines and the existence of many public and social campaigns encouraging their adoption, vaccination programs both in Poland and around the world meet with reluctance, which may be related to the limited clinical trials on their safety or the existence of numerous conspiracy theories, as well as decreasing trust in vaccinations overall [13,27]. In recent years, the number of people in Poland confident about the safety of vaccination against other infectious diseases has been decreasing, in contrast to many other countries [28].
The main aim of this study was to assess the knowledge of vaccinated Poles about the side effects following COVID-19 vaccination. Secondary objectives are to determine whether the respondents' knowledge

of all vaccines is the same, which sources of information they most often use, and whether their sex, age, education level, or place of residence are related to their knowledge about vaccination.

MATERIAL AND METHODS

The research was conducted in the form of an anonymous online questionnaire addressed to the citizens of Poland. The surveys were collected from May to August 2021. The questionnaire was widely shared on online forums and social media platforms, mostly on Facebook groups with announcements. It consisted of a demographic section and the main section, the latter of which was divided into a part dedicated to all respondents and one only for those who had been vaccinated.

RESULTS

Demographic section

The population for our research consisted of people living in all Polish voivodeships. The final number of responses was 2,345. Most of them (1,851; 78.9%) were sent by women, while 470 (20%) were sent by men; the remaining 24 (1%) of our respondents chose not to share their sex. Based on Erik Erikson's stages of psychological development, we distinguished the following age groups in our questionnaire: ≤ 17 years old, 18–35 years old, 36–55 years old, 56–65 years old, and ≥ 66 years old [29]. The next question referred to the population of the town where our respondents lived. They could choose between the following: up to 50,000 citizens, up to 150,000, up to 500,000, and over 500,000 citizens. Lastly, we asked the respondents about their education level (Table I).

Table I. Characteristics of the study group

Parameters		Respondents [n (%)]
Gender	Women	1,851 (78.9)
	Men	470 (20)
	Did not share that information	24 (1)
Age	≤ 17 years old	89 (3.8)
	18–35 years old	1,468 (62.6)
	36–55 years old	660 (28.1)
	56–65 years old	85 (3.6)
	≥ 66 years old	43 (1.8)
Population of place of residence	< 50,000	1285 (54.8)
	50,000–150,000	428 (18.3)
	150,000–500,000	350 (14.9)
	> 500,000	282 (12)
Educational stage	Elementary	94 (4)
	Secondary	729 (31.1)
	Vocational	168 (7.2)
	Higher	944 (40.3)
	College student	410 (17.5)

Main section

Questions concerning all respondents

Out of 2,345 respondents, 805 (34.3%) had experienced a COVID-19 infection, of which 79.1% (637) were women and 19.9% (160) were men. People in the 36–55 age group were more likely to suffer from COVID-19 (35.91%), followed by the 18–35 age group (34.47%; Table II).

Table II. COVID-19 infection, by age group

Age group [years]	COVID-19 infection [% (n)]	
	Yes	No
≤ 17	31.46 (28)	68.54 (61)
18–35	34.47 (506)	65.53 (962)
36–55	35.91 (238)	64.09 (422)
56–65	29.41 (25)	70.59 (60)
≥ 66	18.60 (8)	81.40 (35)

In total, 703 respondents (29.28%) had been fully vaccinated. A single dose had been administered to 765 respondents (32.62%). Further in the article, both of these groups are referred to as "the vaccinated." Over one third of the respondents (877; 37.4%) were unvaccinated. We analyzed the relationships between vaccination rate, gender, and age group among our respondents (Table III).

Men and women were vaccinated to the same extent. The age group with the highest vaccination rate was ≥ 66. Due to the large amount of data obtained in the survey, the remainder of the article focuses on the vaccinated respondents.

Most of the respondents (901; 61.37%) were vaccinated with the Comirnaty vaccine. The second most common vaccine was Vaxzevria (297; 20.26%), followed by Moderna (137; 9.32%), and the least popular was Janssen vaccine (133; 9.05%).

Next, the vaccinated respondents answered questions about complications after COVID-19 vaccination. From that group, 694 (47.3%) admitted that they had experienced post-vaccination complications (Figure 1).

The most frequent answers were fatigue (25.72%), muscle pain (25.67%), and fever (19.06%). Our research also showed that 385 people (26.6%) were afraid of long-term complications that may occur after vaccine administration.

Next, the respondents were asked if they had sought information about complications from COVID-19 vaccination. Out of all the vaccinated respondents, 65.4% answered positively.

They were also asked about what sources of information they used. The most frequent answer was the vaccine leaflet (17.92%), followed by social media (15.54%), doctors (15.15%), official government websites (13.98%), internet forums (13.51%), conventional media (10.93%), and family and friends (10.86%).

Table III. Vaccination rate, gender, and age group

Parameters		Are you vaccinated? [% (n)]		
		No	Yes (1 dose)	Yes (fully)
Gender	Women	36.79 (681)	32.47 (601)	30.74 (569)
	Men	38.09 (179)	34.04 (160)	27.87 (131)
	Did not share	70.83 (17)	16.67 (4)	12.50 (3)
Age group [years]	≤ 17	65.17 (58)	33.71 (30)	1.12 (1)
	18–35	39.92 (586)	33.79 (496)	26.29 (386)
	36–55	30.91 (204)	29.70 (196)	39.39 (260)
	56–65	28.24 (24)	31.76 (27)	40.00 (34)
	≥ 66	11.63 (5)	37.21 (16)	51.16 (22)

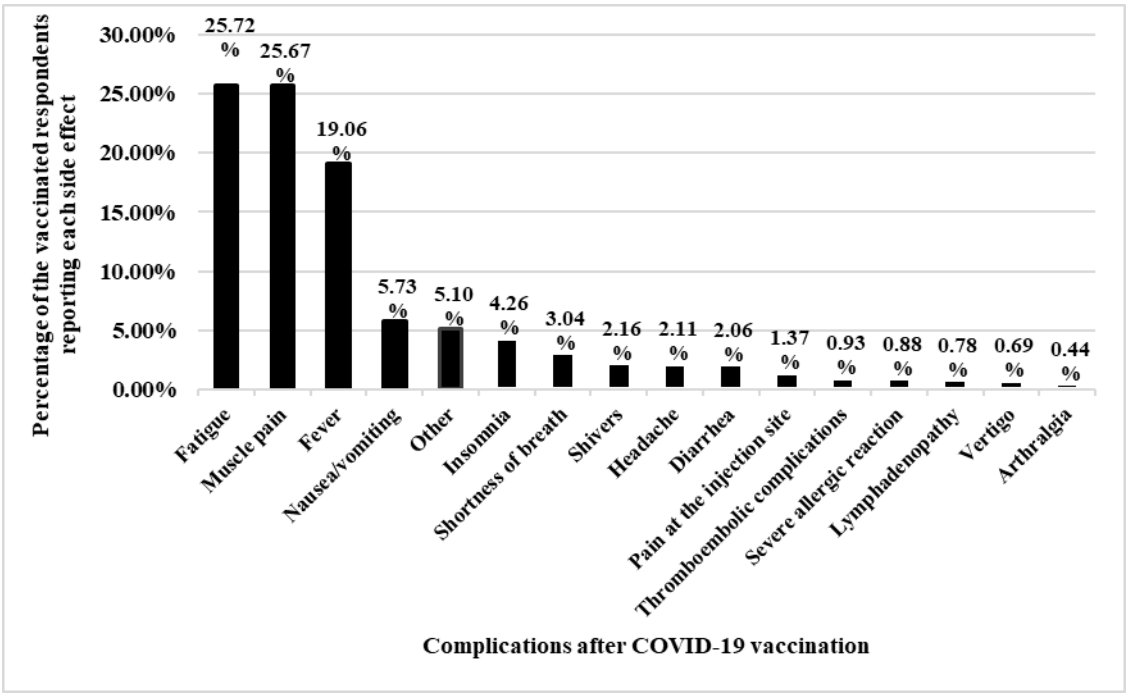

Fig 1. What side effects did you experience after receiving the COVID-19 vaccine? (%)

The respondents were then asked if SARS-CoV-2 infection might develop as a result of vaccination. Only 186 people (12.67%) chose the answer "yes"; 810 (55.18%) picked "no" and the rest of the respondents chose "I don't know."

On the next question, the majority of our respondents (1,300; 88.56%) stated that not every vaccinated person will develop complications. Only 40 of them (2.72%) thought that this was the case, while the rest selected "I don't know."

Next, we asked the interviewees if a severe allergic reaction might occur as a result of vaccination. The vast majority thought that this was possible (1,111; 75.68%), while 79 (5.38%) respondents answered negatively and 278 (18.94%) chose "I don't know."

To the question "Which vaccine is the safest in your opinion?" 618 (42.10%) respondents answered that the specific vaccine did not matter to them. For 712 respondents (48.50%), the safest one was the Comirnaty vaccine. The least safe vaccine, in the opinion of the majority of our respondents, was Vaxzevria.

The following questions examined the respondents' knowledge about the most common side effects that may occur after COVID-19 vaccination. They were allowed to choose more than one answer, so we present the results as the number and percentage. Detailed information is presented in Table IV.

The most commonly chosen complications for the Comirnaty vaccine were muscle pain (26.82%), fatigue (25.08%), and fever (22.99%). For the Moderna vaccine, 26.51% respondents did not know the most common complications. The next most frequent answers were muscle pain (20.38%), fatigue (19.94%), and fever (18.75%). Answers to the same question about the Janssen vaccine were similar, including "I don't know" (30.39%), muscle pain (17.80%), fatigue (17.54%), and fever (17.43%). Lastly, the most common complications after Vaxzevria in the respondents' opinion were fever

(21.07%), muscle pain (20.25%), and fatigue (18.72%). Moreover, the respondents more often reported thromboembolic complications as a frequent side effect of the Vaxzevria vaccine than other vaccines (323 vs. 64 for Comirnaty, 54 for Moderna, and 89 for Janssen; Figure 2).

To sum up, the most common responses to the questions about post-vaccination complications are shown in Figure 3.

We then analyzed the relationship between the incidence of complications among the respondents and their research of information on this topic. Side effects occurred more often among the respondents who had researched potential complications beforehand (50.52% vs. 41.14%).

Next, we analyzed the relationship between the sources of information accessed by the vaccinated respondents and the factors of sex, education, age, and place of residence. Women sought information on complications from COVID-19 vaccination slightly more often than men: 66% (777) and 61% (178), respectively. Representatives of both sexes most often sought information about post-vaccination complications from the vaccine leaflets. In addition, women used all sources of information listed in the survey more often than men.

Vaccinated individuals with elementary, secondary, and higher education, as well as current college students, sought information about complications with similar frequency: 67% (26), 65% (269), 68% (433), and 66% (180), respectively. In contrast, those with vocational education did so less frequently (51%; 52). People with higher education and enrolled in college most often used vaccine leaflets as a source of information about complications (35.60% and 35%, respectively). In contrast, the leaflet was least often used by people with vocational education (14.70%).

The age groups ≤ 17, 18–35, 36–55, and ≥ 66 searched for information on complications after vaccination with a similar frequency: 65% (20), 66% (584), 66% (300), and 63% (24), respectively. However, in the case of the 56–65 age group, this percentage was 52% (32). Social media was the most common source of information on complications after vaccination against COVID-19 in the ≤ 17 age group (35.5%). The vaccine leaflet was the most common source in the 18–35 and 36–55 groups, but the least common among the ≤ 17 and 56–65 groups.

Inhabitants of cities over 500,000 residents used social media (29.17%; 56), vaccine leaflets (36.98%; 71), official government websites (33.85%; 65), traditional media (21.88%; 42), family and friends (23.96%; 46), and family doctors/specialists (30.21%; 58) when looking for information about complications more often than representatives of other groups. As the size of the town grew, so did the percentage of people using leaflets and official government websites as sources of information on complications. Detailed information is presented in Table V.

Table IV. Post-vaccination complications, by vaccine brand

Post-vaccination complications	Brand of vaccine [% (n)]			
	Comirnaty (Pfizer/BioNTech)	Moderna	Janssen (Johnson & Johnson)	Vaxzevria (AstraZeneca)
Muscle pain	26.82 (898)	20.38 (565)	17.80 (485)	20.25 (768)
Fatigue	25.08 (840)	19.94 (553)	17.54 (478)	18.72 (710)
Fever	22.99 (770)	18.75 (520)	17.43 (475)	21.07 (799)
Nausea/vomiting	3.49 (117)	3.89 (108)	4.29 (117)	5.35 (203)
Thromboembolic complications	1.91 (64)	1.95 (54)	3.27 (89)	8.52 (323)
Severe allergic reaction	1.88 (63)	1.73 (48	1.69 (46)	2.53 (96)
Shortness of breath	1.79 (60)	1.77 (49)	2.09 (57)	3.35 (127)
Diarrhea	1.70 (57)	2.02 (56)	2.31 (63)	3.43 (130)
Insomnia	1.49 (50)	1.41 (39)	1.83 (50)	2.66 (101)
Arm ache	1.28 (43)	0.58 (16)	0.33 (9)	0.24 (9)
Swelling / pain at the injection site	0.75 (25)	0.50 (14)	0.37 (10)	0.29 (11)
Headache	0.51 (17)	0.18 (5)	0.26 (7)	0.26 (10)
I don't know	9.50 (318)	26.51 (735)	30.39 (828)	12.53 (475)
Other	0.81 (27)	0.39 (11)	0.40 (11)	0.80 (30)

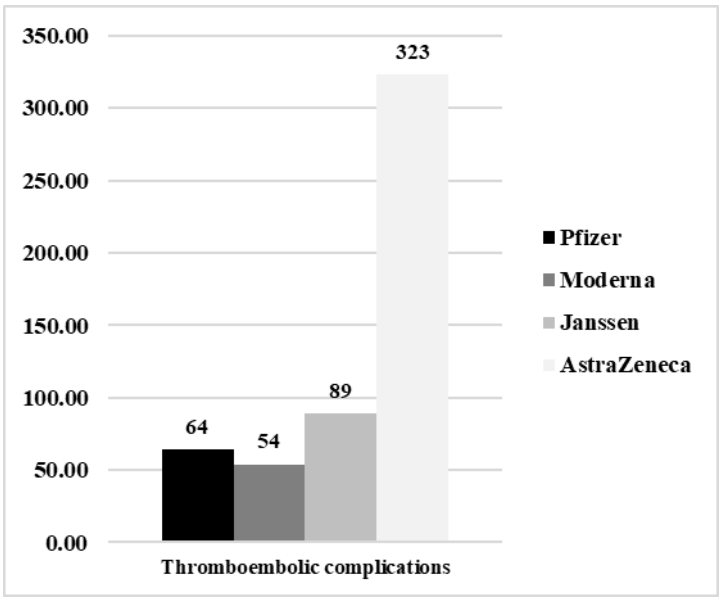

Fig. 2. Comparison of the number of thromboembolic complications reported as a complication of the vaccine

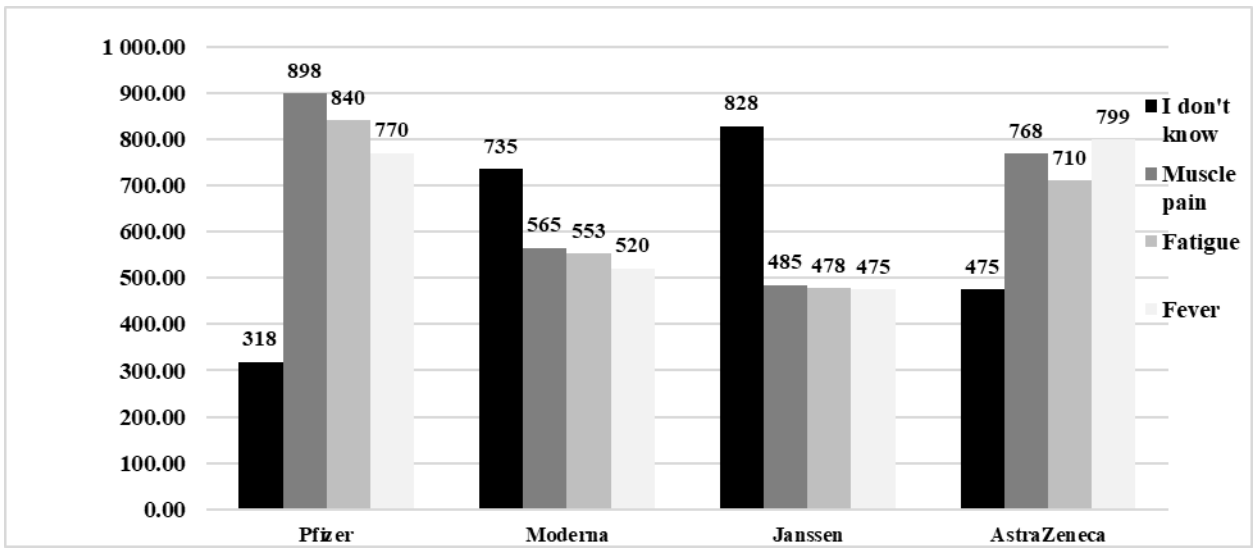

Fig. 3. Most common responses to the questions about complications after receiving a COVID-19 vaccine

Table V. Sources of information on vaccination complications, by sex, education, age, and place of residence [% (n)]

Parameters	Internet forums	Doctors	Family members/Friends	Conventional media	Official government websites	Vaccine leaflets	Social media
1	2	3	4	5	6	7	8
Sex							
Women	23.80 (279)	26.80 (313)	19.20 (225)	20.30 (238)	24.80 (290)	32.10 (376)	28.40 (332)
Men	23.00 (68)	24.40 (71)	17.90 (52)	13.70 (40)	22.70 (66)	27.10 (79)	22.40 (65)
Education							
Elementary	23.10 (9)	26.60 (10)	23.10 (9)	17.90 (7)	23.10 (9)	30.80 (12)	28.20 (11)
Secondary	27.40 (113)	26.00 (107)	19.20 (79)	20.10 (83)	21.80 (90)	26.20 (108)	29.40 (121)
Higher	22.90 (147)	27.60 (179)	20.60 (132)	21.40 (137)	26.00 (167)	35.60 (228)	27.90 (179)
College student	20.10 (55)	28.80 (79)	16.80 (46)	13.90 (38)	29.60 (81)	35.00 (96)	22.30 (61)
Vocational	21.60 (22)	12.70 (13)	11.80 (12)	14.70 (15)	10.80 (11)	14.70 (15)	25.50 (26)

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1	2	3	4	5	6	7	8
Age group							
≤ 17	25.80 (8)	16.10 (5)	22.60 (7)	29.00 (9)	22.60 (7)	19.40 (6)	35.50 (11)
18–35	24.50 (216)	28.20 (250)	20.70 (183)	15.90 (140)	26.30 (232)	32.90 (290)	26.20 (231)
36–55	23.70 (108)	23.90 (110)	16.40 (75)	22.80 (104)	22.60 (103)	31.80 (145)	28.70 (131)
56–65	13.10 (8)	23.00 (14)	16.40 (10)	27.90 (17)	11.50 (7)	16.40 (10)	24.60 (15)
≥ 66	15.80 (6)	23.70 (9)	7.90 (3)	26.30 (10)	23.70 (9)	21.10 (8)	26.30 (10)
Population of place of residence							
< 50,000	22.34 (172)	25.84 (200)	18.57 (143)	18.44 (142)	21.82 (168)	29.22 (225)	26.88 (207)
50,000–150,000	29.41 (80)	23.16 (63)	16.54 (45)	21.32 (58)	23.53 (64)	30.51 (83)	26.84 (73)
150,000–500,000	20.94 (49)	28.21 (67)	18.80 (44)	16.24 (38)	26.07 (61)	34.19 (80)	26.50 (62)
> 500,000	23.44 (45)	30.21 (58)	23.96 (46)	21.88 (42)	33.85 (65)	36.98 (71)	29.17 (56)

Based on the three questions regarding complications after COVID-19 vaccines, we checked the relationship between the respondents' knowledge and level of education. First, we analyzed the responses to the question "Do you think that SARS-CoV-2 infection may develop as a complication after vaccination against COVID-19?" The correct answer to this question was "no," which was provided by the highest percentage of college students (186; 67.9%), followed by people with higher education, then secondary and elementary education, and with the lowest percentage by those with vocational education (25; 24.51%). Detailed results are presented in Table VI.

Table VI. Responses to the question "Do you think that SARS-CoV-2 infection may develop as a complication after vaccination against COVID--19?" by level of education

Educational level	Chosen answer [% (n)]		
	Yes	No	I don't know
Elementary education	2.56 (1)	46.15 (18)	51.28 (20)
Secondary education	12.14 (50)	45.87 (189)	42.00 (173)
Higher education	14.04 (90)	61.15 (392)	24.80 (159)
College student	9.49 (26)	67.90 (186)	22.63 (62)
Vocational education	18.62 (19)	24.51 (25)	56.86 (58)

Next, we analyzed the responses to the question "Do you think everyone receiving the COVID-19 vaccine will experience complications?" The correct answer to this question was "no," which was most frequently chosen by current students (256; 94.16%), followed by people with higher, elementary, or secondary education, and least often by those with vocational education (74; 72.55%). The answer "I don't know" was most often chosen by the respondents with vocational education, and least often by students, as in the previous question. Detailed data is presented in Table VII.

Table VII. Reponses to the question "Do you think that everyone receiving the COVID-19 vaccine will experience complications?" by level of education

Educational level	Chosen answer [% (n)]		
	Yes	No	I don't know
Elementary education	2.56 (1)	87.18 (34)	10.26 (4)
Secondary education	3.16 (13)	85.20 (351)	11.65 (48)
Higher education	2.50 (16)	90.95 (583)	6.55 (42)
College student	1.45 (4)	94.16 (258)	4.38 (12)
Vocational education	5.88 (6)	72.55 (74)	21.57 (22)

We analyzed the responses to the question "Can a severe allergic reaction occur after administration of the COVID-19 vaccine (regardless of its type and manufacturer)?" An affirmative answer, which was the correct one, was chosen by the greatest number of students (237; 86.50%) and people with higher education (518; 80.81%), followed by people with secondary education (275; 66.75%), vocational, and least often by those with an elementary-school education (22; 56.41%; Table VIII).

Table VIII. Responses to the question "Can a severe allergic reaction occur after administration of the COVID-19 vaccine (regardless of its type and manufacturer)?" by level of education

Educational level	Chosen answer [% (n)]		
	Yes	No	I don't know
Elementary education	56.41 (22)	15.38 (6)	28.21 (11)
Secondary education	66.75 (275)	7.52 (31)	25.73 (106)
Higher education	80.81 (518)	4.52 (29)	14.66 (94)
College student	86.50 (237)	3.28 (9)	10.22 (28)
Vocational education	57.84 (59)	3.92 (4)	38.24 (39)

The next area for analysis was the relationship between the concerns about complications and sex and age. Women expressed concerns about complications after COVID-19 vaccination more often than men: 29% (335) and 16% (48), respectively. Among the vaccinated respondents, those in the 56–65 age group (43%; 26) feared the potential complications the most. The least fears were expressed by the respondents in the 18–35 age group (24%; 210). Detailed data is presented in Table IX.

We then analyzed the relationship between the specific vaccine administered and the presence of fears about complications. Fears of complications after receiving the COVID-19 vaccine were declared by significantly more people vaccinated with the Janssen vaccine (33.83%; 45) than those vaccinated with other products. The least concerns were expressed by the group that received the Moderna vaccine (19.71%; 27), while among respondents vaccinated with products from Pfizer/BioNTech and AstraZeneca, the proportions were comparable (26.3% – 237 and 25.6% – 76, respectively; Figure 4).

Table IX. Relationship between age and the fear of complications after COVID-19 vaccination

Fear of complications	Age group [years]				
	≤ 17	18–35	36–55	56–65	≥ 66
Yes	32.26% (10)	23.81% (210)	27.85% (127)	42.62% (26)	31.58% (12)
No	67.74% (21)	76.19% (672)	72.15% (329)	57.38% (35)	68.42% (26)

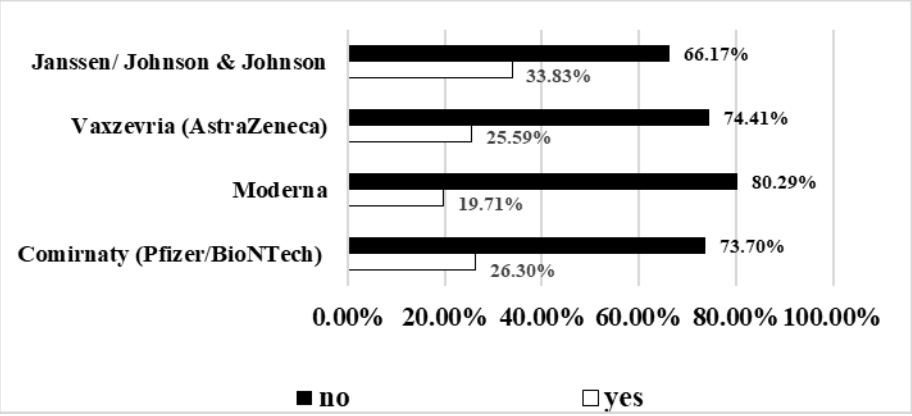

Fig. 4. Relationship between the brand of vaccine and the presence of fears about complication

DISCUSSION

Since the announcement that vaccines against COVID-19 were in development, the population has been polarized regarding their efficacy and safety. Suspicion towards vaccines was reinforced by numerous "fake news" reports and infographics of unverified information shared on social media and distributed in the form of leaflets and posters [30].

The COVID-19 incidence by group and the vaccination status by age and sex among our respondents coincided with the current epidemiological situation in Poland [19]. The vaccination rates also matched Polish statistics (58.96%; 22.59 million) [17]. Almost half of our vaccinated respondents (694; 47.3%) reported having experienced side effects from the vaccine. In comparison to other research, this number is higher than some [31] but lower than others [32,33]. This difference between the numbers of respondents who reported side effects may have been caused by the huge disparity in sample size in each study. The most frequently reported side effects – fatigue, muscle pain, and fever – corresponded with other publications [32,33,34].

Comparing the answers regarding the most common complications after the Comirnaty vaccine to its leaflet, the top three side effects mentioned by the respondents – muscle pain (898; 26.82%), fatigue (840; 25.08%), and fever (770; 22.99%) – were indeed listed as very common side effects, which may affect more than 1 in 10 people [35]. However, according to the "Report on Adverse Events Following Immunization (AEFI)," from Poland's National Institute of Public Health – National Institute of Hygiene (NIPH––NIH) – based on data collected between December 27, 2020 and August 29, 2021 – the most common AEFI following administration of the Comirnaty vaccine was redness and short-term pain at the injection site. This mild AEFI accounted for 80.5%

(4,076) of all Comirnaty vaccine adverse reactions reported to the NIPH–NIH [36,37]. The most frequently reported among severe AEFIs was fever (272; 64.9%). The next most common serious reaction was a severe injection site reaction (148; 20.2%) [36].

Most of the respondents (735; 26.51%) did not know the most common side effects of the Moderna vaccine. The most frequently chosen adverse reactions, as with the Comirnaty vaccine, were muscle pain (565; 20.38%), fatigue (553; 19.94%), and fever (520; 18.75%), which were listed as very common side effects in the vaccine leaflet [38]. In the NIPH–NIH report, the most frequently reported AEFI related to vaccination with Moderna was redness and short-term pain at the injection site, which accounted for 89.9% (1,073) of all AEFIs [36,37]. The most frequently reported serious AEFI was fever (37; 38.1%); another adverse reaction was severe injection site reaction, which accounted for 36.1% (35) of severe AEFIs [36].

When asked about the most common adverse reactions to the Janssen COVID-19 vaccine, most respondents did not know what complications were most commonly associated with this vaccine (828; 30.39%). The respondents identified muscle pain (485; 17.80%), fatigue (478; 17.54%), and fever (475; 17.43%) as the most common adverse reactions. In the Summary of Product Characteristics, muscle pain and fatigue were listed as very common adverse reactions, occurring in more than 1 in 10 individuals, while fever was a common adverse reaction, occurring in less than 1 in 10 vaccinated individuals [39]. The NIPH-NIH report indicated that for the Janssen vaccine, the most common AEFI was redness and short-term soreness at the injection site, accounting for 87.8% (475) of all reported AEFIs [36,37]. The most commonly recorded serious AEFIs were fever (18; 40%), severe injection site reaction (9; 20%), convulsions (9; 20%), and loss of consciousness (8; 17.8%) [37].

Our respondents considered fever (799; 21.07%]), muscle pain (768; 20.25%), and fatigue (710; 18.72%) to be the most common complications after Vaxzevria. These side effects were listed as very common adverse reactions in the Summary of Product Characteristics for Vaxzevria [40]. In the NIPH-NIH registry, the most common adverse reaction, as with other vaccines, was redness and short-term soreness at the injection site, accounting for 88.3% (3,814) of all recorded AEFIs [36,37]. Likewise, the most common serious AEFI caused by the Vaxzevria vaccine did not differ from those documented with other vaccines. Fever was the most common (272; 64.9%), followed by injection site reaction (113; 26.9%) and muscle and joint pain (73; 17.4%) [36].

Our research suggested that thromboembolic complications after receiving AstraZeneca were more frequent in comparison to other vaccines. This is confirmed by other studies, which show that the occurrence of thromboembolic disorders after receiving AstraZeneca is higher than for other vaccines, but is still not high enough to be classified as a very common complication [41,42]. It is worth noting that even despite the increased risk of a thromboembolic event after vaccination with Vaxzevria, it is still lower than in the case of COVID-19 infection [43].

Out of all vaccinated respondents, more women than men expressed concerns about potential side effects from vaccination. Interestingly, females were also more likely to report post-vaccination side effects, according to published research [31,32].

The respondents were asked three questions regarding the side effects of COVID-19 vaccination. The first was “Do you think that SARS-CoV-2 infection may develop as a complication after vaccination against COVID-19?” As none of the approved vaccines contain live SARS-CoV-2 virus, it is impossible to develop infection as a result of receiving the vaccine [44]. The next question was “Do you think anyone receiving the COVID-19 vaccine will experience complications?” As the statistics show, not every person will develop complications. The percentage of complications varies in different studies, depending on the type of vaccine and the characteristics of the study group [31,32,33,34]. Lastly, the interviewees were asked “Can a severe allergic reaction occur after administration of the COVID-19 vaccine (regardless of its type and manufacturer)?”

Severe allergic reactions may occur with any COVID-19 vaccine, regardless of its type or manufacturer [45,46]. The National Institute of Public Health – National Institute of Hygiene’s “Report on Adverse Events Following Immunization (AEFI) after COVID-19 Vaccines in Poland” between December 27, 2020 and August 29, 2021 provided the following numbers of serious allergic reactions reported as serious AEFIs: Pfizer vaccine – 53, AstraZeneca – 10, Janssen – 8, and Moderna – 2 [36,37].

It might be worth mentioning the fact that, because the questionnaire was completed by the respondents shortly after vaccination and some of them had only received one dose at that time, the actual side effects might have been slightly higher. The disparity between the number of women and men in this study might have also influenced some of the results.

There is still a need for observational research on the safety of each vaccine. The patients should be clearly

informed not only about the benefits they can gain from vaccination, but also the risk of postvaccination side effects.

CONCLUSIONS

1. The participants had the most knowledge about complications that may occur after vaccination with the Comirnaty vaccine.
2. The majority of respondents did not know what complications may occur after vaccination with the Janssen and Moderna vaccines.
3. In the case of the Vaxzevria vaccine, the respondents more often choose thromboembolic disorders as the most common complication in comparison to in other vaccines.
4. People with higher education and current college students used vaccine leaflets as a source of information about complications most often, while people with vocational education used them least often.
5. People with vocational education searched for information least frequently.
6. People in the 56–65 age group searched for information about complications after COVID-19 vaccination least often.
7. Social media was the most common source of information in the ≤ 17 age group.
8. Vaccine leaflets were the most common source of information in the 18–35 and 36–55 age groups.
9. College students and people with higher education most frequently mentioned vaccine leaflets, official government websites, and family doctors/medical specialists as sources of information.
10. Respondents with vocational education based their knowledge mainly on social media and internet forums.
11. Respondents in the 56–65 age group were the most concerned about complications after vaccination.
12. People vaccinated with the Janssen vaccine were definitely more concerned about complications from vaccination than participants vaccinated with other vaccines.
13. Complications after vaccination were more common in people who had searched for information about complications.
14. Along with increasing population in the place of residence, the percentage of people who used vaccine leaflets and official government websites as sources also increased.
15. Both sexes most often turned to vaccine leaflets for information about complications after vaccination.
16. Women searched for information about complications slightly more often than men and they used each source of information more often.
17. Women more often than men were more concerned about complications that may occur after vaccination.
18. College students, followed by people with higher education, were least likely to answer "I don't know" to the questions about complications after COVID-19 vaccination. This made these groups the most confident in their knowledge of the subject.

Authors' contribution

Study design – T. Męcik-Kronenberg, A. Biela, N. Zaboklicka, Z. Puszczewicz, M. Stachura, J. Wypyszyńska
Data collection – A. Biela, N. Zaboklicka, Z. Puszczewicz, M. Stachura, J. Wypyszyńska
Data interpretation – N. Zaboklicka, J. Wypyszyńska, M. Stachura, A. Biela, Z. Puszczewicz, T. Męcik-Kronenberg
Statistical analysis – J. Wypyszyńska, Z. Puszczewicz, A. Biela, N. Zaboklicka, M. Stachura
Manuscript preparation – M. Stachura, Z. Puszczewicz, A. Biela, J. Wypyszyńska, N. Zaboklicka, T. Męcik-Kronenberg
Literature research – Z. Puszczewicz, N. Zaboklicka, M. Stachura, J. Wypyszyńska, A. Biela

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PRACA POGLĄDOWA
REVIEW

Interventions aimed at improving the eating habits of medical students

Interwencje ukierunkowane na poprawę nawyków żywieniowych studentów medycyny

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ABSTRACT

Eating habits refer to the amount, type, and composition of the food that is consumed. They are shaped on many levels, by cultural, demographic, and social aspects. Education and profession also contribute to the formation of specific eating habits. Numerous studies have shown that healthcare workers have better knowledge of nutrition than the population at large. Given this context, medical graduates, including doctors, who will work to promote health in their future careers, should strive to develop and encourage healthy eating behavior among their peers, particularly students. The aim of this paper is to gather and analyze the available literature on eating habits and their potential effects on the health of medical students, as well as to document interventions to change eating behavior.

KEYWORDS

eating habits, medical students, dietary change, educational interventions

STRESZCZENIE

Termin „nawyki żywieniowe” odnosi się do ilości, rodzaju oraz składu spożywanych pokarmów. Kształtują się one na wielu płaszczyznach, w sferze kulturowej, demograficznej, a także społecznej. Wykształcenie oraz wykonywany zawód również przyczyniają się do kształtowania określonych nawyków żywieniowych. Liczne badania wykazały, iż pracownicy opieki zdrowotnej mają większą wiedzę na temat żywienia niż reszta społeczeństwa. W tym kontekście absolwenci kierunków medycznych, w tym lekarze, którzy w przyszłości będą wspomagać działania promujące zdrowie, powinni rozwijać i promować prawidłowe zachowania żywieniowe wśród swoich rówieśników, a zwłaszcza studentów. Celem pracy jest zebranie i analiza dostępnej literatury przedmiotu na temat nawyków żywieniowych i ich potencjalnego wpływu na zdrowie studentów medycyny, a także udokumentowanie stosowanych interwencji, mających na celu zmianę zachowań żywieniowych.

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nawyki żywieniowe, studenci medycyny, zmiana sposobu żywienia, interwencje edukacyjne

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Introduction

Eating habits refer mainly to the amount, type, and composition of food consumed. They are considered to be non-specific, repetitive behaviors that serve the need to provide nutrients and achieve social and emotional goals [1]. Our habits are shaped by cultural, demographic, and social factors [2]. Education and profession may also contribute to specific eating habits, as in the case of medical doctors and dietitians [3]. Some studies have shown that healthcare workers (doctors and dietitians) have better nutrition knowledge than the general public. Taking this fact into account, graduates of medical studies – including medical doctors – who will promote health in their future work, should engage in proper eating behavior themselves, especially because the medical profession enjoys a high level of trust regarding lifestyle advice, including a healthy diet [4].

The review of the literature on the subject also indicates regional differences in dietary habits depending on gender and ethnicity, which in turn impact the incidence of obesity or overweight in the given populations. Studies of the American population have shown, among other things, that men, blacks, and Latinos have a higher risk of being overweight and obese than whites. The lowest risk of overweight and obesity was observed in Asians [5].

It has also been shown that medical students rarely begin their studies with good dietary habits [6]. Therefore, it is essential to take corrective action to improve this. There are many well-known and documented nutritional interventions for medical students, for example, adding content that deals with nutrition to the curricula for clinical and preclinical subjects [7]. Research is essential to evaluate the dietary habits of medical students and to explore ways to improve these habits through education and other activities. This highlights the importance of preventing potential complications arising from poor nutrition [8].

The well-known report on public health by the Canadian Minister of Health, Marc Lalonde (1974), pointed out how crucial "lifestyle" is for the population's health [9]. He proposed that promoting a healthy lifestyle can improve the population's health, reducing the demand for medical care. The concept of New Public Health involves comprehensive scientific procedures aimed at maintaining and improving the population's health by shaping healthy lifestyle habits, including proper nutrition. The medical community, including medical doctors, nurses, and dietitians, actively participates in these tasks [10].

The paper collects and analyzes the available published data on eating habits and their potential impact on the health of medical students, and it documents the interventions used to change eating behavior.

Methods

The literature review used publications in Polish and English from the PubMed database and the search engine Google Scholar. The following keywords were used: "eating behaviors," "medical students," "educational interventions," "dietary habits," "dietary changes," "eating habits influences," "health professionals," and their various combinations. Most of the studies included in this review were in English, and only a few Polish-language articles on eating habits or nutritional interventions among medical students were identified. It should be noted that this is not a systematic literature review, and that only publications from 1990 to 2024 were included in the analysis. It presents a review of 22 full-text papers and 16 abstracts.

Diet and health

Proper nutrition is crucial for human health, alongside regular physical activity. It has been proven that improper nutrition can lead to the development of many diseases, including obesity, lipid and carbohydrate metabolism disorders, rickets, atherosclerosis, diabetes, and tooth decay [11]. Programs that promote healthy lifestyles emphasize the principles of proper nutrition, which provide the necessary nutrients for optimal functioning. A review of the available published data highlights the effectiveness of different diets and beliefs surrounding healthy nutrition. One common belief is that individuals should consume five balanced meals each day, aligned with the recommendations of the current food pyramid [12]. According to experts, a balanced diet is essential for optimal health, growth, and development, so medical doctors are expected to help promote proper nutritional behavior. For decades, the dominant dietary pattern has been a balanced, mixed diet, including plant and animal foods, but this is now widely debated [13].

New dietary patterns are evolving rapidly [14], so correct nutritional advice from physicians can be more challenging to provide in the face of numerous media discussions and aggressive advertising. These circumstances directly affect nutritional knowledge, preferences, purchasing behavior, consumption patterns, and diet-related health [15]. For example, nutraceuticals, defined as foods or food substances that provide medical or health benefits, have a global market and are promoted through various channels in which advertisers refer to the results of clinical trials [16]. Proper nutrition includes proper eating habits, appropriate composition of meals that provide all the

body's energy requirements, and all basic and essential nutrients needed for optimal development and health [17]. The most critical issues are considered to be the need to increase the fiber content and reduce fat intake in one's daily diet, a fluid intake that is appropriate for one's age, health condition, and physical activity, and limited consumption of alcoholic beverages, which according to the International Agency for Research on Cancer (IARC) are considered a human carcinogen [18]. The relationship between alcohol abuse and the presence of depression or suicidal thoughts in medical students and young doctors has been well documented [19], which is why one of the essential recommendations for this group is to stop drinking alcohol frequently and regularly [20].

In a study conducted by Sanne and Bjørke-Monsen [21], most Norwegian medical students declared consuming various food products daily, but at the same time had a healthy negative attitude to meat, preferring fish to meat. It is worth adding that more than half of the respondents never ate lean fish, but usually fatty fish. Among the students who eliminated meat from their daily meals, women were more prevalent than men, and they were more interested in modifying their diet. The most commonly used supplement was cod liver oil or omega-3 fatty acids. In turn, a British study showed that most students believed that white meat was healthier than red meat, which increased the consumption of white meat in everyday diets [22]. It is worth adding that in recent years, in many countries around the world, we have observed excessive consumption of meat, especially red and processed meat, which has a noticeable impact on the health of the population and is also harmful to the environment [23]. In a questionnaire study conducted on a group of 250 medical students and 148 resident physicians employed in primary health care, an electronic, shortened version of the REAP-S questionnaire was used to assess nutritional status. The questionnaire consisted of 13 questions and the answers were rated on a scale of 1 to 3. The results suggest that the respondents maintained a proper diet. In summary, the authors stated that early detection of nutritional irregularities and nutrition improvement are crucial in preventing potential adverse health effects in future primary healthcare employees [24].

The impact of nutritional interventions on health

As mentioned above, there is a consensus that an unhealthy diet is a significant factor in the global burden of disease, and the obesity epidemic remains a major public health problem in many regions of the world [25]. The public's continuing interest in the issue of healthy nutrition, along with the intensive advertising of food products and dietary supplements, makes it necessary to involve medical personnel (including physicians) more in communicating reliable knowledge about healthy nutrition. Without appropriate tools to facilitate the transfer of current evidence-based knowledge, it is impossible to have an informed discussion with patients who need help changing their eating habits. Most patients still treat physicians' recommendations regarding a healthy lifestyle with respect, strengthening their real impact on improving or maintaining patients' health [26].

Despite comprehensive medical school curricula that address the significance of diet for human health, there is no material that empowers potential patients to modify their eating habits [27]. In a study by Berz et al. [28], the impact of interactive monthly meetings on improving dietary patterns for weight loss and hypertension was assessed among senior medical students (90–120 minutes of educational sessions). The eight-month study involved 66 students, of whom only 42 (63.6%) completed a questionnaire summarizing the class. According to them, the interactive sessions were beneficial. The content provided during the classes significantly improved the participants' knowledge and improved their confidence in their competencies. The study's authors also emphasized the importance of repeating the content multiple times to consolidate knowledge and develop counseling skills during medical studies. Similar conclusions were reached by Christensen et al. [29], who tried to assess the impact of knowledge about nutritional therapies among medical students. Including elements of nutrition education in an optional mode turned out to be an effective, efficient method of teaching medicine. In addition, students' attitudes and trust in nutritional counseling, among other things, improved significantly because they were involved in discussions and practical exercises. Therefore, evaluating the effectiveness of nutritional education interventions is essential for their widespread implementation [30].

Patel and Kassam [31] reviewed the literature published between 2015 and 2020 on nutritional education interventions for medical students. Fifteen interventions met the criteria for inclusion in the review, twelve of which were from the USA. The interventions consisted of several methods, such as cooking sessions, lectures, and classes led by dietitians. The publication highlighted the benefits of interprofessional communication, emphasizing individual students' health behavior. The results of a German study are interesting, showing that the main barriers to healthy eating among students are a lack of time due to studying, a lack of nutritious meals in the university canteen, and high prices of nutritious food [32]. Furthermore, the authors demonstrated that these issues primarily affect first-year students, and they emphasized the need for qualitative research to

understand why university students alter their eating behavior during their studies. Similarly, the results of a study on medical students in Australia indicate the need for interventions in people who reported the worst eating habits, including younger students and men [33]. Research on the eating habits of students in Great Britain highlighted the need for universities to encourage students to cook their own food, as well as to improve the availability of affordable, healthier food options [34]. In the above-cited Norwegian study, the authors indicated the need to modify the curricula in medical universities so as to enable future doctors to use reliable knowledge about nutrition consciously (eliminating the influence of social media or food industry marketing) [21]. The results of a cross-sectional study on medical students in Riyadh indicate a need for intervention to mitigate the effects of negative emotions, such as stress, aggression, and boredom, on students' overeating [35]. It was shown that students eat irregularly and consume too much fast food. The authors suggest initiating health promotion programs as early as possible. As mentioned above, there are a few works by Polish authors on nutritional interventions in medical students. Experts suggest that we need more effective programs and methods for improving nutritional education and raising motivation to change health--related behavior in students of Health Sciences, especially in overweight or obese individuals, or those with lower activity levels [36]. This becomes particularly important during exam sessions, when a significant deterioration in daily eating habits was observed [37]. The authors of that work confirmed that the body composition and metabolic rates of medical students in Wrocław changed, deteriorating their health status. Another study revealed that medical students and doctors scored the highest values on the Non-Healthy Diet Index among health professions [38]. In the discussion, the authors stated that physicians recalled having limited or inadequate nutrition education in medical school. The experts concluded that high-quality continuing nutrition education should be provided to all healthcare providers, including medical students and doctors.

Conclusions

The review of existing publications reveals regional differences in the nutritional habits of medical students, highlighting the need for tailored intervention programs to improve these behaviors. Despite these differences, there is a consensus on the individual, socioeconomic, and environmental factors that influence these habits. Key factors include students' place of residence, their year of study, the stress they experience during exam periods, and their participation in student organizations. Among the recommended nutritional interventions, the most successful approaches involve actively engaging students in the practical preparation of meals and menus and encouraging university authorities to enhance the nutritional offerings in student cafeterias.

Authors' contribution

Study design – M. Kowalska
Data collection – A. Jarosińska
Manuscript preparation – A. Jarosińska, M. Kowalska
Literature research – A. Jarosińska
Final approval of the version to be published – M. Kowalska

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PRACA POGLĄDOWA
REVIEW

Single nucleotide variants of *MBD5* in two cases of children with mutations in the sodium channel gene *SCN1A* and *SCN9A* and a review of the literature

Warianty pojedynczego nukleotydu *MBD5* u dwojga dzieci z mutacjami w genie kanału sodowego *SCN1A* i *SCN9A* oraz przegląd literatury

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ABSTRACT

Genetic factors, especially polymorphisms being a consequence of mutations in the genome, are of great importance in the etiology of drug-resistant types of epilepsy. This paper describes the cases of two patients with a very similar course of disease, both of whom were diagnosed developmental disorders, drug-resistant epilepsy and autism spectrum disorders. Both patients have *MBD5* missense mutations, while each case characterized with a different sodium channel mutation: in the case of patient 1, a 5-year-old girl, *SCN1A* gene mutation was observed, and in the case of patient 2, a 6-year-old boy, *SCN9A* mutation was recognized. No currently published articles available in medical literature have described cases with such co-occurrence of mutations so far. In both cases presented here, the recommended pharmacological treatment has not been successful, which may indicate the ineffectiveness of conventional antiseizure medications and suggest focusing on more targeted therapies.

KEYWORDS

drug resistance, epilepsy, developmental disorders, autism

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STRESZCZENIE

Czynniki genetyczne, zwłaszcza polimorfizmy będące konsekwencją mutacji w genomie, mają duże znaczenie w etiologii lekoopornych typów padaczki. W pracy opisano przypadki dwojga pacjentów o bardzo podobnym przebiegu choroby, u których zdiagnozowano zaburzenia rozwojowe, padaczkę lekooporną i zaburzenia ze spektrum autyzmu. U obojga pacjentów stwierdzono mutacje *missense* genu *MBD5*, natomiast każdy z przypadków charakteryzował się inną mutacją kanału sodowego: w przypadku pierwszej pacjentki, 5-letniej dziewczynki, zaobserwowano mutację genu *SCN1A*, w drugim przypadku, u 6-letniego chłopca, rozpoznano mutację *SCN9A*. Dotychczas w literaturze medycznej nie opublikowano artykułów opisujących przypadki z takim współwystępowaniem mutacji. W obu przedstawionych przypadkach zalecane leczenie farmakologiczne nie przyniosło rezultatów, co może wskazywać na nieskuteczność konwencjonalnych leków przeciwpadaczkowych i sugerować skupienie się na bardziej ukierunkowanych terapiach.

SŁOWA KLUCZOWE

lekooporność, padaczka, zaburzenia rozwojowe, autyzm

INTRODUCTION

Genetic factors constitute an important element in the etiology of drug-resistant types of epilepsy. Significant advances in biomedical engineering have allowed the sequencing and identification of genes in patients suffering from epilepsy, which resulted in better clinical evaluation, as well as the development of specific personalized treatments. Among the pathogenic variants *MBD5*, *SCN1A* and *SCN9A* gene mutations can be specified [1].

The *MBD5* gene, located on chromosome 2q23.1 (#OMIM 611472) and encoding a member of the methyl-CpG binding domain (MBD) family that plays critical roles in transcriptional regulation [2], is also involved in nervous system development and behavioral regulation [3].

It contains a PWWP domain which is considered important in cell division, growth, and differentiation [2,3]. *MBD5* disorders can be associated with severe early childhood developmental encephalopathy and epilepsy [4]. The *MBD5* mutation, also referred to as mental retardation autosomal dominant 1 (MRD1) was originally described in the context of the 2q23.1 microdeletion result of which is the pseudo-Angelman syndrome [5]. Majority of phenotypes present in 2q23.1 deletion syndrom stem from haploinsufficiency of *MBD5*, while overexpression of *MBD5* leads to features of 2q23.1 duplication syndrome [3]. Nevertheless, currently used collective term describing a group of disorders associated with *MBD5* gene, *MBD5*-associated neurodevelopmental disorder (MAND), is defined as an autism spectrum disorder (ASD) characterized by intellectual disability, motor delay, severe speech impairment, and behavioral problems [3,6].

SCN1A is a gene that encodes the alpha 1 subunit of the sodium channel, which is associated with many human diseases [7], e.g. Dravet syndrome and migraine, is a member of the voltage-gated sodium channel (VGSC) family (#OMIM:182389) and has been mapped to chromosome 2q24.3 [8]. In 2000, its connection with epilepsy was also confirmed [9]. *SCN1A* is one of four sodium channel genes mainly expressed in the brain and therefore its abnormalities are related to the onset of neurodevelopmental disorders [10]. This results in a broad spectrum of phenotypes, from febrile seizures and generalized epilepsy with febrile seizures (GEFS+) to Dravet syndrome [11] characterized by polymorphic, predominantly febrile, generalized clonic or hemiclonic epileptic seizures usually manifesting in the first year of life [12]. What is more, pathogenic *SCN1A* mutations have been proven not only to occur in subjects with epileptic phenotypes, but they have also been reported in cases of patients suffering from familial hemiplegic migraines, ASDs and arthrogryposis [12]. Pathogenic *SCN1A* variants include missense and truncating variants (nonsense, frameshift and splice site), as well as intragenic microinjuries [13]. A characteristic feature of patients with mild genotypes is high frequency of missense mutations that do not result in protein truncation, whereas in severe phenotypes, missense mutations are less common [14].

SCN9A, which includes 29 exons on chromosome 2q24-q31 (#OMIM 603415) [15], is the gene encoding the alpha sodium voltage-dependent sodium channel unit Nav1.7. Nav1.7 channels placed in dorsal root ganglia and sympathetic neurons [16] play an important role in stimulating cells and gating pain transmission from the peripheral to central nervous system [17]. For that reason, mutations in the *SCN9A* gene have been identified as a cause of pain disorders [18]. Allelic conditions such as primary erythromelalgia (PE), paroxysmal extreme pain disorder (PEPD) and idiopathic small fiber neuropathy (SFN) result from the heterozygous gain-of-function *SCN9A* mutation [19], whereas loss-of-function mutations cause congeneric insensitivity to pain (CIP) and anosmia [20]. These diseases are differentiated by their phenotype, pain distribution and age of onset [15]. Currently suggested therapies for gain-of--function channelopathy include, among other ASDs, medications targeting the sodium channel, as well as

local anesthetics. Unfortunately, abovementioned therapies are inadequate, and symptoms tend to persist throughout life [15].

In the study described in this paper, two cases with *MBD5* missense mutation resulting from a single nucleotide substitution are presented. Moreover, sodium voltage-gated channels (SCN) mutation was proven to be present in both patients. Based on the available medical records, this article aims to present the developmental abnormalities that were present in both cases and which might have resulted from the diagnosed genetic mutations.

CASE REPORTS

Patient 1

The first patient, a 5.5-year-old girl, was diagnosed with epileptic encephalopathy. First epileptic seizures began to appear in the patient's 1st year of life. Since the frequency of seizures noticeably increased, the girl was admitted to the Pediatric Neurology Department at the age of 18 months. The child was from a second pregnancy, second vaginal delivery in the due date, with birth weight 3900 g; she was assigned Apgar score of 10. In the medical history of her relatives, there was a case of epilepsy in her distant family, i.e. her father's cousin. To date, psychomotor development has been described as delayed. She has not achieved milestones on time; she began to sit up at 12 months of age; at the time of the examination, she could stand up with support, and was unable to walk on her own. She did not respond to smiling, verbal contact, and did not react to her name. She did not produce any palm pointing gestures nor play; she chewed clothes and sucked her thumbs. The symptoms listed above, combined with numerous stereotypical behaviors and lack of eye contact, allowed to assume that the child have ASDs. Neurological examination showed 10th percentile head circumference (45.5 cm), decreased muscle tone, and weakly expressed tendon reflexes, especially in the lower extremities. 28 point result of the psychological examination based on the Child Development Scale placed the child under the 1st percentile, which indicated that the psychomotor development was also delayed: she pronounced only single syllables that she was not able to connect, and responded to smiles by smiling and vocalizing.

Electroencephalography (EEG) showed generalized paroxysmal activity. Despite the absence of clinical seizures, valproic acid was included into the outpatient drug treatment. Several weeks after the start of modified pharmacotherapy, due to episodes of immobility with co-occurring cyanosis around the mouth that began to appear, valproic acid was discontinued and changed to levetiracetam. After a brief period of improvement, the frequency of seizures manifested as immobility and cyanosis without convulsions increased to several times per day and they lasted up to 30 seconds. Magnetic resonance imaging (MRI) scan showed normal brain structures. On EEG examination, during hospitalization, the presence of generalized and focal paroxysmal discharges localized to the central-parieto-occipital and mid-thalamo-parietal regions. During video EEG recording, the mother reported alarming disabling incidents. At that time of brain function monitoring, no paroxysmal changes were detected.

Patient 2

A boy aged 6 years 3 months diagnosed with epilepsy and developmental delay was admitted to the Pediatric Neurology Department at the age of 2.5 years for modification of antiseizure treatment and extended diagnosis. The boy was a child from the second pregnancy, born on the due date by vaginal delivery without complications. He received Apgar score of 10/10 points with the birth weight of 4125 g. The history of psychomotor development so far was delayed. The boy started babbling at 9 months, lifted his head from 8 months, sat from 12, stood from 18, crawled from 24 months. On admission, the boy presented with autistic features, without eye and verbal contact. On neurological examination, his head circumference equalled 46.5 cm (4th percentile), also axial hypotonia and spastic paresis of the lower limbs were observed. He could walk supporting himself with his hands while his feet were internally rotated. He could stand up with support and sit up independently from a hands and knees position. The boy did not react to commands and showed no interest in toys apart from grabbing a block with his fingers or manipulating details of toys if brought close enough to his fingers. He did not speak, most frequently uttered single sounds, less often syllables, and responded to his mother's smile with a smile. Psychological examination based on the Child Developmental Scale showed delayed psychomotor development of the child. The boy scored only a few points on the applicable scale.

Patient 2 was hospitalized twice at the age of 7 and 9 months for lasting ca. 2 minutes epileptic seizures that occurred twice per day and expressed themselves in unconsciousness with increased muscle tone, and eye elevation. The EEG recording showed paroxysmal changes, which, set with seizures, allowed to diagnose epilepsy and thus pharmacotherapy with valproic acid was implemented. At the age of 11 months the boy was hospitalized again for atonic seizures which occurred 2–3 times a day. EEG and MRI were performed; epileptiform changes could be observed again in the EEG, while the brain MRI scan showed minor hypoxic-ischaemic lesions. The clinico-

-electroencephalographic correlation was confirmed. On admission at the age of 2.5 years, the patient was taking valproic acid, clobazam (since six months of age) and lamotrigine (since one month of age). The frequency of occurring atonic seizures remained on the level of 2–3 times a day. During hospitalization, the dose of lamotrigine was increased, which resulted in achieving a reduction in the number of seizures. EEG recording was abnormal, with multiple paroxysmal changes expressed in the form of numerous, generalized predominantly temporal region, 0.5–4-second paroxysmal discharges consisting of sharp waves, spikes, multi-spikes, sharp wave-slow wave complexes and occasionally spike-wave complexes of 2.4–2.9 Hz with the highest amplitude up to 580 uV in the right medial temporal region. Photic stimulation did not show any additional effect on the EEG. The electroencephalogram showed certain abnormalities and numerous generalized seizure changes; brain MRI, which was also performed again, showed apparent progression of myelination compared to the previous scan.

Molecular analysis

In both cases, the diagnosis was extended by genetic testing. The girl (patient 1) was identified with potentially pathogenic variants in two genes *MBD5* and *SCN1A*: a mutation in the *MBD5* gene with a single nucleotide substitution c.136T>G resulting in a missense mutation (p.Cys46Gly), and a mutation in the *SCN1A* gene with a single nucleotide substitution c3521C>G resulting in a missense mutation (p.Thr1174Ser). Mutations in both these genes were dominant and each occurred in a heterozygous pattern (in one allele of the gene). The boy (patient 2) was also found to have potentially pathogenic variants in two genes. In the *MBD5* gene, as in the case of patient 1, and in the *SCN9A* gene. The mutation in the *MBD5* gene involved a substitution of one c.25G>A nucleotide, resulting in a missense mutation (p.Gly9Arg). The mutation in the *SCN9A* gene involved a substitution of one c2310G>A nucleotide in exon 14 of the gene. The identified mutation was synonymous (it did not change the amino acid sequence of the encoded protein p.Leu770Leu), but due to its location in the exon/intron junction region (the splicing donor site), it may affect the correct folding of the transcript. Mutations in both genes were dominant and occurred in a heterozygous pattern.

DISCUSSION

In both patients presented, performed genetic testing showed heterozygous missense mutations of the *MBD5* gene involving a single nucleotide substitution that may potentially be of pathogenic character. While *MBD5* deletion or duplication may contribute to a genetic predisposition to ASDs, intellectual disability or epilepsy, the impact of rare single nucleotide variants (SNVs) of *MBD5* on neurodevelopmental traits has not been fully investigated [21]. Rare heterozygous *MBD5* variants were proven to be associated with the clinical heterogeneity observed in a wide range of neurodevelopmental disorders, including ASD [21].

Disruption of *MBD5* gene function has been reported to constitute a direct cause of a syndrome called MAND involving intellectual disability, severe speech impairment, epilepsy, psychiatric features of aggression and hyperactivity, and dysmorphic features including short stature and microcephaly, sleep disorders and ataxia [3,4]. MAND is a collective term describing a group of disorders associated with *MBD5* variants, which can include chromosomal deletions, duplications, disorders or intragenic single nucleotide alterations covering 2q23.1 deletion syndrome and 2q23.1 duplication syndrome. The aforementioned disorders share a common set of neurodevelopmental, cognitive, and behavioral abnormalities, but may differ in frequency and severity of symptoms [3,4]. Individuals with pathogenic variants in *MBD5* characterize with a similar but typically milder 2q23.1 deletion syndrome-like phenotype, while individuals with *MBD5*-including 2q23.1 duplication have a phenotype similar to the ones with 2q23.1 deletion. Every individual with an *MBD5* genetic anomaly is unique [3].

The clinical characteristics of presented patients with *MBD5* variants were examined retrospectively from medical records. Each case was evaluated for clinical symptoms and psychomotor development based on available sources about disruptions in the *MBD5* gene and their impact on the occurrence of developmental disorders. The clinical manifestations noticed in the case of patient 1 and patient 2 (Table I) matched those often present in MAND, including severe intellectual disability, language delay, seizures, autistic-like symptoms, stereotypical movements and motor delay [6,22]. Failure in reaching normal childhood developmental milestones in both cases contributed to

the diagnosis of neurodevelopmental disorder. The literature reports that congenital microcephaly, dysmorphic features, sleep disturbances and feeding difficulties can occur in MAND [3,6,22]. However, in none of the two patients microcephaly, craniofacial dysmorphia or skeletal changes were reported. However, it needs to be noticed that in none of the patients any mention of sleep disorders or feeding difficulties was made.

Table I. Clinical presentation (patient 1 and patient 2)

Features	Patient 1	Patient 2
Variant of *MBD5* mutation	c.136T>G	c.25G>A
Gender	F	M
Age in which examination was conducted (in years)	1.5	2.5
Developmental delay	+	+
Seizures	+	+
Speech impairment	+	+
Sleep disturbances	N	N
Behavioral problems	+	+
Feeding difficulties	N	N
Autisitc-like symptoms	+	+
Stereotypic repetitive behavior	+	+
Hypotonia	+	+
Skeletal abnormalities	N	N
Dysmorphic features	N	N
Microcephaly	–	–
Ataxic gait	+	+
Hyperphagia	N	N
Cardiovascular abnormalities	N	N

M – male; F – female; (+) feature present; (−) feature absent; N – not reported.

Both patients were identified ASD, symptoms of which included language deficits, social withdrawal and stereotypes. Currently, more than 100 genes and genomic regions have been reliably associated with autism, mostly based on studies of heterozygous, germline *de novo* mutations [23]; one of these genes is *MBD5*, which is critical for normal development. However, the biological role of methyl-CpG-binding domain 5 (*MBD5*) in neurodevelopment and ASD remains largely undefined [5]. Deletion or duplication of *MBD5* has been found to contribute to a genetic predisposition to ASD [24]. Talkowski et al. [25] proposed a mixed model of deleterious, fully penetrant *MBD5* deletions causing neurodevelopmental disorders associated with features of the 2q23.1 microdeletion syndrome and missense variants with reduced penetrance that significantly increase the risk of ASDs. In both cases presented in this paper, the autistic-like symptoms may be determined by the occurrence of SNVs resulting in a missense mutation.

In addition, the *SCN1A* mutation, which has been recognized as a constituent of ASDs as well, is also present in the case described in this article. Pathogenic variants of *SCN1A* and *SCN2A* have been identified in genetic studies of patients with ASD, which indicates its genetic etiology. Loss-of-function variants of these two genes have been recognized in post-mortem brain DNA testing of ASD patients [26]. Majority of available study publications mentions lack of verbal communication, social problems, poor peer relationships, withdrawn behavior and lack of emotional reciprocity as autistic features in patients [7]. The patient with *SCN1A* presented in this paper does not maintain eye contact, does not respond to smiles or words, and presents numerous motor stereotypies.

Myers et al. [4] analyzed the phenotypes of a global cohort of twenty-three people patients with *MBD5* deletion, duplication or point mutation and a history of epileptic seizures and found a spectrum of phenotypes associated with pathogenic *MBD5* variants that often resulted in severe developmental and epileptic encephalopathy in early childhood. Seizure incidence started at a median age of 2.9 years (range 3 days to 13 years), which suggests that the onset of epileptic seizures can occur at different stages of childhood. Developmental disorders were present in all patients: severe in 14, moderate in 8 and mild in 1. Prominent behavioral difficulties were noted in 16 patients. Childhood sleep disorders were reported in 17 patients and involved frequent nighttime awakenings. Jing et al. [27] also evaluated the clinical phenotypes and genetic features of epilepsy in 9 children with variants of the *MBD5* gene. *MBD5* gene variants include single nucleotide variations and deletions. Age of seizure onset ranged from 5 to 89 months, and multiple seizure types were observed. All patients expressed symptoms of developmental delay before the seizures started to occur: nine patients had marked language delay, and six patients had autism-like symptoms.

The heterogeneity of the *SCN1A* mutation, combined with a wide phenotypic spectrum, makes interpretation of patients' genetic tests challenging for clinicians [28]. *SCN1A* mutation can cause heterogeneous clinical phenotypes such as febrile seizures, febrile seizures plus, unclassified seizures and self-limiting focal childhood epilepsy [29]. In addition, Dravet syndrome, severe developmental and epileptic encephalopathy are caused by missense and truncation variants of the *SCN1A* protein. Patients affected by this mutation typically characterize with behavioral, motor and cognitive disorders, including depression and stroke-like episodes [30,31]. The c.3521C>G mutation in the *SCN1A* gene present in patient 1 has also been noticed in described cases of patients whose hemiplegic migraine symptoms were incidental to epilepsy symptoms [32]. Unlike other sodium channel

mutations, in which symptoms start to appear in the neonatal or early infantile period, the onset of seizures caused by the *SCN1A* mutation usually occurs in the period of infancy [28]. Patient 1, a girl with *SCN1A* mutation, diagnosed with epileptic encephalopathy, was admitted to the Pediatric Neurology Department at 18 months of age because of an increased seizure frequency. Article by Scheffer and Nabbout [7] reported that, in the case of such patients, the development usually progresses normally in the first year of life, but then rapidly slows down, usually leading to intellectual disability; patients show delayed motor skills, speech and language, as well as social skills [8]. Patient 1, presented in this article, did not reach normal milestones for her age and presented delayed psychomotor development. Problems appeared also in the area of speech and word formation.

Mutation in the *SCN9A* gene is expressed in different genotype-phenotype forms. Some patients with *SCN9A* mutation meet clinical criteria for erythromelalgia, which include the presence of severe, temperature-related pain and erythema in the feet, hands and ears (aggravated by heat and relieved by cold) [33]. The described boy with the *SCN9A* mutation does not present the abovementioned characteristics, which may be related to the young age of the patient, as cases of onset of symptoms at the age of 6 years are described in the literature [34]. In addition to erythromelalgia, patients with the *SCN9A* mutation may also show psychomotor retardation along with pain attacks that are resistant to analgesic treatment. Severe pain attacks contribute to reduced social interactions and may lead to self--destructive behaviors (such as self-injury) [15]. The *SCN9A* mutation also causes PEPD, which characterizes with present from birth recurrent seizures with closed or staring eyes, limb stiffness, cessation of crying in the neonatal period, redness of the skin and trunk along with cyanosis in the face and mouth area. While the process of intellectual development of patients with PEPD progresses normally, their motor development is delayed [35]. Another extremely rare disorder caused by loss-of--function mutations in the *SCN9A* gene is CIP. Patients suffering from it are incapable of feeling pain and show no response to injuries [36]. The *SCN9A* mutation is also suspected of being one of the possible causes of epilepsy, but this correlation is still being discussed among the research communities [37]. Albaradie et al. [38] described a patient with an identified *SCN9A* mutation who complained of myoclonic seizures which frequency of occurrence ranging from 10 to 15 times a day. Furthermore, the patient was diagnosed with global developmental delay: even though the patient was walking, he experienced frequent falls due to myoclonic jerks, and tremor impaired his normal daily activities. In addition, the patient had significant difficulties in school. Among the cases of patients with the *SCN9A* mutation and epilepsy described in literature, there is an interesting study of twin sisters. Liu et al. [39] reported on two 10-year-old siblings with a normal birth and developmental history. Their first clonic seizures started to appear at the age of 7 as an incident of a nocturnal clonic seizure involving movements of the right upper limb and an oropharyngeal region, while a generalized tonic-clonic seizure appeared a few months later. The subsequent diagnosis indicated Roland's epilepsy. Similarly, patient 2 reported in this paper was diagnosed with epilepsy and developmental delay, and did not reach normal developmental milestones for his age. A severe reduction in muscle tone, which occurred when he was 2.5 years old, was followed with his significant problems with walking. The patient also showed features of autism, such as short eye contact, difficulty in connecting and lack of speaking, replaced with pronouncing only single sounds. The boy experienced seizures in form of unconsciousness with increased muscle tension and supraduction.

In the article assessing the phenotypic spectrum of seizure disorders in MAND Myers et al. [4] closely examined EEG graphs of patients were abnormal in 17/21 cases, and usually showed slow generalized spike wave complexes and background slowing. An important aspect for this paper is that electroencephalograms of both patients described here presented paroxysmal discharges. In a study described by Jing et al. [27] comparing nine patients with different *MBD5* mutation variants, five patients had slow background activity in the EEG. Interictal EEG showed abnormal discharges in nine patients. It is worth noting that brain MRI was normal in all patients.

EEG in patients with *SCN1A* mutation is normal at the onset of the disease [7]. In the research performed by Kong et al. [28] on a group of patients with these mutations, almost half of the interictal EEG recordings were normal, and more than a half of the recordings showed focal epileptiform discharges. In comparison Ma et al. [8] found epileptiform discharges also in the interictal phase in most of the studied cases. EEG examination of patient 1 presented abnormalities with generalized and focal epileptic discharges.

The patient whose mutation in *SCN9A* caused PEPD on EEG did not present interictal or symptomatic abnormalities [35]. In comparison, the patient with this mutation causing epilepsy on EEG recorded generalized epileptiform discharges and multiple polymorphic seizures [38]. In the abovementioned twin sisters with Roland's epilepsy, the EEG graph showed prominent interictal high-voltage spike and spike-and-slow waves in the bilateral medial temporal

regions, which were exacerbated during sleep [39]. In the reported patient 2, the EEG showed an abnormal recording with multiple paroxysmal discharges.

MAND is usually associated with normal brain neuroimaging or thin corpus callosum with mild hypomyelination in rare cases. There are rare reports of focal cerebral malformations with pathogenic *MBD5* variants but these have been associated with relatively large heterozygous deletions involving loss of multiple genes other than *MBD5* [40,41]. In hereby paper, MRI of both patients showed normal images of brain structures.

Brain MRI examinations in patients with *SCN1A* mutations usually show no abnormalities [7]. Similarly, MRI imaging of brain structures of patient 1 also showed no brain structural changes.

In a paper by Meijer et al. [15] describing an atypical case of SCN9A mutation of a patient with paroxysmal pain attacks, with sweating and erythema of her lower limbs and hands with a slight asymmetry of the anterior ventricular horns on computed tomography scans. In contrast, the patient with PEPD and the patient with congenital insensitivity to pain described in the article by Hua et al. [35], Sun et al. [36] showed no abnormalities on head MRI. In a patient observed in the research by Albaradie et al. [38] diagnosed with epilepsy and a mutation in SCN9A, MRI revealed mild generalized atrophy. In twin sisters from Liu et al. [39] study head MRI was normal. Similarly, in the case of the presented patient with SCN9A mutation, the head MRI showed a brain image within normal limits with apparent progression of myelination compared to the previous MRI.

Epilepsy associated with variants of the *MBD5* gene is usually refractory to treatment [4,27]. Anticonvulsant drugs such as valproate, clonazepam, zonisamide and clobazam usually used in treatment prove to be effective in reducing the incidence of seizures [3]. In a study evaluating the phenotypic spectrum of seizure disorders in MAND ten of the patients had previously been diagnosed drug-resistant epilepsy [4]. Although none of the substances drug was recognized as clearly superior, valproate showed the most consistent beneficial effect (12/14 cases), while carbamazepine exacerbated seizures in one patient. There is currently no cure for MAND, and treatment is based on managing the symptoms of the disorder. Treatment typically involves a combination of therapies, including behavioral and educational interventions, speech and language therapy, as well as physical and occupational therapy [3,42]. Medications may be used to manage specific symptoms, such as epileptic seizures or sleep disturbances. In terms of targeted therapies for the specific *MBD5* mutation, there are currently no approved treatments. However, the ongoing research will allow to develop new therapies and understand the underlying biology of MAND better. Gene therapy and other precision medicine approaches may hold promise for a successful treatment of genetic disorders like MAND in the future [42].

Epilepsy caused by *SCN1A* mutation characterizes with drug-resistance and requires multidirectional therapy [7]. The literature indicates that the most commonly used drugs are sodium valproate and levetiracetam, stiripentol, fenfluramine, cannabidiol, which are effective in reducing seizure frequency [43]. Antiepileptic drugs such as sodium channel blockers may exacerbate the seizures [44]. Most *SCN1A* mutations tend to be of loss-of-function type. Advances in genetic research and more detailed biophysical analysis allowed to discover new mutation variants resulting in an increase in channel function or decrease, as well as a mixture of loss- and gain-of--function. This heterogeneity of mutations is the reason why a treatment effective for one patient, may exacerbate symptoms in another [45]. It is important to individualize patient therapy and gain a better molecular understanding in the aspect of the range of mutation variants.

The individually recommended pharmacotherapy would, thus, depend on the phenotypic form associated with the mutation in the *SCN9A* gene. In erythromelalgia, sodium channel blockers such as mexiletine, lidocaine and carbamazepine are used, however, the scope of information regarding their efficacy is limited [33]. In patients with pain attacks, a partial therapeutic response was achieved with carbamazepine, to which mexiletine was added [15]. A patient with PEPD, treatment with carbamazepine allowed to achieve an improvement in motor skills and reduction in seizure frequency [35]. Another patient with recognized *SCN9A* mutation and epilepsy was treated with sodium valproate, which initially ceased the seizures, but after several months the patient's condition deteriorated and sodium valproate was changed to levetiracetam, which resulted in seizure reduction to some extent [38]. In the case of twins, seizure control was achieved after

administration of oxcarbazepine; however, their pharmacological treatment included levetiracetam as well. After noticing a recurrence of seizures clonazepam was introduced, which resulted in patients remaining seizure-free [39]. The patient described in the paper was treated with valproic acid, clonazepam and lamotrigine. Adjustment of lamotrigine dose reduced the number of seizures, but the boy is still not seizure-free.

CONCLUSIONS

In the study we present two cases of patients with a very similar course of disease, whose common feature is the presence of a missense *MBD5* mutation resulting from a single nucleotide substitution. On this basis, we can speculate that the presence of this mutation results in developmental disorders, epilepsy and ASDs, in each of the presented patients. Nevertheless, patients differ in the co-occurrence of other sodium channel mutations *SCN1A* and *SCN9A*, respectively. To date, no patients with such co-occurrence of mutations have been described. It is not known whether the co-occurrence of both mutations deteriorates the course of the disease in children, but it is certain that these mutations are also linked to developmental disorders, including epilepsy and ASD. Diagnosis of these mutations is extremely difficult, as evidenced by the small number of cases described to date due patients presenting very different phenotypes. Furthermore, the observed differences in genotype-phenotype characters pose another difficulty in terms of patients' comparison and make it impossible to establish a definite treatment. The presented patients suffer from drug-resistant epilepsies, which may indicate that conventional antiepileptic treatment in patients with genetic background of epilepsy is ineffective, and therefore it is worth to focus more on targeted treatments. Also, further follow-up of the patients is required for future delineation of the new phenotype of co-occurrence of some pathogenic variants.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Informed consent statement

Written informed consent was obtained from the patient's parents.

Ethical approval

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Authors' contribution

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Data collection – P. Rozwadowska-Kunecka, M. Rodak
Manuscript preparation – P. Rozwadowska-Kunecka, M. Rodak, J. Paprocka
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PRACA POGLĄDOWA
REVIEW

Exploring the connection between several neurosteroid hormones and first-episode psychosis and schizophrenia: A literature review

Wybrane hormony neurosteroidowe a pierwszy epizod psychozy i schizofrenii – przegląd literatury

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ABSTRACT

First-episode psychosis (FEP) and first-episode schizophrenia (FES) are serious psychiatric conditions. Neurosteroids, known to modulate central nervous system function, may play a role in the pathophysiology of these disorders. This review aims to evaluate current evidence on the relationship between these disorders and levels of several neurosteroid hormones. A literature review was conducted using PubMed and Google Scholar, focusing on original articles, reviews, and meta-analyses published between 2016 and 2025. Keywords relevant to neurosteroids and FEP and FES were employed. Findings regarding neurosteroid levels in FEP and FES are inconsistent. Several studies indicate reduced testosterone levels in affected individuals compared to healthy controls. Similar reductions in estrogen and progesterone have been observed, often correlating with increased symptom severity. In contrast, dehydroepiandrosterone and its sulfate show an opposite pattern, though research remains limited. These discrepancies highlight the need for further investigation into the role of individual neurosteroids in early psychotic disorders. Current evidence does not allow for definitive conclusions; however, emerging findings suggest that neurosteroid levels may be significantly altered in FEP or FES patients compared to healthy controls. Moreover, they may contribute to the clinical presentation of these disorders. Neurosteroids have potential as biomarkers for early psychosis, and advancing knowledge in this domain may offer novel diagnostic or therapeutic insight.

KEYWORDS

first episode psychosis, testosterone, DHEA, progesterone, estrogen

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STRESZCZENIE

Pierwszy epizod psychozy (*first-episode psychosis* – FEP) oraz pierwszy epizod schizofrenii (*first-episode schizophrenia* – FES) to poważne zaburzenia psychiatryczne. Hormony neurosteroidowe, które modulują funkcjonowanie ośrodkowego układu nerwowego, mogą odgrywać rolę w ich patofizjologii. Celem przeglądu jest ocena aktualnych danych dotyczących zależności między poziomami wybranych neurosteroidów a wskazanymi zaburzeniami. Przeprowadzono przegląd literatury z wykorzystaniem baz danych PubMed i Google Scholar, uwzględniając artykuły oryginalne, przeglądowe oraz metaanalizy opublikowane w latach 2016–2025. Zastosowano słowa kluczowe związane z hormonami neurosteroidowymi oraz FEP i FES. Wyniki badań nad poziomami hormonów neurosteroidowych w FEP i FES są niejednoznaczne. W kilku badaniach odnotowano obniżony poziom testosteronu u pacjentów w porównaniu z osobami zdrowymi. Podobne tendencje dotyczyły estrogenu i progesteronu, przy czym niższe poziomy korelowały z większym nasileniem objawów. Odmienny wzorzec zaobserwowano w przypadku dehydroepiandrosteronu i jego siarczanu, choć dane są ograniczone. Konieczne są dalsze badania nad rolą poszczególnych hormonów. Dotychczasowe dowody nie pozwalają na jednoznaczne wnioski, jednak sugerują, że u pacjentów z FEP lub FES poziom hormonów neurosteroidowych może znacząco różnić się w porównaniu ze zdrowymi osobami. Co więcej, zmiany poziomów hormonów neurosteroidowych mogą wpływać na obraz kliniczny tych zaburzeń. Hormony neurosteroidowe mają potencjał jako biomarkery wczesnej psychozy, a pogłębienie wiedzy w tym zakresie może przynieść istotne korzyści diagnostyczne i terapeutyczne.

SŁOWA KLUCZOWE

pierwszy epizod psychozy, testosteron, DHEA, progesteron, estrogen

Introduction

The first time a person experiences psychotic symptoms is known as the first episode of psychosis (FEP). In some cases, FEP is a standalone episode in a patient's life, while in others it can be a sign of a developing illness. Diagnoses may include schizophrenia-spectrum disorders, mood disorders, and other psychotic disorders such as delusional disorder [1]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), the key features that characterize psychotic disorders are abnormalities across one or more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms [2]. Depressive symptoms are common in schizophrenia-spectrum and other psychotic disorders, often accompanied by suicidal ideation or attempts. Suicide is one of the leading causes of death in this population, with 40%–50% experiencing suicidal thoughts, 20%–50% attempting suicide, and 4%–13% dying by suicide. FEP represents a particularly high--risk period, with suicidal ideation reported in 26.2%––56.5% of cases. Additionally, the risk of suicide death is 60% higher than at later stages of the illness [3]. Broad cognitive deficits are observed during FEP, with the largest in immediate verbal memory, executive function, processing speed, and social cognition [4]. Typically, FEP occurs in the third decade of life [5]. It appears that 12%–35% of individuals later diagnosed with schizophrenia experienced their first symptoms before the age of 20 [6].

Schizophrenia is a chronic psychiatric disorder. The lifetime prevalence is estimated to be approximately 0.3%–0.7% [2]. Since the diagnosis of schizophrenia frequently follows an initial diagnosis of FEP, the five aforementioned symptoms constitute part of the diagnostic criteria. For a formal diagnosis of schizophrenia, there must be continuous signs of the disorder present for a minimum of six months. Schizophrenia is classified into several types based on the predominant symptoms. These are paranoid schizophrenia, hebephrenic schizophrenia, catatonic schizophrenia, simple schizophrenia, residual schizophrenia, and undifferentiated schizophrenia [5]. Additional symptoms may encompass mood disturbances, anxiety disorders, and self-related abnormalities. Affected individuals may exhibit phenomena such as derealization and depersonalization, as well as engage in behavior that is incongruent with contextual norms [2].

Schizophrenia is widely recognized as a multifactorial disorder, with a range of contributing factors influencing its onset. Genetic susceptibility, early-life brain injuries, and childhood infections play significant roles in the development of first-episode schizophrenia (FES). Additionally, psychosocial stressors are considered critical in the pathogenesis of the disorder. Longstanding evidence indicates that the onset of FES may be precipitated by the use of psychoactive substances [7]. Furthermore, it has been recognized over time that sex differences, gonadal steroid hormone fluctuations in particular, contribute to the emergence of FES and FEP. A hypothesis has been stated that sex hormones take part in the pathophysiology of schizophrenia [8]. Sex hormones – particularly estrogen, testosterone, progesterone, and dehydroepiandrosterone (DHEA), which will be discussed in this paper – interact with the central nervous system (CNS). Due to this function, they can be referred to as neuroactive steroids (NASs) [9].

NASs are synthesized both centrally (e.g., in the cortex, striatum, hippocampus, or hypothalamus) and

peripherally (e.g., in the adrenal glands, gonads, or placenta). Their lipophilicity enables blood–brain barrier penetration, allowing modulation of neuronal activity via diverse cellular targets. They act through rapid and slow mechanisms involving ligand-gated ion channels, G protein-coupled receptors (GPCRs), and nuclear receptors. Key non-genomic targets include γ-aminobutyric acid (GABA) and N-methyl-D--aspartate (NMDA) receptors [10]. NASs modulate GABA receptors as either positive allosteric modulators (e.g., allopregnanolone) to enhance GABA activity or as negative modulators (e.g., DHEA-S) to inhibit receptor function. In the CNS, NASs are synthesized by neurons and glial cells, acting as local signaling molecules to modulate intercellular and synaptic communication. Neuronal NASs are produced at both presynaptic and postsynaptic sites; presynaptic synthesis contributes to activity-dependent release, influencing neurotransmission, while postsynaptic NASs modulate nearby receptors or presynaptic terminals. These actions position NASs as key modulators of neurotransmitter systems, including GABA, glutamate, and dopamine [10]. The detailed effects of individual NASs will be discussed in the following paragraphs. A summary of NASs' effects on the CNS is provided in Table I.

Table I. Impact of selected hormones on the central nervous system

Hormone	Influence on the CNS
Testosterone	Regulation of neuroplasticity in the hippocampus; promotion of neurogenesis and neuroregeneration; enhancement of neurotrophin expression; protection against apoptosis; mitigation of beta-amyloid toxicity
DHEA-S	Promotion of neurite growth, neurogenesis, and neuronal survival; modulation of the effects of cortisol on the brain against the potentially damaging effects of excessive cortisol activity; modulation of the action of the GABA-A, NMDA, and sigma-1 receptors
Estrogen	Modulation of the activity of important neurotransmitters: serotonin, dopamine, glutamate, and GABA; regulation of cognition, memory, neurodevelopment, and neuroplasticity; support in the growth of grey matter in the amygdala, the thalamus, and the hippocampal and parahippocampal areas
Progesterone	Influence on myelination; reduction of brain edema and inflammation; support in neuronal survival; modulation of the activity of astrocytes

CNS – central nervous system; DHEA-S – dehydroepiandrosterone sulfate; GABA-A – γ-aminobutyric acid type A receptor; GABA – γ-aminobutyric acid; NMDA – *N*-methyl-d-aspartate receptor.

Given this body of information, multiple questions arise. Are sex hormone levels in patients with FEP and FES different from those in the general population? How do hormonal changes affect the onset and development of schizophrenia? Are there any sex--specific differences in these fluctuations? This paper aims to address these questions and provide insight into the potential role of NASs in the onset of FEP and the manifestation of schizophrenia.

The relationship between steroid sex hormones and psychosis is extremely complex and is still being investigated [9]. Gaining a deeper understanding of it may be crucial to unraveling the pathophysiology of schizophrenia and paving the way for new therapeutic methods.

Methodology

A review of the available literature was performed by searching PubMed and Google Scholar. The search string that was used to search the database was ("first episode psychosis" OR "first episode schizophrenia") AND ("testosterone" OR "testosterone level" OR "DHEA" OR "DHEA level" OR "DHEA-S" OR "DHEA-S level" OR "estrogen" OR "estrogen level" OR "progesterone" OR "progesterone level"). All relevant articles published between 2016 and 2025 were considered. In addition, the references cited within the identified studies were manually examined, leading to the inclusion of 3 additional articles published prior to the defined timeframe. Only articles written in English were considered. Duplicate records were removed. An initial screening was performed based on titles and abstracts and the studies that did not meet the inclusion criteria were excluded. The remaining articles were subjected to a comprehensive analysis of the study characteristics, sample sizes, methodologies, and key findings.

The database search, conducted using predefined search terms alongside the established inclusion and exclusion criteria, yielded 418 articles after duplicates were removed. Based on a review of titles and abstracts, 98 articles were shortlisted for further evaluation. A comprehensive full-text analysis of these articles was then carried out. Following the application of the selection criteria, 22 studies were ultimately included in the review. The necessary data was then extracted from the texts and compiled into a narrative synthesis.

Inclusion and exclusion criteria

This literature review concentrated on observational studies and randomized controlled trials that investigated the relationship between levels of various NASs and FEP or FES. A total of 16 clinical studies that met these specific criteria were identified and included. Additionally, 3 clinical studies that did not

focus solely on first-episode cases but provided particularly relevant data were also incorporated. To enhance the contextual understanding and to support the interpretation of findings, 2 review articles and 1 meta-analysis were included. These sources offered comprehensive syntheses of existing evidence and helped to frame the individual studies within the broader scientific landscape. Case reports, animal studies, technical notes, dissertations, textbooks, studies involving children and studies that did not address the relationship between NASs levels and mental health disorders were excluded from the review. The quality of the selected studies was evaluated based on the appropriateness of the study design in relation to the research objectives, the risk of bias, the robustness of the findings, the rigor of statistical analysis, and the overall quality of reporting.

Testosterone

Role of testosterone in males and females

Testosterone, a key androgen, regulates male development, maturation, and aging [11]. In healthy adult males, Leydig cells synthesize 5–10 mg of testosterone per day, with minor contributions from the adrenal cortex and peripheral metabolism [12]. Testosterone drives secondary sexual characteristics, spermatogenesis, libido, and anabolic effects during puberty and adulthood [11]. Circulating testosterone is mostly protein-bound: ~66% to sex hormone-binding globulin (SHBG), ~30% to albumin, and only 2%–4% remains free, constituting the biologically active form.
In females, testosterone serves distinct physiological roles, acting as both an androgen and a precursor for estradiol synthesis [13]. During reproductive years, it is primarily produced by the ovaries and via peripheral conversion of adrenal and ovarian androgens: androstenedione and DHEA. Aromatization to estradiol occurs in ovarian and extragonadal tissues, the latter becoming predominant post-menopause. Testosterone influences both reproductive and non--reproductive functions and is positively associated with female sexual function. Therapeutically, testosterone has shown efficacy in treating female sexual dysfunction [13].

Testosterone in the CNS

In the CNS, testosterone acts mainly via androgen receptors (ARs), which are widely expressed, particularly in the cerebral cortex. Their distribution suggests broad neural functions mediated through intracellular ARs [14]. Beyond nuclear sites, ARs are also found in axons and dendrites, where they engage kinase signaling pathways. Classic AR signaling involves cytoplasmic AR dissociation from heat shock proteins, nuclear translocation with chaperones, and binding to androgen response elements in order to regulate gene transcription. In contrast, non-genomic actions are mediated by membrane-associated ARs, activating rapid pathways such as Akt and ERK/MAPK [15]. Testosterone promotes remyelination via neural ARs. In mouse models of demyelination (cuprizone and LPC), myelin repair was absent in Tfm mice lacking functional ARs and impaired in ARNesCre mice with neural-specific AR deletion, confirming the essential role of neural ARs [16]. Testosterone confers neuroprotection by upregulating neuroglobin in astrocytes and microglia under stress (e.g., injury, glucose deprivation, or kainic acid). It promotes neuronal differentiation, plasticity, synaptic density, hypothalamic connectivity, and neurite outgrowth. Testosterone also reduces astrocyte reactivity post--injury and protects against age-related neurodegeneration, partly by stabilizing mitochondrial membranes and reducing reactive oxygen species [17].

Correlations between testosterone and several neurotransmitters

Beyond its interaction with ARs, testosterone also modulates neurotransmitter and hormone levels. Notably, it has been shown to enhance serotonergic activity by upregulating the mRNA expression of the serotonin (5-HT) transporter [18]. This effect supports the therapeutic potential of testosterone in depressive disorders, although additional mechanisms, such as the promotion of neurogenesis, may also contribute [19].
Testosterone levels appear to be particularly significant in relation to dopaminergic function. Preclinical and clinical studies have linked NASs metabolized via 5α-reductase (5αR) – including testosterone – to dopaminergic dysfunction in neurological disorders [10]. 5αR inhibitors such as finasteride suppress dopaminergic activity by negatively modulating dopamine D1 and D3 receptors, without affecting D2 receptors, and have been proposed as potential therapies for neuropsychiatric disorders with dopaminergic hyperactivity [20]. As 5αR inhibitors do not directly bind to dopamine receptors, their effects likely stem from NAS-induced alterations in downstream D1 and D3 signaling [10].
An additional important consideration is the relationship between testosterone and estradiol levels. Both hormones can cross the blood–brain barrier, and neural estradiol is locally synthesized from testosterone [21], making this interaction complex and challenging to fully delineate. Further discussion on this topic is presented in the section addressing estrogen.
A key consideration is the reciprocal interaction between testosterone and the hypothalamic–pituitary––adrenal (HPA) axis, which regulates peptide and

steroid hormones from the hypothalamus, pituitary, and adrenal glands [22]. Testosterone suppresses corticotropin-releasing hormone (CRH)-induced HPA activation, while HPA activation inhibits testosterone secretion. Although testosterone generally appears to reduce cortisol levels [22], findings are inconsistent, with some studies linking it to elevated cortisol and enhanced stress responses. Individuals with high trait dominance and elevated testosterone may be more susceptible to stress-related conditions such as mood disorders and substance abuse [23].

As demonstrated, the effects of testosterone on the CNS are multifaceted and remain incompletely understood.

Are testosterone levels different in FEP/FES patients?

Research investigating testosterone levels in individuals with FEP and FES remains limited. Among the available studies, findings have been inconsistent. Knytl et al. [9] examined testosterone levels in 16 FEP patients, 22 biological siblings of these patients, and 29 healthy controls. The siblings showed significantly higher testosterone levels than the controls, correlating with increased psychosis risk. No significant difference was found between the FEP patients and the controls, possibly due to early antipsychotic treatment, though conclusions cannot be drawn about the effects of medication because of its short duration. A study conducted in 2020 yielded similar findings, enrolling 51 drug-naive individuals with FEP who met the diagnostic criteria for schizophrenia [24]. Despite the absence of prior antipsychotic treatment, no significant difference in testosterone levels was observed between the patients and the healthy controls. Two additional studies reported findings consistent with those described above. The first study, conducted as an extension of one by the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) at its facility in Bologna, Italy, examined a sample of 32 individuals with FEP who had already undergone antipsychotic treatment [25]. The second study included the same number of drug-naive FEP patients, comparing them to individuals experiencing an acute exacerbation of schizophrenia due to treatment nonadherence (DFP group), as well as to healthy controls [26]. Both studies found no significant differences in testosterone levels between the patients and the controls. Furthermore, the second study did not identify any significant differences in testosterone levels between FEP patients and those with previously diagnosed schizophrenia.

In contrast to the aforementioned findings, several studies have reported significant differences in testosterone levels. A 2016 study conducted at the First Affiliated Hospital of Zhengzhou University examined testosterone levels in 39 male and 42 female drug-naive individuals with FES [27]. Testosterone levels were lower in the male FES patients and "dramatically" higher in the female patients compared to the controls. In males, testosterone negatively correlated with negative symptoms; in females, it positively correlated with positive symptoms. It has been proposed that endogenous testosterone may protect cognitive function, with reduced levels being linked to cognitive impairment in drug-naive male FES patients. Thus, testosterone may serve as a biomarker for symptom severity. The neuroprotective role of testosterone was also highlighted and partially supported in a 2019 study by Petrikis et al. [28]. In that study, testosterone levels were compared between 87 drug-naive individuals of both sexes with FEP and healthy controls. The male patients showed significantly lower testosterone and SHBG levels than the controls, with no difference observed among the females. Additionally, a multivariate logistic regression indicated that each unit increase in total testosterone reduced psychosis risk by ~34%, and each unit of free testosterone by ~14%. These findings are particularly significant, as they suggest that testosterone may play a role in the pathophysiology and potential etiology of psychosis in men, rather than being solely a consequence of the disorder. One potential explanation for this phenomenon lies in the neuroprotective role of testosterone. It binds to ARs primarily in the hypothalamus and amygdala, with less binding in the hippocampus and frontal cortex. Its neuroprotective effects include regulating neuroplasticity in the hippocampus, promoting neurogenesis and neuroregeneration, enhancing neurotrophin expression, protecting against apoptosis, and mitigating beta-amyloid toxicity [28]. Two studies published in 2024, one by Hu et al. [29] and another by Hill et al. [30], confirmed a significant correlation between testosterone levels and FEP or FES in patients. The first study also revealed an intriguing finding: the female patients exhibited a higher rate of abnormal testosterone levels than the male patients. This result contrasts with the findings of the 2019 study discussed above. The authors concluded that abnormal testosterone levels have a more substantial impact on the course of FEP in females than in males.

The relationship between testosterone levels and the onset of FEP or FES appears to be highly complex. As outlined above, findings have been inconsistent across studies. A critical factor contributing to these discrepancies may be the treatment status of the participants, as some studies included drug-naive patients, while others did not. This distinction could significantly influence the interpretation of results. Despite these variations, the existing evidence suggests that further investigation is warranted, as

testosterone levels may represent a potential biomarker for the prediction and progression of FEP/FES.

DHEA/DHEA-S

DHEA and its sulfated metabolite, DHEA-S, are endogenous hormones produced by the adrenal glands [31]. Their biological roles are still not fully understood, but without a doubt DHEA is a pivotal precursor for several other steroids, including testosterone, dihydrotestosterone (DHT), and androstenedione in men and estradiol, estriol, and estrone in women [32]. DHEA, like other androgens, mineralocorticoids, and glucocorticoids, is derived from pregnenolone, which in turn is synthesized from cholesterol. DHEA-S is the most abundant circulating steroid hormone in humans [31]. It is formed from DHEA through the action of SULT2A1. Although a small portion of circulating DHEA originates from the gonads, skin, and brain, the majority of DHEA and virtually all DHEA-S is produced by the adrenal cortex [33].

DHEA and DHEA-S are classified as neurosteroids because they can be synthesized de novo in the CNS, meaning that the brain does not rely solely on serum levels of DHEA-S. These hormones serve as precursors to approximately 50% of androgens in adult men, 75% of active estrogens in premenopausal women, and nearly 100% of active estrogens in women after menopause [34]. In addition to their role as precursors, DHEA and DHEA-S also independently exhibit androgenic and estrogenic activity, with androgenic activity being more pronounced.

Both DHEA and DHEA-S are secreted synchronously with cortisol, following a similar diurnal and episodic rhythm. While both hormones are widely distributed throughout the body, their highest concentrations are found in the brain. Plasma levels of DHEA and DHEA-S vary depending on age and gender, with levels being higher in men than in women across all age groups. Peak concentrations of these hormones occur in the third decade of life, after which they decline to 10%–20% of their peak values. It is suggested that, due to its potential influence on cognition, some age-related neurological disorders might be associated with a decline in systemic DHEA-S concentrations, but this subject requires further research [31].

The major biological actions of DHEA-S, excluding their estrogenic and androgenic activity, are neuroprotection, promotion of neurite growth, neurogenesis, neuronal survival, apoptosis, and catecholamine synthesis and secretion; they also exhibit antioxidant, anti-inflammatory, and anti-glucocorticoid effects [34]. DHEA has been shown to exert both agonistic and antagonistic effects on the AR and acts as an agonist at both estrogen receptor-α and estrogen receptor-β. In the brain, DHEA-S modulates the actions of the GABA-A receptor, the NMDA receptor, and the sigma-1 receptor, among others [31]. DHEA-S has also been shown to respond to stress and modulate the effects of cortisol on the brain. The co-release of DHEA in the acute stress response is thought to protect against the potentially damaging effects of excessive cortisol activity [35]. Consequently, alterations in DHEA-S levels, such as the decrease associated with aging, can influence cognition and mood [31].

What are the levels of DHEA/DHEA-S in FEP/FES?

Clinical studies of blood DHEA-S levels in patients with FEP have produced mixed findings.

Beyazyüz et al. [26] compared neurosteroid levels in untreated FES patients, untreated chronic schizophrenia patients in acute exacerbation, and healthy controls. Due to the rapid metabolism of DHEA to DHEA-S, only DHEA-S levels were measured. FES patients showed significantly higher DHEA-S than both chronic patients and controls, indicating a strong neurosteroid response that declines with disease progression. An elevated DHEA-S level may be considered a biomarker for schizophrenia, reflecting neuroprotective and stress-response roles.

Belvederi Murri et al. [25] studied 32 FEP patients (17 men and 15 women), mostly on antipsychotic medication, and 153 controls from normative hormone studies. No significant differences in DHEA levels were found between groups, with levels unaffected by antipsychotic dose, treatment duration, or recent cannabis use. In the women, DHEA correlated positively with negative symptoms and disorganization.

Garner et al. [35] examined cortisol, DHEA-S, and the ratio of the two in 39 FEP patients (14 neuroleptic-naïve and the remainder with ≤10 days of antipsychotic use) and 25 matched controls (ages 15–25) in Melbourne. Blood samples, clinical assessments, and stress ratings were collected at baseline and after 12 weeks to assess hormone differences, perceived stress, and clinical response during early treatment. In the healthy males, perceived stress correlated positively with DHEA-S and cortisol/DHEA-S ratio, whereas no such correlations were found in the male FEP patients. No significant differences in DHEA-S level or cortisol/DHEA-S ratio were observed between the FEP patients and the controls at baseline or 12-week follow-up, regardless of antipsychotic exposure. At baseline, DHEA-S was inversely correlated with negative and depressive symptoms, while the cortisol/DHEA-S ratio showed positive correlations with negative symptoms of depression, anxiety, and psychosis. A reduction in the ratio over time was linked to improved symptoms. The similar DHEA-S levels between FEP patients and controls may reflect adrenal exhaustion from pre-onset

chronic stress, increasing vulnerability to depressive and negative symptoms. Findings suggest impaired stress hormone responses in FEP, with behavioral therapies such as cognitive-behavioral therapy potentially improving hormonal regulation and symptom outcomes [35].
As outlined above, the available data on the relationship between DHEA/DHEA-S and FEP or FES remains limited and yields inconsistent findings.

Estrogen

Role of estrogen in the human body

Estradiol, estriol, and estrone are estrogens, steroid hormones that influence reproductive, neuroendocrine, cardiovascular, skeletal, and immune systems [36]. Estrogen drives reproductive organ development and sexual characteristics [37], but is also implicated in pathologies such as osteoporosis, endometriosis, cancer, infertility, and obesity [36]. In the CNS, estrogen – particularly 17β-estradiol – modulates neurotransmitters linked to schizophrenia (serotonin, dopamine, glutamate, and GABA) [38] and regulates cognition, memory, neurodevelopment, and neuroplasticity [37] via genomic and non-genomic pathways [39]. These effects are mostly controlled by two nuclear estrogen receptors (ERs), alpha (Erα) and beta (Erβ), and G protein-coupled estrogen receptor (GPER-1) [38]. During adolescence, rising estrogen levels drive structural brain changes, including reduced grey matter in the prefrontal, parietal, and temporal regions [28]. Concurrently, regions rich in estrogen receptors – the amygdala, thalamus, hippocampus, and parahippocampus – show increased activity [28]. These same areas exhibit anatomical abnormalities, such as reduced grey matter, in schizophrenia [40].

Estrogen's further role in the CNS

As noted, estrogen is synthesized from testosterone in the CNS via the enzyme aromatase, which plays key roles in neural function [21]. Its presynaptic location and co-expression with ERs at synapses support the role of locally synthesized estradiol in modulating synaptic transmission. Aromatase is also found with ERs at the plasma membrane, indicating a mechanism for rapid, non-genomic estradiol function. Its activity is regulated by synaptic signals and neurotransmitters such as glutamate and dopamine [21]. During development, brain aromatase converts fetal testicular testosterone into estradiol, contributing to brain masculinization. It also influences sex-specific seasonal brain plasticity in males, which is linked to testosterone fluctuations [41]. Despite its importance, the estrogen-testosterone interaction via aromatase remains complex and not fully understood.

Importantly, estrogen levels influence both the dopaminergic and serotonergic systems. Estrogens modulate dopaminergic neurotransmission by enhancing dopamine synthesis in regions such as the nucleus accumbens and the striatum, while also reducing dopamine degradation in the nucleus accumbens. In addition, estrogens regulate the serotonergic system by increasing the activity of tryptophan hydroxylase, thus promoting the synthesis of serotonin (5-HT), and by modulating 5-HT receptor expression – both of which have substantial implications for mood regulation and the pathophysiology of depression. Estrogen exerts antidepressant-like effects by prolonging serotonergic signaling and decreasing 5-HT reuptake into presynaptic neurons. Once internalized, 5-HT reduces monoamine oxidase activity, thereby decreasing its own metabolic breakdown [42].
As demonstrated, estrogen exerts significant effects on the CNS beyond its well-established role in reproductive function.

The estrogen hypothesis

For the longest time, scientists have been pondering: "Why do women with schizophrenia often experience a later onset and milder symptoms than men?" Evidence shows that gonadal hormones influence the age of onset and symptom profile in FEP patients [8]. This has prompted research into hormone-related life events – menstruation, pregnancy, childbirth, and menopause – in psychiatric populations. As early as 1909, Kraepelin observed increased psychotic symptoms during periods of estrogen decline [43]. Subsequent studies have linked estrogen and disruptions in its signaling to schizophrenia pathophysiology [44]. In the 1990s, estrogen was termed "nature's natural psycho-protectant," leading to the "estrogen hypothesis" [45], which posits that low estrogen levels – e.g., during menstruation or menopause – worsen psychotic symptoms [46].
In a thorough systematic review and meta-analysis, Reilly et al. [47] analyzed 19 full-text studies involving 1,193 women diagnosed with a psychotic disorder with regard to demonstrating the menstrual exacerbation of psychotic symptoms. It outlined the significantly higher rates of psychiatric hospital admissions during the perimenstrual rather than the non-perimenstrual phase. Additionally, the authors highlighted a study conducted by Bergemann et al. [48], which identified a clear dependence between psychotic symptoms and low estrogen levels, and a concomitant worsening of well-being, as assessed by positive scores on the Positive and Negative Syndrome Scale (PANSS).
Expanding on this, a Spanish study conducted by Barrau-Sastre et al. [49] on 42 women with FEP between the ages of 18 and 45 analyzed the estrogen

levels based on their cycle length, age at menarche, and years of difference between the onset of FEP and menarche. The research did not find a relationship between age at menarche and onset of illness, yet it documented that women with shorter menstrual cycles demonstrated enhanced cognitive flexibility and inhibition capacity. This study did not rely on laboratory data, such as blood samples, but rather on questionnaires and clinical interviews, which are often prone to biases and personalized responses, thereby limiting its overall reliability and the generalizability of its findings.

A retrospective case-control study by Pons-Cabrera et al. [43] compared sex hormone levels in drug-naive women of reproductive age with FEP and healthy controls, with samples collected during the luteal phase. FEP patients showed elevated follicle--stimulating hormone – FSH (7 U/L) and luteinizing hormone – LH (8.4 U/L) compared to controls (3.5 U/L and 5.7 U/L, respectively). Despite the higher FSH, 17β-estradiol levels were lower in the FEP patients (75.3 pg/mL) than in the controls (151 pg/mL), supporting the estrogen hypothesis that reduced estrogen may contribute to psychotic symptoms.

Supporting the estrogen protection hypothesis, a narrative review by Culbert et al. [46] examined whether menopause and hormonal fluctuations increase the risk of psychosis. Schizophrenia is more common in men (1.4:1) [8], with male incidence peaking at 20––29 years; there are two peaks in women: at ages 20––39 and around menopause [8]. While psychosocial factors may contribute, the menopausal peak is largely attributed to declining estrogen. The review highlights studies linking low estrogen to increased psychotic symptoms and calls for further research into hormonal and psychosocial factors in midlife psychosis to inform treatment [46].

Sezer et al. [50] studied FSH, LH, prolactin, estradiol, and progesterone in 32 female schizophrenia patients, taking samples during follicular and periovulatory phases and assessing symptoms via PANSS. Mean estradiol levels were 25.16 pg/mL (follicular) and 59.83 pg/mL (periovulatory), below normal ranges (25–100 and 150–450 pg/mL, respectively). Although estrogen is typically lower in schizophrenia, these abnormal levels may also result from antipsychotic treatment. Contrary to the earlier research by Barrau--Sastre et al. [49], this study found a positive correlation between late age of menarche and severe schizophrenic symptoms.

Another study, conducted by Hursitoglu et al. [38], consisted of 36 schizophrenia patients and 30 controls aged 18–65, excluding those with menstrual irregularities, hormone therapy, pregnancy, or menopause. GPER-1 levels were measured and symptoms were assessed via PANSS. The men showed elevated GPER-1 compared to the controls, while there was no difference among the women. Nevertheless, this study highlights ERs' role in schizophrenia and suggests that elevated GPER-1 in male patients warrants exploring GPER-1 agonists for potential treatments to reduce symptom severity.

As shown, the role of estrogen in the pathophysiology of FEP and FES could be significant. There are numerous studies and clinical observations in the literature related to abnormal levels of estrogen in schizophrenic patients. Notwithstanding these reports, the precise mechanism of how the sex hormones influence the onset, progression, and course of schizophrenia remains unknown. Therefore, further studies with larger sample sizes and laboratory methodologies are needed to confirm these results.

Progesterone

Progesterone is a steroid hormone. It is produced by gonadal tissue, the adrenal cortex, and the placenta during pregnancy [51]. It is a precursor for glucocorticoids and other sex steroids, such as testosterone and estradiol. Beyond its primary role, progesterone also attaches to intracellular progesterone receptors in the cytoplasm of cells across the body. Once bound to these receptors, progesterone is transported into the nucleus, where it interacts with genetic material to control the activity of specific genes [51]. Progesterone also exerts an influence on the brain, impacting myelination and reducing brain edema, inflammation, and the activity of various substances, such as hemostatic proteins [52].

Progesterone, as well as other NASs like cortisol, is a key factor in the development and functioning of the CNS throughout life. In adulthood, these steroids have a considerable impact on the activity of various neurotransmitter systems involved in the pathophysiology of psychosis, including the dopaminergic, glutamatergic, and GABAergic systems [25]. Within the CNS, progesterone is synthesized from cholesterol. The initial step involves the enzymatic conversion of cholesterol to pregnenolone via the action of cytochrome P450 side-chain cleavage enzyme. Pregnenolone is then further metabolized into progesterone by 3β-hydroxysteroid dehydrogenase [53]. Like other NASs, progesterone exerts its effects in the CNS through two distinct mechanisms. The first involves the classic pathway via nuclear progesterone receptors (PRs), while the second operates through non-classic, membrane-associated receptors that mediate rapid, non-genomic actions. The enzymes involved in these pathways are expressed in both neuronal and glial cell populations [16]. Evidence suggests that membrane-bound PRs play a role in promoting neuroregeneration and may underlie progesterone's neuroprotective effects by supporting neuronal survival [54].

Are progesterone levels different in FEP/FES patients?

The role of progesterone in schizophrenia has been less studied than estrogen's role. There are studies on progesterone in the context of schizophrenia, but the results are not conclusive. Some studies propose that the hormone may have a neuroprotective effect, as seen in animal models of cognitive dysfunction and positive symptoms, while others indicate a negative correlation between the hormone and symptom modulation in patients [55]. Based on the available clinical studies, it has been suggested that there is a link between lower symptom scores and high progesterone levels (which occur during the luteal phase of the menstrual cycle in women). As Belvederi Murri et al. [25] proved, male patients experiencing FEP had lower progesterone levels than healthy controls. In addition, lower progesterone levels were associated with more severe positive symptoms, implying a possible involvement of this hormone in the pathophysiology of psychotic disorders. Animal studies also demonstrate an inhibitory effect of progesterone on hyperactive behavior. Recent reports indicated that baseline progesterone levels were significantly elevated in FES patients who had not yet received antipsychotic treatment, in comparison to healthy controls [39]. This has led to the hypothesis that lower progesterone levels in the early phase of the illness may be linked to more effective response to antipsychotic treatment. Other studies reported that males receiving long-term treatment had notably higher progesterone levels than the healthy male subjects, but subsequent research showed that the increase occurred only in men [56].

Endogenous progesterone levels fluctuate throughout a woman's life, influenced by factors such as contraceptive use and the premenopausal period. During perimenopause, progesterone declines, potentially increasing the risk of initial psychiatric disorders. However, no specific association with schizophrenia-spectrum disorders has been identified [57]. Hormonal fluctuations also occur with contraceptive use. Oral contraceptives vary in composition, dosage, and administration. Studies indicate that progestogen-only pills (POPs) are more frequently associated with psychiatric symptoms than combined oral contraceptives (COCs) [58]. It has also been found that different types of progestogens can affect mood in different ways, with newer formulations being linked to fewer adverse effects. Hormonal contraception suppresses endogenous hormone production, replacing it with synthetic analogs; COCs additionally reduce testosterone and increase SHBG. While scant research has been published on the mental health effects of these changes in women using oral contraceptives, we already know that hormonal fluctuations can cause mood swings in women who are not using contraception. It is also worth noting that fluctuations in estrogen and progesterone, particularly premenstrually, can exacerbate psychiatric symptoms in sensitive individuals. Puberty and menopause further elevate mental health risk [49,58].

In summary, after analyzing the available studies and publications, no definitive relationship between progesterone levels and the occurrence of FEP and FES can yet be established. More research on larger patient groups is needed to draw concrete conclusions. Such studies may potentially lead to disease prevention.

Conclusions

As discussed above, the data regarding the potential role of NASs in FEP and FES is relatively recent and presents compelling avenues for investigation. Findings appear to vary based on the specific type of hormone being examined. In the case of testosterone, multiple studies have reported reduced hormone levels in FEP/FES patients. Notably, an especially important logistic regression analysis conducted by Petrikis et al. [28] highlighted the potential involvement of testosterone levels in the onset of FEP, possibly attributable to its neuroprotective properties. Moreover, certain studies emphasize the significance of testosterone in female patients with respect to FEP/FES, thereby extending the focus beyond male populations, where this hormone is traditionally considered to play a central role. With regard to DHEA/DHEA-S, the available studies are limited and have yielded inconsistent results. Nonetheless, elevated DHEA-S levels have been proposed as a potential biomarker for schizophrenia.

In the context of estrogen, several studies examining FEP/FES in female patients lend support to the estrogen hypothesis, highlighting the hormone's neuroprotective properties. Reduced estrogen levels – such as those observed during menstruation or menopause – have been positively correlated with increased severity of FEP symptoms, with positive symptoms notably intensifying during the perimenstrual phase. Although the findings remain somewhat inconclusive, the evidence suggests that, akin to testosterone, estrogen plays a significant neuroprotective role in the pathophysiology of FEP and FES. Our review identified the least amount of available data concerning progesterone. In comparison to estrogen, the effects of progesterone in the context of FEP have been substantially less explored. While some evidence suggests reduced progesterone levels in FEP patients and indicates that progesterone, similar to estrogen, may exert neuroprotective effects on the CNS, the current body of literature does not allow for definitive conclusions.

In conclusion, additional research is necessary to clarify the potential involvement of NASs in the

pathophysiology of FEP and FES. Although the current findings are preliminary, they underscore the promise of this area of study. Advancing knowledge in this domain may contribute substantially to improving clinical insight and optimizing therapeutic approaches for affected individuals.

Authors' contribution

Study design – A. Gładysz
Data collection – A. Gładysz, A. Dydyna, M. Mościcka, M. Gierlik
Manuscript preparation – A. Gładysz, A. Dydyna, M. Mościcka, M. Gierlik
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PRACA POGLĄDOWA
REVIEW

The burden of atherosclerotic cardiovascular disease in an aging population: A comprehensive review of risk factors, risk assessment, and prevention

Obciążenie chorobami układu sercowo-naczyniowego związanymi z miażdżycą w starzejącej się populacji – kompleksowy przegląd czynników ryzyka, oceny ryzyka i profilaktyki

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ABSTRACT

Aging is a key risk factor for atherosclerotic cardiovascular diseases (ASCVDs), leading to high morbidity and mortality among older adults. As the population ages and medical advances prolong survival, more individuals live with ASCVD, necessitating personalized management that addresses complex medical, social, and functional challenges. Besides traditional risk factors, geriatric syndromes and non-cardiovascular comorbidities – commonly referred to as competing risks – significantly impact outcomes. Although assessment tools exist, their clinical use is limited by complexity and patient diversity. Early prevention of geriatric conditions such as frailty, sarcopenia, malnutrition, and multimorbidity is essential to reduce adverse events and cardiovascular risk.

KEYWORDS

ASCVD in the elderly, SCORE2-OP, QRISK3, malnutrition, polypharmacy, sarcopenia, frailty, multimorbidity

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STRESZCZENIE

Starzenie się jest istotnym czynnikiem ryzyka miażdżycowych chorób układu sercowo-naczyniowego (*atherosclerotic cardiovascular diseases* – ASCVDs), powodujących wysoką zachorowalność i śmiertelność w populacji osób starszych. Wraz ze starzeniem się społeczeństwa oraz postępem medycyny, wydłużającym przeżycie, rośnie liczba osób żyjących z ASCVD, co wymaga spersonalizowanego leczenia, uwzględniającego złożone problemy medyczne, społeczne i funkcjonalne. Poza tradycyjnymi czynnikami ryzyka na wyniki kliniczne istotny wpływ mają także zespoły geriatryczne oraz współistniejące schorzenia niezwiązane z układem sercowo-naczyniowym, określane jako ryzyka konkurencyjne. Pomimo dostępności narzędzi oceny tych stanów ich zastosowanie w praktyce klinicznej jest ograniczone ze względu na ich złożoność, a także heterogenność pacjentów. Wczesne działania prewencyjne ukierunkowane na zespoły geriatryczne, takie jak sarkopenia, zespół kruchości, niedożywienie i wielochorobowość, są kluczowe w redukcji zdarzeń niepożądanych oraz ryzyka sercowo-naczyniowego.

SŁOWA KLUCZOWE

ASCVD u osób starszych, SCORE2-OP, QRISK3, niedożywienie, polipragmazja, sarkopenia, zespół kruchości, wielochorobowość

Introduction

ASCVD and its significance in the elderly population

Atherosclerotic cardiovascular disease (ASCVD) arises from the accumulation of plaque along the walls of arteries and encompasses various conditions, including:

- coronary artery disease (CAD), which includes acute coronary syndrome (ACS) and chronic coronary syndrome (CCS)
- peripheral artery disease (PAD), which encompasses conditions affecting the carotid, renal, and lower-extremity arteries due to atherosclerosis
- aortic conditions, including atheromatous disease of the aorta and aortic aneurysms [1,2].

Despite age serving as a strong risk factor for cardiovascular problems and mortality, older adults are less frequently prescribed therapy that aligns with clinical guidelines for ASCVD [3]. Several pertinent questions emerge: What are the underlying causes of this phenomenon? What consequences does it entail? What therapeutic challenges does it present? Firstly, the exclusion or insufficient representation of older individuals in numerous clinical trials significantly restricts the evidence base for this demographic [4]. Secondly, the presence of multiple health conditions in older adults often leads to intricate interactions between medications and various diseases. Furthermore, the processes of drug metabolism and response are influenced by aging, which is associated with diminished kidney function, changes in body composition, and variations in medication tolerability. This issue holds particular significance due to the prevalence of polypharmacy among older populations [5]. Another critical consideration is the challenges of compliance, since physical limitations such as difficulties with coordination and vision can impede adherence to prescribed therapies. Moreover, treatment costs are considerable in this population and should not be underestimated. Likewise, effective treatment of medical disorders in the elderly necessitates a holistic approach that considers various risks, including frailty, accidental falls, and mental impairment, alongside the evidence underpinning treatment recommendations [6]. Taking into account these issues related to seniors and the global demographic shift towards an aging population, the clinical management of ASCVD in older patients requires a comprehensive understanding of these complexities to ensure both effective and safe treatment.

Demographics of older adults

In 2020, the global population of individuals aged 60 and older exceeded that of children under 5 years old. Research suggests that by 2030, one in six people around the world will be at least 60 years old and the elderly population will reach 1.4 billion [7]. In Europe, over 20% of the population was aged 60 or older in 2017, and this figure is expected to rise to 35% by 2050 [8]. Due to the rise in life expectancy, the primary objective of doctors is not just to extend the number of healthy years lived, but also to enhance the quality of life during those years. Moreover, older adults need medical care more often and more frequently undergo outpatient procedures or hospitalization. The elderly make up a significant portion of the healthcare system's users, with individuals over 65 years accounting for about 40% of patients discharged from hospitals [9]. Key factors influencing healthcare costs include not just age, but also the presence of comorbidities.

Healthy aging

The process of aging is a fundamental aspect of the life cycle inherent to all living organisms, unfolding progressively over an extended period. Despite various efforts to identify, characterize, and categorize the aging process in humans, a unified and comprehensive definition remains elusive [10]. According to the new definition adopted by the World Health Organization (WHO) in 2016, "healthy aging is more than just the absence of disease; it is the

process of developing and maintaining the functional ability that enables well-being in older age" [11]. This definition encompasses two critical components: intrinsic capacity and environmental elements. The former represents a synthesis of all personal, somatic, and cognitive capabilities. The latter pertains to environmental factors that evolve over time and are significantly influenced by governance structures, financial systems, societal beliefs, and resource availability. The dynamic interplay between two of these crucial conditions ultimately contributes to functional ability in older adults (Figure 1) [12].

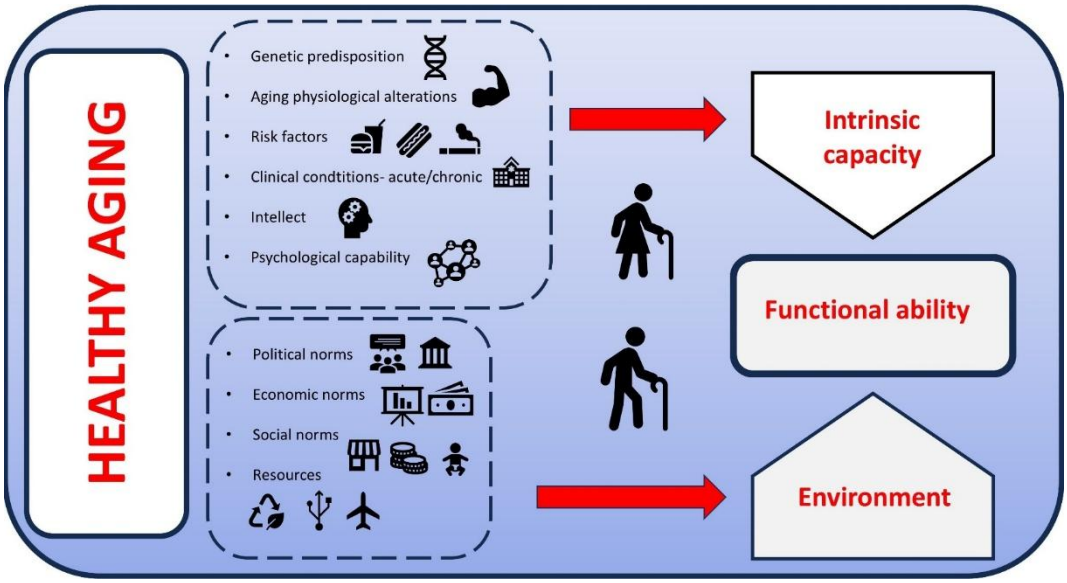

Fig. 1. Definition of healthy aging

In the initial phases of life, intrinsic capacity and functional ability follow the same course. As individuals reach middle age, though, these routes start to diverge, primarily due to the cumulative impact of health-related factors on intrinsic capacity. Although environmental factors can partially offset this decline, inadequate environmental support in later stages of life may result in a rising need for support, reduced capability, and overall deterioration [12].

Epidemiology

Prevalence of ASCVD and mortality among older adults

ASCVD is a major cause of mortality and greatly contributes to a decreased quality of life, particularly in older adults [13,14]. According to the Global Burden of Disease Study 2019 [15], in the year 2019 there were 21.17 million new cases of cardiovascular disease (CVD) globally among individuals aged over 70 years, alongside 12.17 million deaths attributed to this condition. Additionally, the total prevalence reached 195.9 million cases, resulting in 162.4 million disability-adjusted life years (DALYs) lost. Notably, since 1990, there has been a significant reduction in the global incidence, prevalence, DALYs lost, and mortality rate associated with elderly CVD [15,16]. Furthermore, the highest incidence, prevalence, DALYs lost, and mortality rates were found in individuals aged ≥95 years, while the lowest figures were observed in those aged 70 to 74 years [16]. Over the past 30 years, the burden of CVD has decreased in high-income regions, while remaining substantial in low-income areas (Figure 2) [17,18].

Globally, nearly twice as many deaths occur due to CVD compared to cancer [13]. Ischemic heart disease, followed by stroke and PAD, was the predominant type of ASCVD among the elderly; it was the leading cause of mortality and DALYs lost in older patients with CVD across both genders worldwide [19].

Fig. 2. Global burden of elderly cardiovascular disease in 2019 and its annualized changes from 1990 to 2019

Coronary artery disease

CAD is a pathological condition defined by the buildup of atherosclerotic plaque in the epicardial arteries, which can be classified as either obstructive or non-obstructive [20]. Given its dynamic characteristics, CAD manifests in a variety of clinical syndromes, which can be classified into ACS – encompassing ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina [21] – and CCS [22]. CAD constitutes the most significant disease burden among all types of CVD worldwide. In 2019, the global prevalence of CAD reached approximately 197.2 million cases, resulting in 9.14 million deaths and accounting for 182.03 million DALYs lost. Although these figures have shown an upward trend since 1990, the age--standardized rates for these metrics have exhibited a decline over the same period [23]. Moreover, across all age groups, the global mortality rate from CAD was higher in men than in women, with the highest rates found in the oldest age category. Up to the age group of 75–79 years, the total number of deaths was greater in men than in women, peaking in the 80––84 age group for both genders [24]. The age-specific analysis reveals that while men experience the highest burden of CAD at a relatively younger age (60––64 years), women tend to experience a delayed onset of severe disease, with peak DALY rates occurring later in life (80–84 years) [24]. In 2019, the incidence and prevalence of CAD were highest in settings with a low to middle sociodemographic index (SDI), while high-SDI regions exhibited the lowest rates. Conversely, the lowest mortality rates and fewest DALYs lost were also observed in high-SDI regions; however, the highest occurred in high to middle SDI settings [16].

Stroke

Stroke is recognized as the second most common cause of mortality worldwide and is regarded as one of the most incapacitating illnesses among older adults [15]. Strokes can be categorized into two primary types: ischemic and hemorrhagic. The former accounts

for about 85% of all stroke cases, while the latter occurs less frequently but tends to cause more severe damage than ischemic strokes [25]. According to the GBD 2019 Stroke Collaborators [26], the distribution of new stroke cases in 2019 revealed that ischemic strokes represented 62.4%, while intracerebral hemorrhages accounted for 27.9% and subarachnoid hemorrhages 9.7%. Notably, from 1990 to 2019, reductions in age-standardized rates were more significant for both intracerebral and subarachnoid hemorrhages than for ischemic strokes. In accordance with Li et al. [27], the prevalence of ischemic stroke in 2021, as indicated by age-standardized rates, exhibited a steady rise among older adults, reaching its highest point in individuals aged 80 to 95 years. In the various age categories examined, it was consistently observed that men demonstrated higher age--standardized prevalence when compared to their female counterparts [28]. This trend indicates a significant disparity in the prevalence of the condition between genders but within the same age group. Similarly, the incidence of ischemic stroke also demonstrated a gradual rise with age in 2021, peaking among older adults who are ≥95 years. Although the incidence in older men progressively exceeded that of women, the gender gap narrowed for those over 85 years of age [29]. The age-standardized mortality rates for ischemic stroke in 2021 decreased for both sexes in comparison with data from 1990, although these rates continued to rise with age. Men experienced higher age-standardized mortality rates than women across most age groups [27]. Approximately 75% of all stroke-related fatalities occurred in low- and middle-income countries, whereas high-SDI settings exhibited the lowest mortality rates and fewest DALYs lost [16]. Additionally, lost DALYs reflected a downward trend in 2021 compared to 1990 [27].

Peripheral artery disease

PAD is increasingly recognized as a significant public health issue, primarily due to its escalating prevalence across the globe. Despite this rise, it frequently goes undiagnosed and inadequately treated [30,31]. According to the GBD 2019 Peripheral Artery Disease Collaborators [18], in 1990, the estimated global number of individuals with PAD was 65.7 million. By 2019, this figure had increased by 72.5%, reaching a total of 113.4 million people affected by PAD. Over the 29-year period, the global population had increased by 45%, while the population of those aged 65 and older had risen significantly (by 122%), highlighting the contrast with this finding [26]. Moreover, according to Eid et al. [32], age-adjusted prevalence decreased by 22% from 1990 to 2019, while the total lost DALYs doubled during the same period (Figure 2). The worldwide prevalence of PAD is greater among older adults, with the highest rate being in the oldest group: 20.7% (95% confidence interval [17.58–24.18]) of individuals aged 90 to 94 years [31,32]. Interestingly, the incidence of PAD diminishes with advancing age after 75 to 79 years [16].

The impact of ASCVD on men and women varies significantly. Following menopause, the likelihood of cardiovascular issues in women increases markedly [33,34]. The prevalence of PAD varies significantly across different regions categorized by SDI. Specifically, regions with low SDI exhibited the lowest prevalence, while those with high SDI reported the highest prevalence for both overall and age--standardized measures [34]. Based on a 29-year follow-up period, a two-fold increase in mortality related to PAD was observed; however, the age--standardized mortality rate associated with PAD remained stable at an estimated 1 per 100,000 individuals [28]. Remarkably, between 1990 and 2019, DALY rates associated with ischemic stroke and ischemic heart disease exhibited a nearly 30% reduction, whereas the change in lost DALYs related to PAD was minimal [35,36].

Aortic aneurysm

An aortic aneurysm is defined as a localized increase in the size of the aorta where the diameter exceeds normative values by at least 50% for individuals of similar age and sex [37]. Studies have demonstrated a significant relationship between patient age and the adjusted death rate for aortic aneurysms. The most pronounced increase occurs in individuals older than 65 years, with the highest rate reaching a 12.3-fold rise in the oldest age cohort (older than 95) [38]. Worldwide, aortic aneurysms resulted in an 82.1% rise in mortality from 1990 to 2019, increasing from 94,700 to 172,400 deaths. In contrast, the age-adjusted mortality rate for aortic aneurysms decreased by 17.9% over the same timeframe [39]. In seniors, the highest increase in the age-adjusted death rate for aortic aneurysm was observed in high-SDI areas [15]. Furthermore, the age-adjusted DALY rate increased significantly among individuals older than 55, with the highest values being in the oldest group (over 85 years) [38]. In the Global Burden of Disease 2019 analysis [15], the major risk factors associated with aortic aneurysm include smoking, high blood pressure, a high-sodium diet, and lead contamination. Moreover, according to Roth et al. [35], records regarding the prevalence and incidence of aortic aneurysm were lacking. Nonetheless, prior research indicates that the prevalence of abdominal aortic aneurysm among men aged 65 and older is declining in developed countries, primarily attributed to smoking withdrawal.

Pathophysiology

Mechanisms of atherosclerosis – vascular aging and inflammation

Vascular aging is a critical element in the pathophysiology of atherosclerosis, but the precise mechanisms driving this connection remain insufficiently understood [36,40]. This process represents a complex interplay between biological and cellular aging, together with the progression of atherosclerosis (Figure 3).

The responses of the human system are modulated by a range of physiological changes associated with aging, such as reactive oxygen species (ROS), angiotensin II, lipid levels, mechanical stress, glycemia, impaired insulin response, and the inflammatory process, which involves mechanisms essential to vascular aging [36,40,41]. Aging is attributed to a persistent, mild inflammatory condition affecting the whole body [42]. All the factors mentioned above affect inflammatory mediators, including tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), interleukin 6 (IL-6), interleukin 18 (IL-18), and fibrinogen, which may cause an elevated procoagulant state, generate ROS, and release pro-inflammatory cytokines [36]. Moreover, these determinants collectively contribute to the remodeling of the blood vessel layers (primarily the tunica intima and the tunica media), along with the dilation of the lumen [40,43]. Additionally, the accumulation of deteriorating cells may also play a crucial role in vascular aging, which causes disruptions in cellular regulation, alterations in secretory activity, and modifications to the epigenetic landscape [36,40,41].

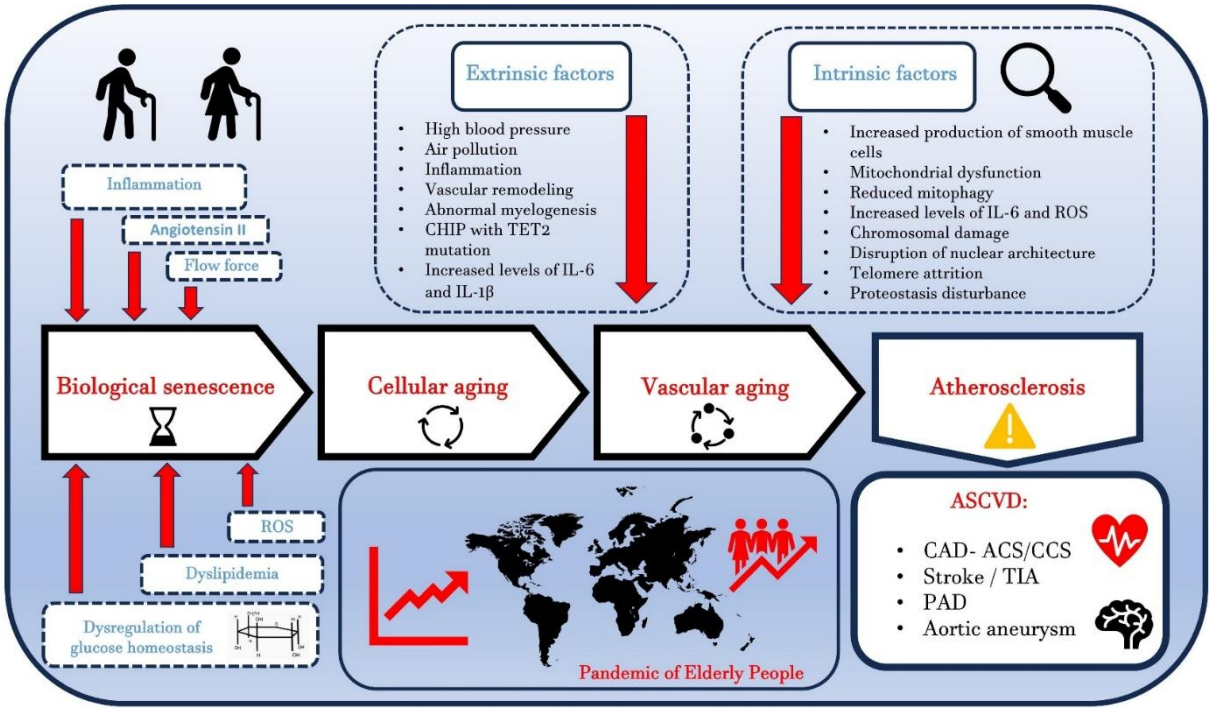

Fig. 3. Vascular aging and atherosclerosis

Intrinsic and extrinsic factors influencing disease progression

There are two primary ways in which aging contributes to the development of atherosclerosis: through intrinsic and extrinsic mechanisms (Figure 3). Internal changes are driven by several factors, such as mitochondrial malfunction, impairment of proteostasis, disruption of nuclear architecture, chromosomal injury, telomere attrition, and epigenetic alterations [40]. Conversely, external elements caused by global, regional, national, and local environmental factors – such as high blood pressure, air pollution, persistent inflammation, vascular remodeling, and disruptions in intercellular signaling – have the potential to affect physiological regulation and deteriorate blood vessels [36,44]. Interestingly, changes in the bone marrow associated with aging enhance the occurrence of clonal hematopoiesis of indeterminate potential (CHIP). This, in turn, can create a bias in the process of myelogenesis and further promote atherosclerosis [41]. Consequently, the elevated risk of ASCVD could be determined by CHIP-related changes, the higher level of IL-6, and an inappropriately regulated mitochondrial cycle, which are related to the aging process [40,41].

Senescence-linked atherosclerosis is a complex and heterogeneous process in which both internal and external factors contribute to the deterioration of the circulatory system, working in conjunction with the immunological system, independent of any lipid disorders [41].

Vascular aging mechanisms and their clinical implications

As individuals age, the arterial walls undergo thickening, which is primarily caused by a decrease in elastin content alongside an accumulation of collagen fibers, which lack elasticity [45]. Consequently, the aorta and other major arteries become stiffer, which is reflected by higher systolic blood pressure (SBP), lower diastolic blood pressure, wider pulse pressure, and higher pulse wave velocity. This heightened vascular resistance contributes to left ventricular hypertrophy, augmented myocardial workload, and a mismatch between the oxygen supply and the demand of the myocardium [6,46]. Additionally, reduced nitric oxide synthase activity impairs the coronary circulation's ability to adapt to the higher oxygen demands of the myocardium. Together, these factors increase the susceptibility of elderly individuals to a higher incidence of type 2 myocardial infarction (MI) and NSTEMI [6]. Although inflammation contributes to the onset and advancement of CAD, the coexistence of age-related conditions, including multimorbidity, cognitive impairment, and frailty, exacerbates the emergence of subclinical CAD. Chest pain is more commonly associated with ACS in younger patients, whereas in older individuals it is often attributable to noncardiac causes [47]. ACS in these individuals often presents with symptoms such as dyspnea, syncope, or abrupt cognitive changes [6,47]. Advancing age is associated with an increased prevalence of abnormalities on resting electrocardiograms (ECGs) – affecting nearly 70% of elderly patients. These disturbances – such as left bundle branch block, arrhythmias (e.g., atrial fibrillation), and paced rhythms – pose challenges to accurately interpreting ECGs in older individuals suspected of ACS, especially when compared to younger populations [48].

Similar mechanisms of vascular aging play a role in the pathogenesis of ischemic stroke. Impaired cerebral microvasculature contributes to altered resistance with a reduced ability to vasodilate. These key changes lead to a predisposition to hypoperfusion and diminished oxygen and nutrient delivery, resulting in the progression of cerebral microvascular disease. Compared to older vasculature, that of younger individuals shows a heightened ability to withstand ischemic damage, which is evidenced by the prompt initiation of angiogenic pathways and robust vasodilatory mechanisms [49,50]. In addition, elderly patients exhibit a greater prevalence of comorbidities, including atrial fibrillation, hypertension, and a history of coronary heart disease. Older age is correlated with more pronounced neurological deficits upon stroke onset; however, there is also a higher incidence of cardioembolic stroke, attributed to the higher occurrence of atrial fibrillation, which carries a mortality risk exceeding that of atherosclerotic infarctions. Conversely, smoking has been identified as a significant factor linked to an earlier onset of acute ischemic stroke [51].

Risk factors

The main CVD risk factors in older adults were found to be consistent across both sexes. The primary health risks for both include elevated SBP, dietary risks, high levels of LDL cholesterol (LDL-C), and higher fasting plasma glucose levels (Table I) [16].

Table I. Primary CVD risk factors for the elderly in 2019

1. High systolic blood pressure
2. Dietary risk
3. High fasting plasma glucose
4. High LDL cholesterol

Among the elderly, hypertension is a dominant driver of cardiovascular disease, cerebrovascular disease, and increased mortality [52]. It is estimated that more than 60% of individuals over the age of 60 are affected by hypertension; this prevalence is expected to rise as the population continues to age [53,54]. Inadequate control of blood pressure can lead to various complications affecting the vascular, cardiovascular, neurological, and renal systems, which represents a significant challenge to global public health. Consequently, antihypertensive treatment offers considerable advantages for older adults [52,55].

Malnutrition is a common issue among the elderly that represents a considerable strain on healthcare and welfare services. This demographic is especially susceptible to malnutrition due to factors such as the physiological deterioration associated with aging, restricted access to nutritious food, and the presence of comorbidities [56]. While the causes of malnutrition are intricate and multifaceted, extensive research has recognized it as a significant risk factor for arteriosclerosis, in addition to the well-documented traditional risk factors for CVD [57,58]. Poor nutrition is linked to negative health consequences across many types of cardiovascular disease [59]. Malnourished elderly individuals are more prone to death if they undergo percutaneous coronary intervention and are more susceptible to long-term complications after MI [60]. Furthermore, in patients diagnosed with heart failure, a diet deficient in essential nutrients may

exacerbate deterioration, as reflected by elevated levels of brain natriuretic peptides [59,61]. Moreover, together with protein deficiency and a decline in bone mineral mass, accelerated muscle atrophy contributes to an increased likelihood of premature bone loss and fractures. This compromised physical state can further impair immune function by enhancing susceptibility to infection and prolonging the duration of an illness. Additionally, it decreases functional reserve and increases reliance on others [62]. According to the ESPEN guidelines [63], older adults should aim to consume around 30 kcal per kilogram of their body weight daily. Protein consumption should be a minimum of 1 g per kilogram daily. Diets should include fiber-rich foods and sufficient hydration; healthy women are advised to drink around 1.6 liters of fluids daily – and men at least 2.0 liters. Dietary limitations are typically discouraged, micronutrients should be consistently supplied, and physical activity is promoted to preserve or enhance muscle mass and function.

In light of the above-discussed factors, regular evaluation of nutritional status is crucial for identifying malnutrition in elderly patients and facilitating timely preventive interventions. The Malnutrition Universal Screening Tool and the Mini Nutritional Assessment are widely employed to evaluate nutritional status. The former evaluates risk based on BMI, recent weight loss, and acute illness, whereas the latter incorporates anthropometric measurements, overall health, dietary habits, cognitive conditions (e.g., dementia or depression), and mobility restrictions [64]. Consequently, this approach enables healthcare providers to tailor diagnostic and therapeutic strategies to an individual patient's needs [65].

Elevated LDL-C level in middle-aged individuals is a significant risk factor for future cardiovascular events [1,66]. However, previous studies indicate that there is no correlation between elevated levels of LDL-C and an increased risk of ASCVD in patients aged ≥70 [67]. Consequently, the efficacy of LDL-C--lowering treatment in older adults remains a subject of ongoing debate [68,69]. According to Mortensen and Nordestgaard [67], among the 91,131 individuals enrolled in the CGPS study, the highest incidence of MI and ASCVD was observed in those aged 70 to 100 years, which was associated with an increase of 1.0 mmol/L in LDL-C levels (hazard ratio [HR] = 1.34 for MI and HR = 1.16 for ASCVD). Preventive strategies for older adults without ASCVD are an important issue, as they may reduce morbidity and mortality in this globally growing population; however, shared decision-making is essential and the advantages, potential side effects, anticipated lifespan, and any age-related disorders must be taken into consideration [68,69,70].

Fasting plasma glucose serves as a significant risk factor for overall glycemic control and is associated with an elevated risk of ASCVD and heart failure [71,72]. Interestingly, different cut-off values for diagnosing pre-diabetes are established by various health organizations: 5.6–6.9 mmol/L according to the American Diabetes Association and the European Society of Cardiology (ESC), and levels from 6.1 to 6.9 mmol/L according to the WHO [73]. According to the findings of Dong et al. [74], the burden of CVD attributable to impaired fasting glucose (IFG) is significantly greater in the elderly population compared to their younger counterparts. Furthermore, males exhibit a higher prevalence of CVD associated with IFG than females across all age groups. In 2019, the primary contributors to the global CVD burden linked to IFG were ischemic heart disease, stroke, and peripheral arterial disease. Furthermore, Gao et al. [75] conducted a cohort study which revealed that IFG elevates the risk of both all-cause mortality and mortality due to cancer. In this regard, it is important to explore the development of more focused and tailored strategies for mitigating various negative health outcomes associated with IFG.

It is noteworthy that there is a significant correlation between advancing age and the prevalence of diabetes mellitus (DM) [76]. Elderly individuals who are 65 years of age or older represent almost 50% of all DM diagnoses worldwide [77]. Type 2 DM is the predominant form of diabetes in older adults, accounting for over 90% of cases. Over time, the aging process leads to a progressive decline in β-cell function, which exacerbates insulin secretion deficiencies and contributes to insulin resistance through multiple mechanisms [68]. In advanced stages, this progression gives rise to both microvascular and macrovascular complications, thereby elevating the risk of ASCVD, with a particular emphasis on CAD, stroke, and PAD [78]. DM can negatively impact overall well-being and may lead to reduced self-determination among older adults. Diabetic seniors face an elevated risk of developing various age-related conditions: they are 1.5 to 2 times more likely to develop Alzheimer's disease and vascular dementia [79]. Reports indicate that 50% to 90% have at least one additional chronic disease, with 40% having four or more comorbidities [80]. Polypharmacy increases the risk of drug interactions and adverse effects [80]. Additionally, they are 1.5 times more likely to experience sarcopenia than non-diabetics [81]. Furthermore, frailty affects around 25% of diabetics over 65 years of age [82]. As a consequence of the higher risk of developing cardiovascular and non-cardiovascular disorders associated with diabetes, it is essential for elderly diabetics to receive holistic, specialized care management. Clinical decisions should take into

account the advantages and disadvantages of treatment goals to avoid detrimental effects and maintain a comfortable life. An appropriate level of effort and dietary status should be chosen to address sarcopenia, physical inactivity, and frailty in these diverse groups [76,77,78,79,80,81,82].

Considering the significant association between frailty and CVD, it is essential that the diagnostic and therapeutic approach for older adults commence with a comprehensive evaluation of frailty [83]. Although numerous definitions exist, two key approaches to understanding frailty stand out: frailty as a biological syndrome linked to aging, as defined by Fried et al. [84], and frailty as a condition characterized by a build-up of health shortcomings, as proposed by Rockwood and Mitnitski [85]. Research by Shamsalinia et al. [86] identifies several factors that can potentially elevate the risk of CVD in frail individuals, including advanced age (>84 years), female sex, obesity, elevated uric acid levels (>7 mg/dL), hyperglycemia (fasting glucose ≥126 mg/dL), and diabetes. Apart from the existence of traditional cardiovascular risk factors, frailty elevates the likelihood of cardiovascular incidents and is frequently observed among elderly individuals with aortic stenosis and heart failure [87]. Regardless of age, coexisting conditions, and impairment, frailty contributes to the worst outcomes in patients with CVD, including increased mortality, hospitalization, and major adverse cardiovascular events [88,89]. Moreover, frailty is associated with changes in muscle force and physical performance. Frailty is commonly linked to low body mass index (BMI), yet paradoxically, individuals with higher BMI are also at a higher risk of frailty. This phenomenon is partly attributed to the growing incidence of sarcopenic obesity, a condition in which muscle mass is substituted with adipose tissue [83,90]. Sarcopenia is precipitated by a disruption in anabolic-catabolic equilibrium. Contributory factors include chronic diseases, sedentary lifestyle, and inadequate nutrition. Ultimately, sarcopenia leads to enhanced susceptibility to CVD and increased likelihood of death, loss of balance, and diminished general well-being [91]. These conditions co-occur with higher frequency among the elderly and are modifiable. Therefore, implementing several early interventions may help in preventing these conditions along with their negative impacts on older adults, which include well-balanced exercise routines and dietary practices [92].

Roughly two in three older adults experience multimorbidity, while the overwhelming proportion of patients with chronic CVD have comorbidities [93]. Among individuals with multimorbidity, CVD is the leading comorbidity and CAD stands out as a particularly common chronic disorder [94]. Multimorbidity is associated with an enhanced likelihood of mortality and necessitates greater consumption of medical services such as hospitalization, outpatient care, and consultations with specialists. It also has a deleterious effect on physical function and overall wellbeing. The complexity introduced by multiple comorbidities often leads to disjointed care due to the participation of numerous healthcare professionals, resulting in substantial challenges for both the patients and those providing care for them [93,95]. A substantial hurdle arises when healthcare practices adhere strictly to disease-centric guidelines that fail to effectively address the multifaceted nature of multimorbidity. Moreover, clinical trials typically have a limited number of participants with multiple chronic conditions due to restrictive eligibility requirements. Consequently, these studies yield data that may not adequately reflect real-world scenarios involving patients with complex health profiles. The inconsistency among these guidelines poses a considerable obstacle in devising an effective care plan for patients with multimorbidity. Furthermore, managing one disease can inadvertently exacerbate coexisting health issues. It is crucial not to overlook potential drug interactions and associated complications that may arise during treatment [93,94,95,96,97].

Polypharmacy, typically characterized by the simultaneous use of five or more medications, is especially common among older adults who frequently experience multiple chronic health issues. Although the use of several medications can be essential for addressing intricate healthcare needs, it also constitutes an independent risk factor for significant cardiovascular events, as well as mortality – both cardiovascular disease-specific and overall – in individuals aged 65 and older [96,97,98].

Given the prevalence of these factors in older adults, integrating recommendations from multiple disease-specific guidelines can reduce therapeutic conflicts. Key strategies include developing unified protocols, delivering individualized care, enhancing communication and coordination, applying deprescribing and medication reviews, and utilizing epidemiological and real-world data. This holistic approach promotes comprehensive patient management [99,100].

Diagnosis and risk assessment

Methods for assessing ASCVD risk in older adults

The global phenomenon of population aging represents one of the most significant demographic shifts of our era [13]. Concurrently, because the incidence of cardiovascular events rises steadily with advancing age, evaluating cardiovascular risk in older adults becomes an increasingly critical responsibility [101]. The application of diverse cardiovascular risk

calculators in clinical settings has been instrumental in managing patients at risk for cardiovascular issues. Nevertheless, it is important to recognize that most of these calculators were based on studies primarily involving middle-aged populations [95]. This focus has resulted in a significant gap in the literature regarding the specific factors and algorithms that should be adapted to accurately evaluate cardiovascular risk in older adults [102,103]. When assessing cardiovascular risk in older adults, several commonly used tools are available:

1. SCORE2-OP – an algorithm developed by the ESC, it assesses the 10-year cardiovascular event risk in older adults (70–89 years old) across four different geographic regions. The key factors considered in this model are age, sex, smoking status, non-HDL cholesterol levels, and SBP [1]. The model, developed mainly from European cohorts such as the CONOR study, may have limited generalizability to populations with varying demographic and epidemiological characteristics. Furthermore, evidence suggests that it may underestimate or overestimate risk in individuals over 80, largely due to diminished risk discrimination in this age group. Moreover, important factors such as multimorbidity, functional status, and geriatric indicators are not incorporated, which may potentially affect the accuracy of predictions [104,105].
2. QRISK3 – this model, applicable to those between 25 and 84 years old, includes parameters such as age, sex, ethnicity, smoking status, diabetes status, cardiovascular events, chronic kidney disease, atrial fibrillation, blood pressure, migraine, rheumatoid arthritis, systemic lupus erythematosus, severe mental illness, atypical antipsychotic medications, steroid tablets, erectile dysfunction, lipid status, SBP, and BMI [106]. The QRISK3 model is not specifically calibrated for the very elderly, especially those over 80, which may overestimate the risk. This is because aging increases the likelihood of non-cardiovascular mortality, a factor not fully accounted for in the model. Although QRISK3 includes multiple comorbidities, its precision is limited by the challenges in accurately capturing competing risks of death in this age group [107].
3. CVDPoRT – a model which can be used for patients ranging from 20 to 105 years, it evaluates a comprehensive set of sociodemographic factors, such as academic achievement, culture, resident status, neighborhood poverty, and measures of community integration. Importantly, it does not incorporate conventional biomarkers such as lipid levels or direct blood pressure measurements [108]. Developed and validated with large Canadian population health surveys, this predictive algorithm focuses on sociodemographic and behavioral factors. Nevertheless, it insufficiently addresses competing mortality risks and excludes specific geriatric risk indicators, potentially resulting in overestimated risk among older adults, especially those over 80 years old [108].
4. Pooled cohort equations – these encompass a range of factors, including age, total and HDL cholesterol levels, SBP readings, diabetes status, and smoking habits, to evaluate risk in individuals aged 40 to 79 years [109].
5. Revised WHO CVD risk estimation charts – intended for patients aged 40 to 74 years, these encompass a laboratory-based model that considers factors such as age, smoking habits, SBP, diabetes history, and total cholesterol levels and a non-laboratory-based model that uses age, smoking status, SBP, and BMI [110].

In 2021, the ESC introduced the SCORE2-OP model as a novel tool to evaluate the 10-year risk of cardiovascular outcomes resulting in death or survival among seniors (individuals aged 70 years or older) who appear healthy [1]. A novel algorithm, modified to account for comorbidities unrelated to CVD, provides an assessment of cardiovascular risk across four distinct geographic areas. These regions are stratified according to their risk levels: low, moderate, high, or very high [104]. When utilizing these risk calculators, it is important to recognize that some rely on traditional risk factors, which tend to have a diminishing effect on CVD risk as individuals age [1]. Additionally, they do not incorporate data from radiological assessments and circulating biomarkers [111], which may also cause considerable misjudgments of the 10-year cardiovascular risk, with potential discrepancies ranging from 3% to as much as 1430% [112]. Given that no ideal risk assessment calculator exists, easy-to-use predictive tools combined with a comprehensive approach to treatment and prognosis are likely to be most effective in routine medical care [101,103].

Primary prevention

Finally, primary prevention of ASCVD in older adults is crucial because individuals who reach the age of 65 without any signs of ASCVD still face a lifetime risk of over 50% for developing cardiovascular issues [113]. Furthermore, ASCVD accounts for 39% of all fatalities in the population aged 75 to 84 [114]. Based on the 2021 ESC Guidelines for preventing cardiovascular disease in clinical settings [1], statin therapy for primary prevention is supported by class IIb and level B evidence for older individuals (70 and older) who are regarded as at least high risk for CVD. Although the cut-off for LDL-C levels of <2.6 mmol/L (<100 mg/dL) seems rational, there are no strict goals for primary prevention in older

individuals [1]. Nevertheless, additional evidence indicates that statin therapy for primary prevention is clinically significant for older adults without a diagnosis of ASCVD. The PROSPER study marked the first major investigation into the effects of statin therapy in older adults aged 70 to 82. This trial included 5,804 participants and found that pravastatin significantly reduced the rates of CAD deaths, non--fatal MI, and strokes [115]. Following the PROSPER study, several other trials – such as ASCOT-LLA, CARDS, JUPITER, and HOPE-3 – further confirmed the advantages of statins for primary prevention in older adults, especially those between 70 and 75 years of age. These studies revealed notable reductions in cardiovascular event risks for older patients receiving statin treatment. For example, atorvastatin led to a 37% decrease in non-fatal MI and fatal CAD among participants aged 65 and older in the ASCOT-LLA trial [116]. Similarly, the JUPITER trial found that rosuvastatin treatment resulted in a 39% reduction in first cardiovascular events among individuals aged 70 and over [117]. It is crucial to note that as individuals age, the relationship between the duration of life free from CVD and overall life expectancy begins to diverge due to the increasing risk of death unrelated to CVD, often referred to as "competing risk." This significant factor may contribute to the potential benefits of treatment being overestimated [1]. Despite the reduced relative impact of statins, the notably elevated absolute risk of CVD in older adults indicates that the overall advantages of statin therapy may remain considerable [118]. In two randomized trials, JUPITER and HOPE-3, participants aged 70 and older made up 32% and 24% of the study cohort, respectively. Nonetheless, in the first trial, older adults were responsible for 55% of the recorded cardiovascular events, while in the second trial, they accounted for 43% [119]. However, the recommendation from the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease [120] and the US Preventive Services Task Force [121] is more liberal, as both recommend statin management for up to 75 years of age (class I for a 10-year risk of ≥7.5% and grade B for a risk of ≥10%, respectively). Based on the guidelines mentioned earlier, there is a discrepancy in the recommendations for statin treatment, which highlights the uncertainty surrounding the benefits of such treatment for older individuals, especially those aged 75 and above [122]. Two major ongoing randomized trials aim to clarify the effectiveness of atorvastatin at a dosage of 40 mg daily compared to a placebo in elderly populations:

- The PREVENTABLE trial, currently underway in the United States, seeks to recruit 20,000 individuals at least 75 years old [123]
- The STAREE trial in Australia is a randomized, double-blind, placebo-controlled study designed to evaluate overall survival and disability-free survival among 18,000 participants aged 70 and over [124].

Conclusions

The older adult population is highly heterogeneous, presenting unique challenges in the context of cardiovascular health. ASCVD represents a significant concern among elderly individuals, particularly given the aging global population and its implications for future healthcare needs. While CAD remains the most prevalent form of ASCVD in this demographic, the distribution of other types varies significantly. In high--income countries, there has been a decline in the burden of ASCVD; however, low-income areas continue to experience substantial challenges due to factors such as culture, habits, education system, and ecological conditions. Additionally, geriatric issues – including multimorbidity, polypharmacy, frailty, sarcopenia, and cognitive impairments – complicate both diagnosis and treatment strategies for older adults. These critical conditions necessitate a tailored approach that integrates geriatric principles into cardiovascular care. To better understand and address the patterns of CVD burden in this population, it is essential to increase the inclusion of older adults in randomized clinical trials. Furthermore, developing specific guidelines and recommendations for this group, alongside adopting a holistic approach to care, is imperative to optimizing outcomes.

Authors' contribution

Study design – W. Żurański, M. Gąsior, B. Hudzik
Manuscript preparation – W. Żurański, M. Gąsior, B. Hudzik
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PRACA ORYGINALNA
ORIGINAL PAPER

The dopaminergic system is able to modulate the central histamine-induced pressor effect in hemorrhage-shocked rats

Układ dopaminergiczny może wpływać na reakcję presyjną ośrodkowo działającej histaminy u szczurów we wstrząsie krwotocznym

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ABSTRACT

INTRODUCTION: Histamine administered intracerebroventricularly (icv) induces a resuscitating effect in hemorrhage--shocked rats. Dopamine receptors are present in neuronal pathways involved in central cardiovascular regulation; therefore, the aim of the study was to examine the effects of pre-treatment with dopamine receptor antagonists on histamine-induced cardiovascular effects in hemorrhagic shock.

MATERIAL AND METHODS: Male Wistar rats subjected to a reversible hemorrhagic hypotension with mean arterial pressure (MAP) of 30–35 mmHg were anaesthetized with ketamine/xylazine (100 mg/kg + 10 mg/kg, intraperitoneally). Immediately after bleeding terminated, the animals were pre-treated icv with dopamine receptor antagonists or saline; 5 min later they were treated icv with histamine (50 nmol) or saline.

RESULTS: Hemorrhagic hypotension was accompanied by decreases in pulse pressure (PP), heart rate (HR), and mesenteric blood flow (MBF). Histamine induced increases in MAP, HR, and MBF, with a decrease in PP as compared to the control group. Pre-treatment with the dopamine D_4 receptor antagonist L-745,870 potentiated histamine-induced MAP and MBF changes, with no influence on PP or HR. There were neither the influence of the other dopamine receptor antagonists on histamine-mediated action nor the effects of dopamine receptor antagonists given alone in the control groups.

CONCLUSIONS: Dopamine, acting via D_4 receptors, is able to modulate the central histamine-induced pressor effect in hemorrhage-shocked rats.

KEYWORDS

dopamine, histaminergic system, hemorrhagic shock, rats

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STRESZCZENIE

WSTĘP: Histamina podawana do komory bocznej mózgu (*intracerebroventricular* – icv) wywołuje efekt resuscytacyjny u szczurów we wstrząsie krwotocznym. Receptory dopaminowe występują w drogach neuronalnych związanych z ośrodkową regulacją układu krążenia, dlatego celem pracy było zbadanie wpływu zablokowania receptorów dopaminowych na efekty działania histaminy we wstrząsie krwotocznym.

MATERIAŁ I METODY: Badania przeprowadzono u znieczulonych ketaminą/ksylazyną (100 mg/kg + 10 mg/kg, dootrzewnowo) samców szczurów szczepu Wistar, u których indukowano odwracalną hipotensję krwotoczną ze średnim ciśnieniem tętniczym krwi (*mean arterial pressure* – MAP) 30–35 mmHg. Niezwłocznie po zakończeniu krwotoku u zwierząt stosowano icv premedykację antagonistami receptorów dopaminowych lub 0,9-proc. roztworem NaCl; 5 minut później podawano icv histaminę (50 nmol) bądź 0,9-proc. roztwór NaCl.

WYNIKI: Hipotensji krwotocznej towarzyszyło obniżenie ciśnienia tętna (*pulse pressure* – PP), częstości rytmu serca (*heart rate* – HR) i krezkowego przepływu krwi (*mesenteric blood flow* – MBF). Histamina wywołała wzrosty MAP, HR i MBF, pozostając bez wpływu na PP. Premedykacja antagonistą receptorów dopaminowych D_4 L-745,870 nasilała wywoływane przez histaminę zmiany MAP i MBF, nie miała natomiast wpływu na PP i HR. Nie stwierdzono ani wpływu antagonistów innych receptorów dopaminowych na działanie histaminy, ani efektów samodzielnego działania blokerów receptorów dopaminowych w grupach kontrolnych.

WNIOSKI: Dopamina, działając poprzez receptory D_4, jest zdolna do modulowania reakcji presyjnej, wywoływanej przez ośrodkowo działającą histaminę u szczurów we wstrząsie krwotocznym.

SŁOWA KLUCZOWE

dopamina, układ histaminergiczny, wstrząs krwotoczny, szczury

INTRODUCTION

Hemorrhagic shock is a consequence of inadequate tissue perfusion following blood loss. It is one of the most frequent preventable causes of death in humans [1]. Taking into account hemodynamic changes, there are two phases of the response to massive hemorrhage. The initial phase results from baroreflex inhibition and is characterized by an increase in sympathetic nervous system activity (the sympathoexcitatory phase) and in total peripheral resistance (TPR) and heart rate (HR). In the second phase, there is a withdrawal of the sympathetic tone (the sympathoinhibitory phase), with decreases in cardiac output, TPR, and HR [2]. Both phases correspond to the pathophysiological/therapeutic hemorrhagic shock classification proposed in 2012, in which moderate and mild phases of shock are generally characterized by sympathoexcitation, while severe and critical shock phases – by sympathoinhibition [3].

The activity of the sympathetic nervous system originates in pre-sympathetic neurons, located mainly in the rostral ventrolateral medulla (RVLM). These neurons play a crucial role in cardiovascular regulation, in both normo- and hypotension. In hemorrhage-induced hypotension, the function of RVLM neurons is influenced by many neurotransmitters/neuromodulators. According to the classic work by Bertolini [4], opioid peptides are generally able to inhibit the activity of RVLM neurons, while non-opioid neurotransmitters/neuromodulators prolong the sympathoexcitatory phase.

In our previous studies, we clearly demonstrated a resuscitating effect of centrally acting exogenous and endogenous histamines in experimental models of hemorrhagic shock in rats [5,6,7]. Interestingly, in hemorrhagic shock conditions, histamine-induced rises in mean arterial pressure (MAP) and HR after the administration of equal doses of the amine are a few times higher than in normovolemic animals [5]. This finding allowed us to classify histamine as a central non-opioid neurotransmitter with anti-shock properties.

Dopaminergic neurons are located mainly in the substantia nigra pars compacta and the ventral tegmental area of the midbrain and form the nigrostriatal, mesocortical, and mesolimbic projections. The degeneration of dopaminergic neurons of the substantia nigra, with subsequent decreased dopamine secretion in the striatum, is responsible for the development of Parkinson's disease, the best known result of dopaminergic system dysfunction [8]. However, centrally acting dopamine also plays a role in numerous brain functions, including cognitive processes [9], motivation and reward-related behavior [10], appetite control [11], hormone secretion [12], and addiction mechanisms [13]. Moreover, dopaminergic neurons are able to influence central cardiovascular regulation. An initial study by Granata and Woodruff [14] has demonstrated increases in MAP and HR resulting from bilateral microinjections of dopamine into the area of the nucleus of the solitary tract (nucleus tractus solitarii – NTS). Since dopamine receptors are present in the NTS and are able to affect the baroreflex activity/pathway, the aim of this study

was to examine the effects of dopamine receptor blockage on the central histamine-induced pressor reaction in hemorrhage-shocked rats.

MATERIAL AND METHODS

Animals

All procedures were carried out in accordance with EU directives and were reviewed by the Local Ethics Committee in Katowice, Poland (Notification 47/2018). Male Wistar rats weighing 255–295 g (3––6 months old), housed in an animal colony under controlled conditions (temperature: 20–22 °C; humidity: 60%–70%; and 12 h light/dark cycle), and provided with standard food and water *ad libitum* were used in the experiment.

Surgical preparation

After the induction of general anesthesia with ketamine/xylazine (100 mg/kg + 10 mg/kg intraperitoneally [ip], supplemented if required), the rats were implanted in the right femoral artery and vein with catheters filled with heparinized saline (100 IU/ml). MAP, pulse pressure (PP), and HR were measured using a TAM-A transducer amplifier module and an ECGA amplifier (Hugo Sachs Elektronik, Germany), respectively.
To monitor mesenteric blood flow (MBF; transit time flowmeter module, Transonic Systems Inc., USA), an electromagnetic perivascular probe (type 1RB, Hugo Sachs Elektronik, Germany) was implanted around the superior mesenteric artery. All cardiovascular measurements started after the adaptation period (30 min).

Experimental protocol

The animals were prepared for intracerebroventricular (icv) treatment 3–5 days before the experiment by stereotaxic implantation of polyethylene cannulae into the right brain lateral ventricle under ketamine/xylazine anesthesia, as previously described [5]. All icv injections were made at a volume of 5.0 µl. The correctness of the injections was verified after experiments [5].
Reversible hemorrhagic hypotension was induced by intermittent blood withdrawal (up to 0.5 ml/min) from the catheter in the right femoral vein over a period of 15–25 min, until MAP was stabilized at 30–35 mmHg. Immediately after MAP stabilization, the animals in separate groups (each n = 6) were icv pre-treated with dopamine $D_{1/5}$, D_2, D_3, and D_4 receptor antagonists: SCH-23390 (0.1 µg), remoxipride (1 µg), U-99194 (0.16 µg), and L-745,870 (0.13 µg), respectively. After 5 min, the rats were icv injected with histamine (50 nmol) or 0.9% NaCl solution. The dosages for the dopamine receptor antagonists were taken from the literature [15,16,17]. According to the recommendations of the Local Ethics Committee, and to implement 4R principles and avoid unnecessary duplication of studies performed previously on the same rat strain using the same experimental protocol, we did not repeat experiments in the control saline--injected group and the saline-pre-treated histamine--injected group, instead citing previously published results [18,19].
Animals, always under anesthesia, were continuously monitored for 2 h after treatment to evaluate mortality. Body temperature was monitored by a rectal thermometer and was maintained at 37 ± 0.5 °C using a heat lamp throughout the experiment. The experiments were performed between 9:00 am and 2:00 pm.

Drugs

The following drugs were used: heparin (Polfa, Poland), histamine hydrochloride, U-99194 maleate (Sigma-Aldrich, USA), L-745,870 trihydrochloride, remoxipride hydrochloride, SCH-23390 hydrochloride (Tocris Bioscience, UK), ketamine hydrochloride, and xylazine (Biowet Sp. z o.o., Poland). All drug solutions were prepared on the day of the experiment.

Statistics

All values are given as means ± SD and $p < 0.05$ was considered the level of significance. Statistical evaluation of the other results entailed analysis of variance (ANOVA) and the post-ANOVA Student––Newman–Keuls test.

RESULTS

Initial, pre-bleeding values of MAP, PP, HR, and MBF did not reveal significant differences between the groups (in the control group: MAP: 87.46 ± 4.36 mmHg; PP: 23.43 ± 5.88 mmHg; HR: 215 ± 30 beats/min; and MBF: 8.15 ± 1.88 ml/min; Table I) [18,19].

Table I. Cardiovascular parameters in animals pre-treated with dopamine receptor antagonists/saline and treated with histamine/saline

Pre-treatment (icv)	Treatment (icv)	Before bleeding	After bleeding	20 min after treatment
MAP (mmHg)				
saline	saline	87.46 ± 4.36	32.88 ± 1.5*	54.73 ± 5.18* [18,19]
saline	histamine	82.65 ± 6.93	32.55 ± 1.22*	84.7 ± 4.27# [18,19]
SCH-23390	saline	88.23 ± 7.53	32.45 ± 1.12*	51.96 ± 3.91*
SCH-23390	histamine	88.31 ± 6.66	32.16 ± 1.15*	85.43 ± 5.59#
remoxipride	saline	89.01 ± 4.61	32.77 ± 1.23*	52.31 ± 5.8*
remoxipride	histamine	86.3 ± 6.52	32.16 ± 1.12*	82.9 ± 4.75#
U-99194	saline	89.61 ± 7.32	32.21 ± 1.38*	56.03 ± 7.74*
U-99194	histamine	87.98 ± 7.87	32.38 ± 1.01*	81.8 ± 5.66#
L-745,870	saline	90.3 ± 7.96	32.31 ± 1.49*	52.45 ± 6.72*
L-745,870	histamine	89.25 ± 6.36	31.66 ± 0.75*	94.43 ± 3.61#^
PP (mmHg)				
saline	saline	23.43 ± 5.88	8.49 ± 2.36*	22.74 ± 3.85 [18,19]
saline	histamine	22.23 ± 4.57	6.98 ± 2.13*	17.48 ± 3.1*# [18,19]
SCH-23390	saline	21.54 ± 3.52	8.91 ± 0.94*	20.56 ± 1.72
SCH-23390	histamine	21.68 ± 5.23	7.56 ± 2.79*	19.95 ± 3.22
remoxipride	saline	21.17 ± 4.93	9.53 ± 1.19*	20.84 ± 4.31
remoxipride	histamine	23.58 ± 5.32	7.95 ± 1.78*	20.29 ± 3.18
U-99194	saline	20.75 ± 4.47	9.41 ± 1.83*	21.67 ± 2.34
U-99194	histamine	20.92 ± 4.7	7.68 ± 2.29*	18.56 ± 3.94
L-745,870	saline	20.84 ± 6.99	9.01 ± 2.0*	19.7 ± 3.0
L-745,870	histamine	19.34 ± 3.41	8.25 ± 3.37*	19.8 ± 5.76
HR (beats/min)				
saline	saline	215 ± 30	145 ± 27*	107 ± 35* [18,19]
saline	histamine	218 ± 34	162 ± 27*	181 ± 37# [18,19]
SCH-23390	saline	214 ± 29	139 ± 29*	112 ± 26*
SCH-23390	histamine	204 ± 34	149 ± 35*	176 ± 28#
remoxipride	saline	206 ± 38	140 ± 28*	113 ± 32*
remoxipride	histamine	208 ± 25	144 ± 26*	170 ± 32#
U-99194	saline	204 ± 36	130 ± 27*	117 ± 18*
U-99194	histamine	212 ± 31	152 ± 33*	188 ± 17#
L-745,870	saline	199 ± 33	145 ± 24*	120 ± 21*
L-745,870	histamine	209 ± 34	133 ± 32*	172 ± 24#
MBF (ml/min)				
saline	saline	8.15 ± 1.88	1.62 ± 0.39*	1.48 ± 0.78* [18,19]
saline	histamine	8.82 ± 1.95	1.51 ± 0.31*	2.25 ± 0.57*# [18,19]
SCH-23390	saline	8.51 ± 1.86	1.48 ± 0.2*	1.27 ± 0.49*
SCH-23390	histamine	8.25 ± 1.39	1.16 ± 0.26*	2.03 ± 0.33*#
remoxipride	saline	9.53 ± 1.8	1.43 ± 0.42*	1.36 ± 0.56*
remoxipride	histamine	8.79 ± 1.01	1.21 ± 0.45*	2.09 ± 0.2*#
U-99194	saline	8.95 ± 1.65	1.44 ± 0.31*	1.28 ± 0.54*
U-99194	histamine	8.41 ± 1.62	1.22 ± 0.45*	2.17 ± 0.35*#
L-745,870	saline	8.89 ± 1.57	1.62 ± 0.39*	1.33 ± 0.41*
L-745,870	histamine	9.0 ± 0.78	1.2 ± 0.35*	2.73 ± 0.24*#^

Dopamine receptor antagonists: SCH-23390 ($D_{1/5}$), remoxipride (D_2), U-99194 (D_3), and L-745,870 (D_4);

six animals per group; *p < 0.05 vs. pre-bleeding value; #p < 0.05 vs. corresponding value in the saline-treated group; in animals pre-treated with dopamine antagonist: ^p < 0.05 vs. group pre-treated with saline and injected with histamine.

The total bleeding volume necessary for the induction of hypotension (30–35 mmHg) in all animals was 1.95 ± 0.18 ml/100 g of body weight. In the control (saline-treated) group, the induction of hypotension was associated with decreases in PP, HR, and MBF to 8.49 ± 2.36 mmHg, 145 ± 27 beats/min, and 1.62 ± 0.39 ml/min, respectively (Table I) [18,19].

There was a spontaneous partial recovery in MAP as measured 20 min after treatment in the saline-treated group (Table I). The animals in all groups survived 2 h [18,19].

In the histamine-treated group pre-treated with saline, MAP, HR, and MBF were significantly higher and PP was lower compared to the control group as measured 20 min after treatment (Table I) [18,19]. Pre-treatment with L-745,870 potentiated histamine-induced MAP and MBF changes, with no influence on PP and HR. In contrast, SCH-23390, remoxipride, and U-99194 did not affect histamine action (Table I).

In the control animals, dopamine receptor antagonists did not affect the measured cardiovascular parameters (Table I).

DISCUSSION

The results of our study demonstrate for the first time functional interactions between the histaminergic and dopaminergic systems in central cardiovascular regulation in a rat model of hemorrhagic hypotension. According to the hypothesis by Brown et al. [20], the central histaminergic system is involved in the maintenance of multisystemic homeostasis. Histamine, acting as a neurotransmitter secreted from neurons in the tuberomammillary nuclei of the posterior hypothalamus, seems to activate different compensatory mechanisms, leading to at least partial recovery of homeostatic balance. Our results are in line with this hypothesis, since we confirmed a histamine-induced pressor effect leading to MAP and HR normalization within 20 min of treatment in a model of reversible hemorrhagic hypotension. This model, in which a smaller volume of blood is withdrawn and reflex-induced bradycardia occurs, is more relevant to clinical conditions in humans than the previous model of irreversible shock with lower initial blood pressure (MAP: 20–25 mmHg) and 100% mortality within 30 min in the control group [3,5]. In contrast, in this model, all control animals survived for 2 h, with a spontaneous increase in MAP. Similar cardiovascular changes are observed in the post-bleeding period after non-fatal blood loss in humans [3].

The hypothalamic histaminergic neurons are activated in response to different kinds of stress, including dehydration and hypovolemia, as immunohistochemical studies demonstrate [21]. On the other hand, an increase in endogenous histamine content within the central nervous system after the inhibition of histamine N-methyltransferase, the enzyme responsible for histamine catabolism, leads to the activation of the sympathetic and the renin-angiotensin systems, as well as increased release of arginine vasopressin, and proopiomelanocortin-derived peptides in hemorrhage-shocked rats [22]. Hemodynamic effects elicited by centrally acting histamine include the mobilization of blood from venous reservoirs, with subsequent increases in peripheral blood flows – especially in the renal and skeletal muscle vascular beds – and long-lasting vasoconstriction, with a relatively lower increase in the perfusion of the mesenteric region [23]. Our results confirm persistently reduced MBF after histamine treatment, despite a complete recovery of MAP and HR to the pre-bleeding values at 20 min, which confirms the centralized circulation in conditions of hypovolemia.

Previous studies demonstrate functional interactions between the histaminergic and other neuronal systems, such as the cholinergic [24], adrenergic [25], and serotonergic systems [26], in the central cardiovascular regulation in experimental models of hemorrhagic hypotension in rats. In this study, we decided to verify possible interactions between the histaminergic and dopaminergic systems under these conditions. We used antagonists of dopamine receptors which in mammals are divided into two families: D_1-like and D_2-like receptors. D_1-like receptors consist of D_1 and D_5 receptors, while D_2-like receptors are comprised of D_2, D_3, and D_4 receptors [27]. The studies show an augmented histamine-induced pressor effect after D_4 receptor blockage with L-745,870. In contrast, we did not find an influence of the other dopamine receptor antagonists through histamine-mediated action on the measured cardiovascular parameters, nor did we observe any effects of the dopamine receptor antagonists when administered to the animals pre-treated with saline.

Dopamine D_4 receptors are involved in addictive behaviors related to alcohol [28], morphine [29], and nicotine [30] intake, the regulation of food intake [31], and copulatory behavior [32]. In addition, D_4 receptors are able to influence the cardiovascular responses to stress. A study by Sato et al. [33] demonstrated the pressor effect accompanied by bradycardia following the stimulation of neurons located in the lateral habenula (LHb), which is an essential structure for the activation of the response to stressful stimuli [34]. Interestingly, intravenous pre-treatment with L-745,870 (0.1 mg/kg) decreased the pressor effect resulting from LHb neuron stimulation [33]. However, the effect may be dose-dependent, since a selective D_4 receptor antagonist (L-741742) at a low dosage (0.025 µg) administered locally into the LHb induced a short-lived decrease in the firing rate of the LHb

neurons, followed by a prolonged excitatory effect [35]. Interestingly, L-741742 at a high dosage (0.1 µg) evoked only a brief decrease in the firing rate of LHb neurons [35]. The effect of L-741742 (0.25 µg) was accompanied by an increased release of GABA, dopamine, and glutamate in the LHb; the action of D_4 receptors located pre- and post-synaptically was demonstrated [35]. Since LHb neurons project directly to hypothalamic histaminergic neurons [36], dopamine D_4 receptor antagonist-mediated activation of LHb neurons may be involved in the enhanced histamine--induced pressor effect observed in our study.

Interestingly, a study by Bazzani et al. [15] showed the involvement of dopamine D_1-like receptors in ACTH-induced reversal of hemorrhagic shock in rats. We suggest that since ACTH-mediated anti-shock effect is associated with the activation of the cholinergic anti-inflammatory pathway [37], and the activation of the sympathetic nervous system plays a predominant role in the histamine-induced resuscitating effect in hemorrhagic shock [7], therefore, different types of dopamine receptors may participate in these mechanisms.

Although we demonstrated the potentiation of the central histamine-induced pressor effect in hemorrhagic hypotension after pre-treatment with a dopamine D_4 receptor antagonist, we are aware of the limitations of this study. Firstly, since the dopamine receptor antagonists and histamine were administered icv, we are unable to precisely determine the location of the neurons involved. Secondly, at this stage of the studies, we cannot show particular mechanisms involved in the dopamine D_4 receptor-mediated modulatory effect. However, a LHb neuron-involved pathway can be postulated.

CONCLUSION

The central dopaminergic system, via D_4 receptors, is able to modify a histamine-induced pressor effect in hemorrhagic hypotension in rats.

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Authors' contribution

Study design – J. Jochem, D. Giuliani, A. Ottani, S. Guarini
Data collection – K. Jasikowska
Data interpretation – K. Jasikowska, J. Jochem, A. Ottani, D. Giuliani
Statistical analysis – K. Jasikowska
Manuscript preparation – J. Jochem, M. Zając, A. Ottani, D. Giuliani, S. Guarini
Literature research – M. Zając, J. Jochem

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PRACA POGLĄDOWA
REVIEW

The role of matrix metalloproteinases in the pathophysiology of acute lymphocytic leukemia: A review

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ABSTRACT

Acute lymphocytic leukemia (ALL) is a hematologic malignancy induced by the uncontrolled proliferation of lymphoid progenitor cells. It is the most frequent malignancy in the pediatric population and it requires prompt treatment. Thus, comprehending its pathophysiological mechanisms is of paramount importance. Matrix metalloproteinases (MMPs) are a group of enzymes that degrade components of the extracellular matrix and have been shown to promote the progression of leukemia. Moreover, polymorphisms of genes encoding these enzymes are known to contribute to higher susceptibility to various cancers and poorer prognosis. This narrative mini-review explores the role of MMPs in the pathophysiology of ALL, the association between the polymorphism of their respective genes and the risk of ALL carcinogenesis and metastasis, as well as the potential role of the enzymes as clinical markers and therapeutic targets in ALL.

KEYWORDS

acute lymphocytic leukemia, matrix metalloproteinases, *MMP* genes

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Introduction

Acute lymphocytic leukemia (ALL) is a hematologic malignancy characterized by the clonal proliferation of immature lymphoid progenitor cells – predominantly of B or T cell origin – within the bone marrow, peripheral blood, and extramedullary sites [1]. It is the most common type of cancer in the pediatric population, but it can also manifest in adults, where the prognosis is generally less favorable [2]. As a rapidly progressing form of leukemia, ALL requires prompt and aggressive treatment, indicating the need for a better understanding of the biological mechanisms through which it progresses [1,3].

Matrix metalloproteinases (MMPs) are a group of enzymes within the large family of calcium-dependent zinc-containing endopeptidases; they play a crucial role in the remodeling of the extracellular matrix (ECM) and are involved in the degradation of various components of the ECM, including collagen, elastin, and glycoproteins [4]. MMPs are important for normal physiological processes such as tissue remodeling, wound healing, and embryogenesis, but they can also contribute to pathological conditions when their activity is dysregulated [5]. The overexpression of MMPs is associated with many types of cancer, as they can facilitate tumor invasion, metastasis, and inflammation [6,7]. Although MMPs are predominantly studied in solid tumors, they also play a role in hematologic malignancies, including leukemia [8,9].

This narrative mini-review aims to explore the role of MMPs in the carcinogenesis and progression of ALL.

MMPs and ALL biology

While MMPs are crucial for physiological functions such as tissue reorganization, their overexpression has been associated with different malignancies [10]. Specifically, ALL patients with MMP-9 and MMP-14 overexpression in bone marrow biopsies have been found to show poorer prognosis and lower overall survival compared to other ALL patients [11]. Moreover, in bone marrow biopsies of ALL patients, a statistically significant correlation has been discovered between MMP-2 overexpression and the presence of extramedullary infiltration, suggesting that the latter enzyme is associated with ALL migration [12].

Indeed, MMP-2 and MMP-9 are known to promote the migration, infiltration, and dissemination of leukemic cells into extramedullary tissues, thereby worsening disease development [13]. MMPs contribute to the remodeling of the bone marrow microenvironment, which is vital for the survival of leukemic cells. By degrading extracellular matrix components such as laminin, fibronectin, and collagen, they help establish a supportive environment for these cells [14]. More specifically, MMP-2 is known to degrade type I collagen, promoting the migration of leukemic cells [15]. Furthermore, MMP-9 has the potential to degrade type IV collagen – an essential element of osseous tissue – and at the same time activate inflammatory factors, including interleukin 1-beta (IL-1β) and transforming growth factor-β, which are known to promote proliferation and drug resistance in ALL [6,16,17]. MMP-14 is known to degrade laminin, an essential component in the adhesion of ALL cells to the basement membrane; its cleavage therefore promotes the motility of malignant cells.

In addition to ECM degradation, MMP activity is closely linked to intracellular signaling cascades. In detail, MMP-mediated ECM cleavage can activate the mitogen-activated protein kinase/extracellular signal--regulated kinase (MAPK/ERK) pathway, enhancing leukemic cell proliferation and survival [18]. Moreover, MMP-driven release of cytokines such as IL-1β can potentially activate the nuclear factor-kappa B (NF-κB) signaling pathway, contributing to chemoresistance and microenvironmental modulation [17]. It is worth mentioning that MMPs also facilitate angiogenesis, establishing an environment that promotes the survival and proliferation of leukemic cells [19]. More specifically, MMP-1 and MMP-9 have been shown to promote angiogenesis in the environment of ALL cells [13].

Nevertheless, these associations may be influenced by other variables, such as the patient's age, leukemia subtype, and treatment regimen. No studies stratifying MMP expression findings by these variables have been conducted yet, making it ambiguous whether MMP overexpression is an independent prognostic factor. Figure 1 summarizes the role of MMPs in the pathophysiology of ALL.

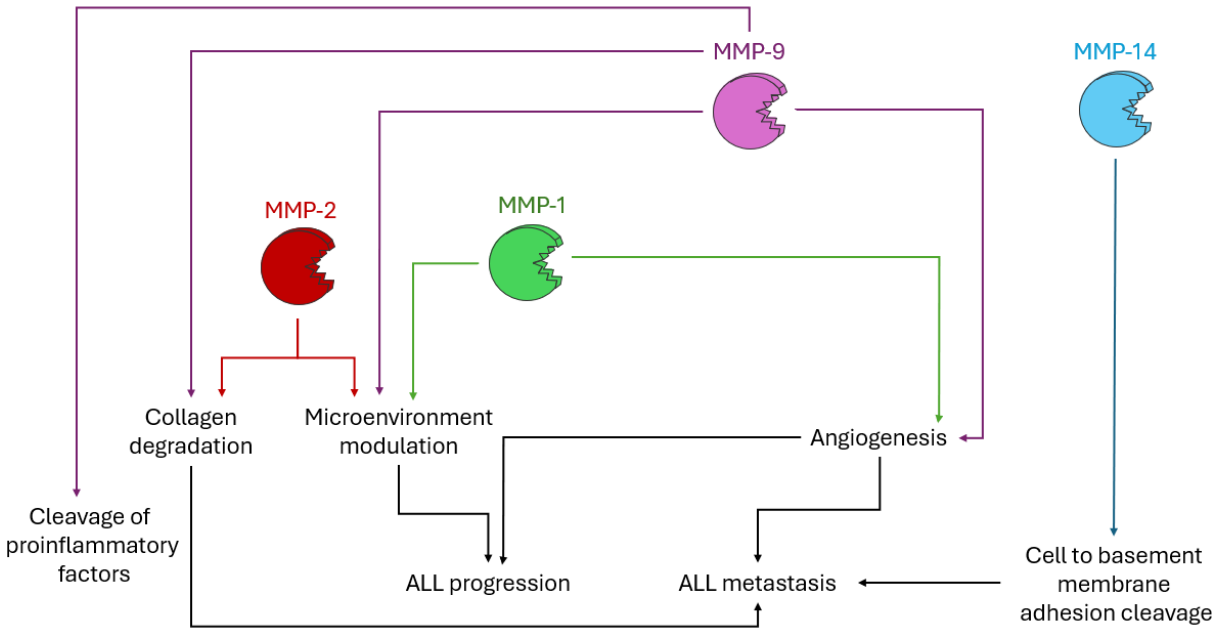

Fig. 1. Role of matrix metalloproteinases (MMPs) in the pathophysiology of acute lymphocytic leukemia (ALL)

Gene polymorphisms of MMPs and ALL

Polymorphisms of genes coding for MMPs have been shown to play a potential role in ALL carcinogenesis and metastasis, as illustrated in Table I. Specifically, the MMP-2 -1306C>T, the MMP-9 -1562C>T, and the MMP-7 -181A>G polymorphisms have been shown to be associated with the pathophysiology of ALL. While all three polymorphisms are linked to an increased risk of carcinogenesis, it is important to note that the *MMP-2* and *MMP-9* polymorphisms are also associated with a higher risk of metastasis, whereas the *MMP-7* polymorphism does not show this correlation, indicating that the MMP-2 and MMP-9 enzymes may play a more significant role in leukemia progression and metastasis than MMP-7 [20,21,22]. This hypothesis can be supported by the fact that MMP-2 and MMP-9 have exhibited a better ability to degrade the bone microenvironment and osseous tissue [23,24].

The latter polymorphisms were studied in case-control studies with relatively small cohorts (N < 300). Lin et al. [20] investigated MMP-2 -1306C>T and MMP-9 -1562C>T in an adult population with a mean age of 48.0 ± 8.1, whereas the other studies were conducted among pediatric populations. All studies were conducted in China and Taiwan with Asian majority populations. Notably, the MMP-9 -1562T allele is relatively common in Asian populations, but rare in Caucasian populations, which may explain differences in the results [25]. Thus, validation in prospective, multi-ethnic cohorts is required before firm conclusions can be reached.

Table I. Polymorphisms of matrix metalloproteinase (MMP) genes in acute lymphocytic leukemia (ALL)

Polymorphism	Genetic model	Genotype correlated with ALL	Increased risk of carcinogenesis	Increased risk of metastasis	References
MMP-2 -1306C>T	Dominant	CT + TT	✓	✓	[17]
MMP-7 -181A>G	Dominant	AG + GG	✓	✗	[20]
MMP-9 -1562C>T	Dominant	CT + TT	✓	✓	[17,19]

Discussion and conclusions

The findings discussed in this review highlight the significant role of MMPs in the pathophysiology of ALL. Among the various MMPs, MMP-1, MMP-2, MMP-7, MMP-9, and MMP-14 have been found to be associated with ALL progression. Despite these insights, several questions remain unanswered. For instance, while correlations between MMP expression and prognosis have been established, the causal relationship between specific MMPs and ALL progression needs to be elucidated through functional studies.

From a therapeutic perspective, targeting MMP activity in ALL presents an intriguing opportunity. The inhibition of MMPs has been explored in solid tumors, with mixed success, but their potential in hematologic malignancies remains underexplored [26,27]. Previous attempts to use small-molecule MMP inhibitors in solid tumor clinical trials were largely disappointing due to a lack of selectivity, off-target effects, and dose-limiting musculoskeletal toxicities, which limited their long-term tolerability [28]. The development of targeted inhibitors capable of selectively blocking the activity of key MMPs, such as MMP-2 and MMP-9 – without disrupting physiological functions – represents a promising avenue for therapeutic intervention. As research in this field continues to evolve, integrating MMP-focused strategies into existing treatment paradigms could pave the way for more precise and effective approaches to ALL management. Additionally, MMP expression profiling could serve as a prognostic tool, helping to stratify patients based on their risk of metastasis and resistance to treatment, as already suggested in other diseases [29].

Alternative approaches may help overcome these limitations. For example, antibody-based inhibition of MMPs may offer greater specificity and may reduce systemic toxicity compared to broad-spectrum inhibitors, as tested in some other malignancies [30]. Moreover, RNA interference technologies and antisense oligonucleotides may be able suppress MMP expression at the transcriptional level [31]. Such approaches may provide a more favorable safety profile and could be combined with conventional therapies to prevent resistance and disease relapse, but further research is certainly required in the field.

Future studies should prioritize mechanistic investigations to determine how MMPs interact with the leukemic microenvironment at a molecular level. Clinical research is also essential to assess whether MMP expression levels correlate with specific ALL subtypes, treatment responses, and long-term prognosis. Additionally, genetic studies exploring the impact of MMP polymorphisms on leukemia risk and progression in diverse populations could further enhance our understanding of disease susceptibility and outcomes.

Beyond their role in risk stratification, MMP polymorphisms may also carry potential clinical utility as predictive biomarkers. For instance, the MMP-2 -1306C>T and MMP-9 -1562C>T variants have been associated with not only ALL susceptibility, but also prognosis, suggesting a role in predicting treatment responses [20]. Because MMPs regulate extracellular matrix remodeling and activate cytokine pathways that drive drug resistance, genotyping of these polymorphisms could help identify patients more likely to experience treatment resistance or relapse, guiding the selection of more intensive or targeted therapies [6,10]. Furthermore, as MMP activity is linked to tissue remodeling and inflammatory responses, genetic variants might also influence chemotherapy-related toxicities, such as musculoskeletal complications or inflammatory side effects – though this hypothesis warrants clinical validation [32]. Thus, incorporating *MMP* genotyping into molecular risk assessment could provide both prognostic and predictive value, complementing existing stratification strategies in ALL management.

Authors' contribution

Study design – A. Angelaki, D. Kalali
Data collection – A. Angelaki, E. Arifagić, E. Zouganeli, D. Kalali
Manuscript preparation – A. Angelaki, E. Arifagić, E. Zouganeli, D. Kalali
Literature research – A. Angelaki, D. Kalali
Final approval of the version to be published – D. Kalali

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PRACA ORYGINALNA
ORIGINAL PAPER

Concentrations of chemerin and leptin in healthy and sick newborns

Stężenie chemeryny i leptyny u noworodków zdrowych i chorych

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ABSTRACT

INTRODUCTION: Chemerin and leptin are adipokines involved in the regulation of metabolism and the inflammatory response. In the neonatal period, they may reflect both fetal nutritional status and early adaptive disturbances associated with infection or perinatal risk factors.
MATERIAL AND METHODS: The study included 127 term, appropriate-for-gestational-age newborns, divided into groups: Ia – early-onset infection (n = 40), Ib – perinatal risk factors without infection (n = 36), and II – control group (n = 51). Chemerin and leptin concentrations were measured in peripheral venous blood serum between the 3rd and 7th day of life. Associations between hormonal, metabolic and clinical parameters were analyzed.
RESULTS: Serum chemerin and leptin concentrations were significantly higher in newborns with early-onset infection and in those burdened with perinatal risk factors compared with healthy infants.
CONCLUSIONS: Chemerin and leptin appear to be markers of metabolic and inflammatory disturbances in the perinatal period. Measurement of their concentrations in peripheral venous blood serum may constitute a valuable adjunctive tool for identifying newborns who require increased clinical surveillance.

KEYWORDS

chemerin, leptin, newborn, early-onset infection, perinatal risk factors

STRESZCZENIE

WSTĘP: Chemeryna i leptyna są adipokinami uczestniczącymi w regulacji metabolizmu i odpowiedzi zapalnej. W okresie noworodkowym mogą odzwierciedlać zarówno stan odżywienia płodu, jak i wczesne zaburzenia adaptacyjne związane z zakażeniem lub czynnikami ryzyka okołoporodowego.
MATERIAŁ I METODY: Badaniem objęto 127 noworodków donoszonych, podzielonych na grupy: Ia – z zakażeniem wczesnym (n = 40), Ib – z czynnikami ryzyka okołoporodowego (n = 36), II – kontrolną (n = 51). Stężenia chemeryny i leptyny w surowicy krwi żylnej oznaczono między 3. a 7. dobą życia. Analizowano zależności między parametrami hormonalnymi, metabolicznymi i klinicznymi.

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WYNIKI: Stężenia chemeryny i leptyny były istotnie wyższe u noworodków z wczesnym zakażeniem i obciążonych perinatalnymi czynnikami ryzyka niż u zdrowych.
WNIOSKI: Chemeryna i leptyna są markerami zaburzeń metabolicznych i zapalnych w okresie okołoporodowym. Oznaczenie ich stężeń w surowicy obwodowej krwi żylnej może stanowić cenne narzędzie w identyfikacji noworodków wymagających zwiększonego nadzoru klinicznego.

SŁOWA KLUCZOWE

chemeryna, leptyna, noworodek, wczesne zakażenie, czynniki ryzyka okołoporodowego

INTRODUCTION

Adipose tissue cells synthesize and secrete numerous adipokines, including chemerin and leptin, which play important roles in carbohydrate and lipid metabolism, angiogenesis, fetal and neonatal development, and the pathogenesis of infections [1]. Elevated levels of chemerin have been reported in individuals with metabolic syndrome, obesity, diabetes mellitus, chronic obstructive pulmonary disease, chronic pancreatitis, psoriasis, neoplastic diseases, and in children with epilepsy [2,3,4,5,6,7]. In inflammatory conditions, chemerin exerts antimicrobial activity and stimulates macrophages, natural killer (NK) cells and dendritic cells [1,8,9,10]. Leptin is a better-characterized adipokine. In newborns, its relationships with gender, anthropometric parameters and gestational age, as well as its involvement in early-onset infections, have been partially elucidated [11,12,13,14,15]. In the present study, we evaluated chemerin and leptin concentrations in healthy and sick term newborns. The aim of the study was to determine whether early-onset infections affects the concentrations of these hormones and to analyze correlations between chemerin and leptin levels and selected inflammatory markers in affected newborns.

MATERIAL AND METHODS

A total of 127 full-term newborns of any gender, appropriate for gestational age and aged 3–7 days, participated in the study. Based on the presence of early-onset infection and perinatal risk factors, the infants were divided into two main groups:

Group I (study group) – 76 newborns, including:

Ia – 40 newborns with early-onset infection diagnosed within the first 72 hours of life

Ib – 36 newborns without infection but burdened with perinatal risk factors:

- maternal and sociomedical: maternal age under 16 years, alcohol abuse during pregnancy, maternal nicotine use, history of recurrent miscarriages, pregnancy-induced hypertension, first-trimester vaginal bleeding, maternal anemia, oligohydramnios, urinary and genital tract infections, zoonotic infectious diseases, group B streptococcus colonization
- labor-related: operative delivery (including caesarean section), premature rupture of membranes with amniotic fluid leakage > 18 hours, meconium-stained amniotic fluid
- neonatal: need for resuscitation procedures, endotracheal intubation and mechanical ventilation

Group II (control group) – 51 healthy newborns from uncomplicated pregnancies, delivered vaginally after spontaneous onset of labor.

All newborns from the study group were treated at the Department of Neonatal Intensive Care and Pathology in Zabrze, while 51 healthy infants from the control group were born during the same period in the Obstetrics and Neonatology Unit in Gliwice. Among the diagnosed infections, the following were identified: pneumonia (11 cases), urinary tract infection (9 cases), sepsis (6 cases), concurrent omphalitis, skin infection and conjunctivitis (6 cases), osteomyelitis (2 cases), and single cases of enteritis, meningitis, extensive oral and pharyngeal candidiasis, systemic inflammatory response syndrome, mastitis and generalized staphylococcal skin infection.

Perinatal risk factors primarily included abnormal, non-physiological labor (26 cases) and adverse socioeconomic conditions or maternal pregnancy pathology (24 cases). Neonatal risk factors accounted for 14% of cases (5 newborns).

Chemerin and leptin concentrations in venous blood serum were measured using the ELISA method between the 3rd and 7th day of life. For laboratory analysis, 1.5 mL of venous blood was collected during routine diagnostic blood sampling. The study was approved by the Bioethics Committee of the Medical University of Silesia in Katowice (Resolution No. KNW/022/KB1/1/I/16). All patients had written informed consent obtained from their parents or legal guardians.

Clinical data were collected from medical records and interviews with parents or legal guardians. Diagnoses of early-onset infections and perinatal asphyxia were established based on widely accepted criteria. Clinical data and laboratory results were analyzed using the licensed software Statistica 12.0 (StatSoft Inc., Tulsa, OK, USA).

RESULTS

Assessment of serum chemerin concentrations in both groups of newborns

In the entire cohort of 127 newborns, serum chemerin concentrations ranged from 115.2 to 466.1 ng/mL, with a mean value of 281.8 ± 67.79 ng/mL. In newborns with early-onset infection (group Ia), the mean concentration of this hormone was 294.30 ± 56.25 ng/mL (range: 175.6–442.8 ng/mL) and was significantly higher ($p < 0.001$) than in the control group (group II), in which the mean concentration was 247.6 ± 54.92 ng/mL (range: 115.2–375.5 ng/mL).
In newborns without infection but with perinatal risk factors (group Ib), chemerin concentrations ranged from 164.8 to 466.1 ng/mL, with a mean value of 316.3 ± 74.86 ng/mL. This value was also significantly higher ($p < 0.001$) than in the control group (group II). The mean concentration of chemerin in group Ib did not differ significantly from that observed in newborns with infection (group Ia). The results of the analysis are shown in Figure 1.

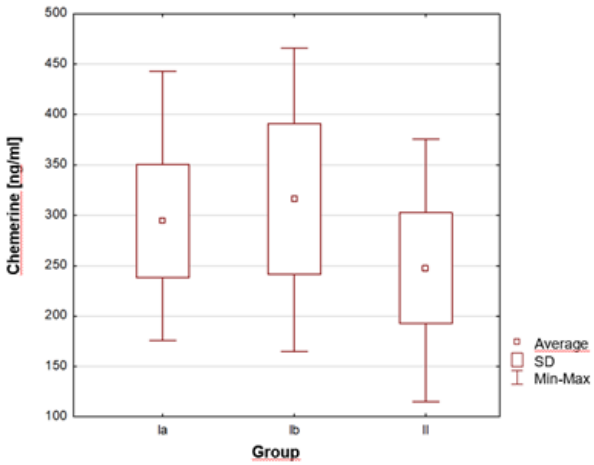

Fig. 1. Comparison of mean serum chemerin concentrations in newborns with early-onset infection (group Ia), newborns with perinatal risk factors (group Ib) and the control group (group II)

Assessment of serum leptin concentrations in both groups of newborns

In the entire cohort of 127 newborns, serum leptin concentrations ranged from 0.342 to 4.273 ng/mL, with a mean value of 1.464 ± 0.86 ng/mL. In newborns with early-onset infection (group Ia), the mean concentration of this hormone was 2.088 ± 0.89 ng/mL (range: 0.687–4.273 ng/mL), which was significantly higher ($p < 0.001$) than in the control group (group II), where the mean concentration was 0.985 ± 0.43 ng/mL (range: 0.342–2.285 ng/mL).

In group Ib, leptin concentrations ranged from 0.447 to 3.229 ng/mL, with a mean value of 1.449 ± 0.84 ng/mL. This value was also significantly higher ($p < 0.05$) than in group II.
The mean leptin concentration in newborns with early-onset infection was also significantly higher ($p < 0.001$) than in newborns without infection but with perinatal risk factors. The results of the analysis are presented in Figure 2.

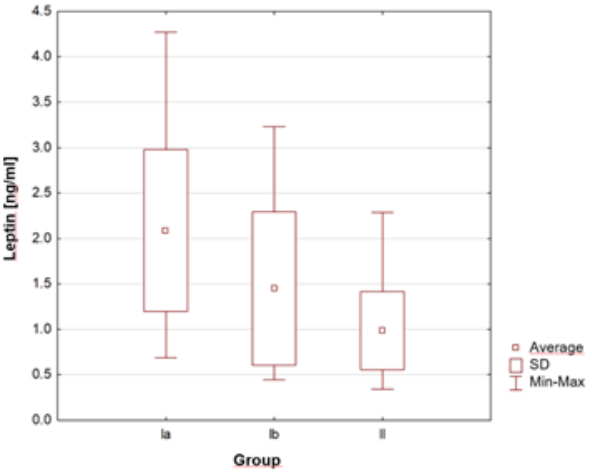

Fig. 2. Comparison of mean serum leptin concentrations in newborns with early-onset infection (group Ia), newborns with perinatal risk factors (group Ib), and the control group (group II)

Assessment of chemerin and leptin concentrations in both groups of newborns according to gender

Table I presents a comparison of chemerin concentrations between male and female newborns in the study and control groups. In healthy female newborns mean chemerin concentrations was significantly higher than in male newborns ($p < 0.05$). No such significant differences were observed in newborns with early-onset infection ($p = 0.599$) or in newborns with perinatal risk factors ($p = 0.110$).

Table I. Analysis of serum chemerin concentrations in both groups of newborns according to sex

Group		Male	Female	p
Ia n = 40	N	26	14	0.599
	Average	287.8	287.8	
	SD	51.27	66.08	
	Range	196.9–442.8	175.6–390.1	
Ib n = 36	N	25	11	0.1104
	Average	329.6	286.2	
	SD	70.79	78.44	
	Range	190.2–466.1	164.8	
Control n = 51	N	27	24	0.0116
	Average	229.6	267.9	
	SD	57.23	45.25	
	Range	115.2–314.0	165.8–375.5	

Table II presents a comparison of mean leptin concentrations between male and female newborns in the study and control groups. Gender did not have a significant effect on leptin concentrations in healthy newborns, in those with early-onset infection, or in those with perinatal risk factors.

Table II. Analysis of serum leptin concentrations in both groups of newborns according to gender

Group		Male	Female	p
Ia n = 40	N	26	14	0.343
	Average	1.989	2.273	
	SD	0.938	0.79	
	Range	0.687–4.275	0.896–3.795	
Ib n = 36	N	25	11	0.216
	Average	1.586	1.137	
	SD	0.85	0.77	
	Range	0.447–3.136	0.497–3.229	
Control n = 51	N	27	24	0.177
	Average	0.901	1.079	
	SD	0.378	0.47	
	Range	0.342–1.587	0.414–2.285	

Taking into account gender within each group, a detailed analysis was performed and revealed significant negative correlations between chemerin and leptin concentrations in newborns with early-onset infection (group Ia). The correlation analysis, presented in Figures 3 and 4, indicates that in both female and male newborns with early-onset infection, higher chemerin levels are associated with lower leptin concentrations.

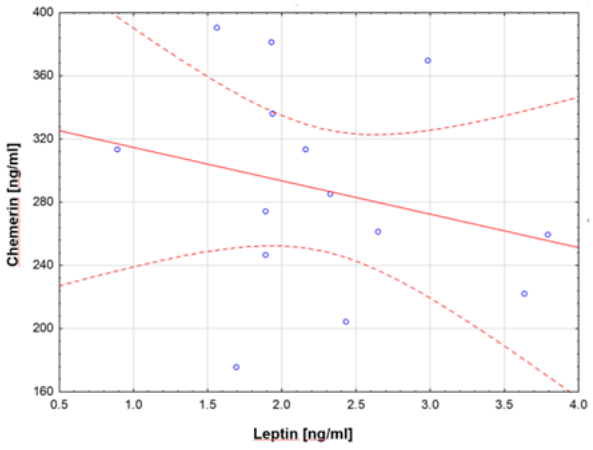

Fig. 3. Correlation analysis between serum chemerin and leptin concentrations in female newborns with early-onset infection

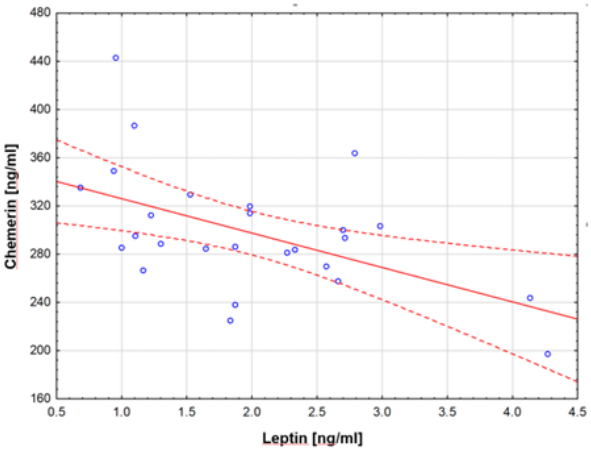

Fig. 4. Correlation analysis between serum chemerin and leptin concentrations in male newborns with early-onset infection

Correlation analysis between chemerin and leptin concentrations with consideration of gender in the study and control groups

The results of the correlation analysis between chemerin and leptin with consideration of gender in the study and control groups are presented in Table III.

Table III. Results of the correlation analysis between serum chemerin and leptin concentrations according to gender in the study and control groups

Group	Gender	Correlation	
		r	p
Ia	Female	-0.2527	0.383
	Male	-0.522	0.006
Ib	Female	-0.067	0.845
	Male	-0.177	0.396
Control	Female	0.276	0.191
	Male	0.117	0.560

A negative correlation ($p < 0.05$) was found in male newborns with diagnosed early-onset infection between chemerin and leptin concentrations (Figure 5).

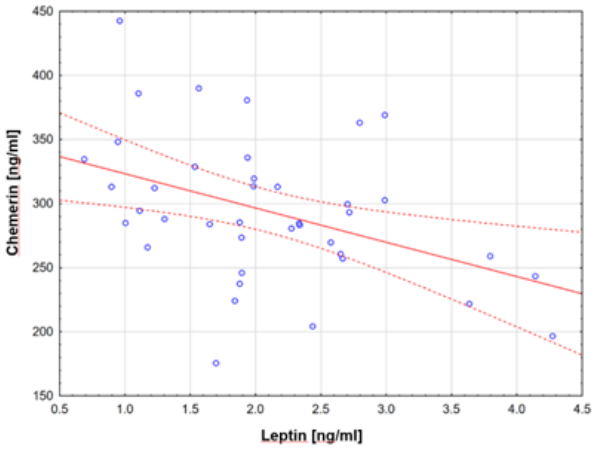

Fig. 5. Correlation analysis between serum chemerin and leptin concentrations and male gender in newborns with diagnosed early-onset infection

Correlation analysis between chemerin and leptin concentrations according to selected biochemical and hematological indicators in the study groups

The results of the correlation analysis between chemerin and leptin concentrations and selected biochemical and hematological markers in newborns with early-onset infection (group Ia) are presented in Table IV, and in newborns with perinatal risk factors (group Ib) in Table V.

Table IV. Correlation analysis between serum chemerin and leptin concentrations in newborns with early-onset infection and selected biochemical and hematological indicators

Indicator	Chemerin		Leptin	
	r	p	r	p
CRP	0.1673	0.302	-0.1160	0.476
Hematocrit	0.2604	0.105	0.0432	0.791
Hemoglobin	0.2513	0.118	0.0087	0.958
Red blood cells	0.1996	0.217	0.0824	0.0613
White blood cells	-0.1491	0.359	0.1859	0.251
Platelets	0.2016	0.212	0.0215	0.895

CRP – C-reactive protein

Table V. Correlation between serum chemerin and leptin concentrations and selected biochemical and hematological indicators in newborns exposed to perinatal risk factors

Indicator	Chemerin		Leptin	
	r	p	r	p
CRP	-0.2290	0.179	-0.2241	0.189
Hematocrit	-0.2986	0.077	-0.1836	0.284
Hemoglobin	-0.2732	0.107	-0.2108	0.217
Red blood cells	-0.2656	0.117	-0.2096	0.220
White blood cells	-0.2809	0.097	-0.1567	0.362
Platelets	0.1870	0.275	-0.0635	0.713

CRP – C-reactive protein

The performed analysis did not reveal any statistically significant correlations between serum chemerin and leptin concentrations and the laboratory parameters assessed in the study groups, either in newborns with early-onset infection or in those exposed to perinatal risk factors.

DISCUSSION

Research conducted in recent years has significantly advanced our understanding of adipose tissue, its structure, metabolism, and interactions with other organs. It has been confirmed that adipose tissue is a complex system of metabolically active cells and functions as an endocrine organ [16,17,18]. Its components – including adipocytes, connective tissue stroma, vascular stromal cells, immune cells, and neural elements – work together to produce a variety of biologically active adipokines that act locally (autocrine/paracrine) or on distant organs (endocrine effects) [3,16,17,18]. Among them, leptin, first described in 1994 as an anorexigenic factor is the best characterized [12,15,16,19,20]. Another adipokine that has recently gained considerable interest is chemerin, discovered more than 20 years ago [1,3,8,16,21,22, 23,24]. Both hormones play important roles in fetal and neonatal development [13,25,26,27].

Normal growth early in life is regulated by numerous factors reflecting complex interactions between the fetus, the mother and the placenta. Proper development depends not only on adequate delivery of oxygen, glucose and protein to the fetus but also on the ability to utilize these substrates in growth processes. These mechanisms are influenced by numerous hormones – including thyroid hormones, growth hormone, insulin, cortisol, adiponectin, leptin, chemerin and somatotropin – whose regulation during the perinatal and neonatal periods remains poorly understood [12,13,26,27,28,29]. Developmental disturbances are only partly due to genetic factors; more often they are the result from maternal systemic diseases, harmful habits, and complications during pregnancy and delivery [30,31,32,33,34,35].

In our study of 127 term eutrophic newborns, we demonstrated that early-onset infections – systemic or localized, primarily affecting the respiratory and urinary systems – caused a significant increase in serum chemerin concentration compared with healthy term newborns. This finding suggests that chemerin is actively involved in infection-related inflammation or supports the hypothesis that early-onset infection in a eutrophic term newborn stimulates chemerin production and secretion. Chemerin is known to have multiple biological functions, including immunologic activity through the stimulation of chemotaxis of macrophage and immature dendritic cells [1,19]. Its exact role in inflammatory processes remains unclear despite numerous experimental and clinical studies [9,10,22,25,36]. The role of chemerin in immune responses is complex, as its effects varies depending on the length of its polypeptide chain and may be both pro- and anti-inflammatory. The largest form (chemerin-157) participates in early inflammatory responses and has a potent chemotactic activity [37], while the 154-amino-acid form suppresses macrophage activation, exerting an anti-inflammatory effect [37]. Elevated chemerin levels are observed in adults with chronic gastrointestinal, renal and joint diseases and during exacerbations of chronic obstructive pulmonary disease [25,38]. In recent years, Godlewska et al. [8] demonstrated antibacterial and anti-*Candida albicans* activity of recombinant chemerin and the chemerin-derived peptide p4 in adults. Eichelmann et al. [16] also demonstrated an association

between chemerin and inflammatory markers (C-reactive protein, tumor necrosis factor α, interleukin 6).

Our research also showed that perinatal risk factors significantly increased chemerin concentrations in newborns without infection compared with healthy infants from uncomplicated pregnancies. This suggests that pregnancy pathology (excluding endocrine disorders and maternal hypertension), cesarean delivery, and associated perinatal stressors may contribute to increased chemerin production in early neonatal life. In these newborns, mean chemerin concentrations were higher not only compared with healthy controls but even (albeit insignificantly) compared with those with early-onset infection. Hyperchemerinemia in newborns from non-physiological pregnancies or delivered by cesarean section – likely resulting from increased placental synthesis and release – may in the future be recognized as a marker of metabolic risk. However, the lack of similar observations in adolescents, children and newborns limits the ability to determine the extent to which early-onset infections activate the immature immune system. It can only be assumed that severe infectious pathology during the first month of life plays an important role in chemerin secretion, and that its overproduction (hyperchemerinemia) may adversely affect hormonal development and predispose to metabolic disturbances later in life.

Leptin, like chemerin, is an adipokine essential for metabolism and growth and an indicator of nutritional status. Concentrations of both hormones are influenced by numerous exogenous factors [12,15,16,24]. In the present study, we confirmed a significant impact of early-onset infection on the increase of leptin concentration, which indicates a substantial stimulation of leptin synthesis and secretion during infection. The observed hyperleptinemia supports the role of leptin – due to its cytokine-like structure – as a hormone involved in inflammatory processes and immune activation [16,20,39]. Leptin is known to activate macrophages and monocytes, stimulate the proliferation of endothelial cells and naïve T-cells, and promote the migration of immunocompetent cells. It may inhibit proliferation of the memory T-cells and influence phagocytic function [16,39]. Korek and Krauss [40] suggest that adipokines, including leptin, which is important in obesity and metabolic dysregulation, may adversely affect inflammation by increasing the synthesis of interleukin 6 and tumor necrosis factor α.

Reports on leptin levels in neonatal infections are inconsistent. In 1996, Frazer-Llado et al. [41] found only minimal expression of the leptin gene and no significant changes in serum leptin levels in newborns with severe infections. Conversely, Orbak et al. [42] reported higher leptin concentrations in newborns with bacterial sepsis than in healthy infants and documented a strong correlation between leptin and other inflammatory markers (C-reactive protein, neutrophil index), suggesting its potential as a future diagnostic marker of severe neonatal infections. In our study, no such correlations were observed between chemerin or leptin and C-reactive protein, platelet count or leukocyte count in newborns with or without infection who had perinatal infectious or non-infectious risk factors.

As with chemerin, we found higher mean leptin concentrations in newborns with perinatal risk factors and no infection than in healthy infants. Numerous studies have emphasized the impact of pregnancy and delivery pathology on hormonal changes in newborns with normal postnatal adaptation [13,14,42]. Determining whether gender influences hormone levels in healthy and ill newborns has long been a subject of interest to researchers. In our study, chemerin concentrations were higher in healthy female newborns compared with males; however, early-onset infection and perinatal risk factors offset this difference, reflecting substantial hormonal disturbances even in eutrophic term newborns born after pathological pregnancies or deliveries. We also demonstrated a significant negative correlations between chemerin and leptin in newborns with early-onset infection – both girls and boys – suggesting biological interactions between these two hormones.

We did not find any significant gender-related differences in leptin concentrations among term newborns, whether healthy or ill, which is consistent with findings by Bury et al. [13]. However, Sadownik et al. [43] showed that newborns of various gestational ages with intrauterine infection had higher leptin concentrations in girls than in boys. Similarly, Stojewska et al. [14] reported significantly higher leptin levels in peripheral blood in healthy female newborns compared with male newborns.

Present findings, combined with the latest neonatal research on the influence of perinatal risk factors and infection on hormonal and lipid profile alterations, confirm that this issue remains unresolved. The neonatal period is a particularly vulnerable phase, during which harmful factors – related to infection, hypoxia and anatomical or physiological immaturity – can have profound long-term consequences. There is a clear need for further research to determine the roles of various disease processes, not only infectious ones, in the hormone secretion mechanisms, their mutual interactions and potential long-term health effects.

CONCLUSIONS

1. Early-onset infections, non-physiological pregnancy and labor in the mother contribute to increased concentrations of serum chemerin and leptin in peripheral venous blood of eutrophic term newborns, regardless of gender.
2. Healthy female newborns born at term exhibit higher chemerin concentrations than male newborns.
3. In both female and male newborns with early-onset infection, there is a correlation between chemerin and leptin concentrations is observed, despite the no differences in leptin levels between healthy and sick newborns of either gender.

Authors' contribution

Study design – A. Nawrat
Data collection – A. Nawrat, A. Szymańska
Data interpretation – A. Nawrat, J. Czubilińska-Łada, A. Sienko, A. Szymańska
Statistical analysis – A. Nawrat
Manuscript preparation – J. Czubilińska-Łada
Literature research – A. Sienko

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W związku z tym, że prace przeglądowe i komentarze redakcyjne polegają na wyborze i interpretacji danych z dostępnego piśmiennictwa, redakcja AAMS oczekuje, iż autorzy tego typu opracowań będą wolni od finansowych związków z firmami, których produkty są przedmiotem pracy (lub z firmami konkurencyjnymi).
Wymaga się, by recenzenci, członkowie redakcji, zastępcy redaktora naczelnego ujawnili w liście do redaktora naczelnego wszelkie zobowiązania i okoliczności mogące wpłynąć niekorzystnie na proces wydawniczy pracy podlegającej recenzji. List ten powinien zawierać oświadczenie o jakichkolwiek powiązaniach finansowych (o ile takie istnieją), np. z firmą produkującą lek będący przedmiotem pracy.

ROZTRZYGANIE SPORÓW

Ewentualne spory z wydawcą czasopisma dotyczące publikacji będą rozstrzygane przez sąd właściwy dla siedziby wydawcy. Stosunki prawne łączące wydawcę czasopisma i autora podlegają prawu polskiemu i obowiązującym Polskę konwencjom międzynarodowym.

POZWOLENIE NA PUBLIKACJĘ

Materiały wcześniej publikowane i chronione prawem autorskim, w tym materiały ilustracyjne (tabele, ryciny, fotografie, rysunki itp.), należy zaopatrzyć w pisemną zgodę – zarówno od poprzedniego wydawcy, jak i autorów oryginalnej pracy – na ponowną publikację. Ewentualne koszty z tym związane ponoszą autorzy. Jeżeli informacje zawarte w opisie przypadku, na ilustracji lub w tekście pracy oryginalnej pozwalają na identyfikację osób, należy dostarczyć ich pisemną zgodę na publikację wizerunku.

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Przesyłając pracę wraz z ilustracjami i tabelami, autor/współautor oświadcza, że nadesłana praca nie była uprzednio publikowana ani nie została złożona do redakcji innego czasopisma (z wyłączeniem streszczeń nieprzekraczających 400 słów) oraz że przysługuje mu pełnia praw autorskich majątkowych i osobistych do utworu (pracy), rozporządza tymi prawami i w tym zakresie zwalnia wydawcę z odpowiedzialności za wady prawne utworu wobec osób trzecich.
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Przesyłając pracę wraz z ilustracjami i tabelami, autor dołącza podpisany przez siebie *List przewodni* (*Oświadczenie autora/współautora*), zgadzając się na warunki publikacji w AAMS, w tym na udzielenie wydawcy nieodpłatnej i niewyłącznej licencji CC BY-SA 4.0. Autor zachowuje prawa autorskie.
Do samodzielnego udostępniania/archiwizowania prac, a także metadanych w dowolnych repozytoriach oraz bazach danych indeksujących czasopisma wydawca zaleca autorom posługiwanie się wersją opublikowaną na stronie AAMS (finalna wersja pracy po recenzji oraz korektach redakcyjnej i autorskiej). Przy udostępnianiu/archiwizowaniu pre-printów (wersja autorska przed recenzją) oraz post-printów (wersja autorska po recenzji, przed redakcją wydawniczą) obowiązuje podanie następujących informacji: a) pre-print – np. „Niniejsza praca została przesłana do redakcji *Annales Academiae Medicae Silesiensis* (annales.sum.edu.pl) i oczekuje na recenzję"; po opublikowaniu na stronie czasopisma

wersji finalnej należy o tym doinformować – np. „Ostateczna wersja pracy jest dostępna na stronie … [należy podać link do pracy] na licencji … [wpisać nazwę licencji]"; b) post-print – np. „Niniejsza praca jest wersją autorską poprawioną zgodnie z uwagami recenzenta, zakwalifikowaną do publikacji w czasopiśmie *Annales Academiae Medicae Silesiensis* (annales.sum.edu.pl)"; po opublikowaniu na stronie czasopisma wersji finalnej należy o tym doinformować – np. „Ostateczna wersja pracy jest dostępna na stronie … [należy podać link do pracy] na licencji … [wpisać nazwę licencji]".
Autorzy nie ponoszą żadnych kosztów związanych z publikacją ani też nie otrzymują za to wynagrodzenia.

ZASTRZEŻENIE

Redakcja oraz wydawca dokładają wszelkich starań, by treści publikowane w AAMS były wiarygodne i dokładne. Opinie wyrażane na łamach czasopisma są jednak publikowane na wyłączną odpowiedzialność autorów. W związku z tym ani redakcja, ani wydawca nie ponoszą odpowiedzialności za konsekwencje wykorzystania jakichkolwiek nieścisłych informacji. Dawki leków i inne wartości liczbowe są sprawdzane z należytą starannością, jednak wszelkie schematy leczenia opisywane w AAMS powinny być stosowane zgodnie z informacjami o leku publikowanymi przez producenta.

PRZYGOTOWANIE PRACY

Praca powinna być przygotowana w formacie A4, z wykorzystaniem powszechnie używanych edytorów tekstu (Word, Open Office etc.). Zaleca się stosowanie standardowych fontów o rozmiarze 12 pkt, marginesy 2,5 cm, interlinia 1,5.
Układ pracy:
1) strona tytułowa,
2) streszczenie w języku polskim, słowa kluczowe w języku polskim (3–10 oddzielone przecinkami),
3) streszczenie w języku angielskim, słowa kluczowe w języku angielskim (3–10 oddzielone przecinkami),
4) tekst pracy z wklejonymi w odpowiednich miejscach tabelami i rycinami,
5) ewentualne podziękowania lub informacje o grantach lub źródłach finansowania pracy,
6) wkład poszczególnych autorów w powstanie pracy,
7) piśmiennictwo.

Kolejne strony należy ponumerować, zaczynając od strony tytułowej. Skróty, wraz z rozwinięciem, należy podać w nawiasie za skracanym określeniem przy pierwszym jego wystąpieniu w tekście. Należy unikać skrótów nieakceptowanych przez międzynarodowe grupy ekspertów.

Prace powinny mieć następującą strukturę:

Strona tytułowa. Powinna zawierać w kolejności od góry:
1) pełne imiona i nazwiska wszystkich autorów*,
2) nazwę (nazwy) instytucji, z której pochodzi praca,
3) pełny tytuł pracy (polski i angielski),
4) tytuł skrócony (polski i angielski; maksimum 40 znaków łącznie z odstępami),
5) adres do korespondencji zawierający tytuł naukowy, imię i nazwisko, nazwę instytucji, adres (miasto, ulica), numer telefonu, faksu i adres e-mail (najlepiej służbowy) autora odpowiedzialnego za korespondencję z redakcją.

* UWAGA: W przypadku gdy pracę współtworzyło kilku autorów (dotyczy to wszystkich rodzajów prac, tj. o charakterze poglądowym, oryginalnym, opisu przypadku), należy ujawnić wkład poszczególnych autorów w jej powstanie (podając informacje, kto jest autorem koncepcji, założeń, zastosowanej metody, przeprowadzonych badań, analizy danych, kto napisał pracę etc.). Wszelkie przypadki nierzetelności naukowej, w tym zjawiska *ghostwriting* i *guest authorship* będą demaskowane, włącznie z powiadomieniem odpowiednich podmiotów (instytucje zatrudniające autorów, towarzystwa naukowe, stowarzyszenia edytorów naukowych itp.). Ze zjawiskiem typu *ghostwriting* mamy do czynienia wówczas, gdy ktoś wniósł istotny wkład w powstanie pracy, ale nie został ujawniony jako jeden z autorów lub w postaci zamieszczonego podziękowania w treści pracy. *Guest authorship* obrazuje sytuację, gdy udział autora jest znikomy lub w ogóle nie miał miejsca, a pomimo to jest autorem/współautorem pracy.
Redakcja zobowiązana jest do dokumentacji wszelkich przejawów nierzetelności naukowej, zwłaszcza dotyczących łamania i naruszania zasad etyki obowiązujących w nauce.

Streszczenie (w języku polskim i angielskim). Nie powinno zawierać więcej niż 250 słów. W streszczeniu pracy oryginalnej należy wyodrębnić cztery akapity zatytułowane: Wstęp, Materiał i metody, Wyniki, Wnioski.

Słowa kluczowe (w języku polskim i angielskim). Pod streszczeniem (odpowiednio w języku polskim i angielskim) należy umieścić od 3 do 10 słów lub wyrażeń kluczowych, w miarę możliwości zgodnych z Medical Subject Headings Index Medicus (MeSH).

Tekst. Prace oryginalne należy podzielić na następujące części: Wstęp, Materiał i metody, Wyniki, Dyskusja, Wnioski. Prace poglądowe mogą być podzielone w inny sposób. Nie należy przekraczać zalecanych

objętości prac: praca oryginalna – 3000 słów, poglądowa – 6000 słów, opis przypadku – 2000 słów, list – 1000 słów. Przedstawione limity nie obejmują streszczenia, tabel, piśmiennictwa. We właściwych miejscach tekstu pracy należy wkleić tabele i ryciny.
Użyte metody statystyczne należy opisać na tyle szczegółowo, aby czytelnik mający dostęp do danych źródłowych i posiadający wiedzę statystyczną był w stanie zweryfikować przedstawione wyniki. Wszędzie, gdzie to możliwe, należy stosować opis ilościowy wraz z odpowiednimi miarami błędu lub niepewności (np. przedziały ufności). Należy unikać opierania się wyłącznie na poziomie prawdopodobieństwa (p-value) obliczanym podczas testowania hipotez statystycznych, który pomija istotne informacje dotyczące wielkości obserwowanego efektu.

Piśmiennictwo. Pozycje piśmiennictwa powinny być ponumerowane zgodnie z kolejnością cytowania w tekście (system vancouverski).

Czasopisma. W wypadku cytowanych czasopism należy podać: kolejny numer pozycji, nazwiska autorów i pierwsze litery imion (jeśli autorów jest nie więcej niż sześciu, należy wymienić wszystkich, jeśli siedmiu i więcej, należy podać sześciu pierwszych z dopiskiem „i wsp." w pracach polskojęzycznych lub „et al." w pracach anglojęzycznych), tytuł pracy, tytuł czasopisma (skróty tytułów czasopism powinny być zgodne z Index Medicus), rok, tom i numer czasopisma (cyframi arabskimi), numer strony początkowej i końcowej, identyfikator DOI. Prosimy nie używać określeń: „w druku", „w przygotowaniu", „informacja ustna", w uzasadnionych wypadkach można je zastosować w odpowiednim miejscu w tekście.
Przykład: Eliasson M., Jansson J., Nilsson P., Asplund K. Increased levels of tissue plasminogen activator antigen in essential hypertension. A population-based study in Sweden. J. Hypertens. 1997; 15(4): 349–356. doi: 10.1097/00004872-199715040-00005.

Książki. W wypadku cytowanych książek należy wymienić: kolejny numer pozycji, nazwiska autorów i pierwsze litery imion, tytuł, wydawcę, miejsce i rok wydania.
Przykład: Domagalska-Szopa A., Szopa A. Postępowanie usprawniające w mózgowym porażeniu dziecięcym. Śląski Uniwersytet Medyczny w Katowicach. Katowice 2018.

Powołując się na treść rozdziału książki, należy podać: nazwisko autora rozdziału, inicjały imion, tytuł rozdziału, nazwisko autora (redaktora) książki, inicjały imion, tytuł książki, wydawcę, miejsce i rok wydania, przedział stron.
Przykład: Kubicek C.P., Karaffa L. Kwasy organiczne. W: Ratledge C., Kristiansen B. [red.]. Podstawy biotechnologii. Wydawnictwo Naukowe PWN. Warszawa 2011, s. 249–265.

Strony internetowe. Opis ten powinien zawierać: nazwę autora tekstu, tytuł, nazwę witryny internetowej i rok ukazania się tekstu, adres witryny internetowej, datę dostępu.
Przykład: Dreisinger E. McKenzie Therapy Classifications. Spine-health, 2007 [online] http://www.spinehealth.com/wellness/exercise/mckenzie-therapy-classifications [dostęp: 2 września 2019].

Tabele, ryciny, fotografie. Mogą być czarno-białe lub kolorowe, ponumerowane (tabele cyframi rzymskimi, ryciny cyframi arabskimi) oraz opisane w języku polskim i poniżej w języku angielskim. Jakość bitmap nie powinna być niższa od 300 dpi przy 100% wielkości (wysokość i szerokość).

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Wysyłanie pracy odbywa się wyłącznie za pośrednictwem strony annales.sum.edu.pl (zakładka „Wyślij swój artykuł"), zgodnie z formularzem Editorial System.
Dopuszczalne formaty plików:
- dla tekstu: dowolna wersja edytora Microsoft Word (doc, docx), rich text format (rtf),
- dla rycin: pliki jpg, jpeg, gif, tif, tiff, bmp, png.

Wymagane dokumenty, tj. *List przewodni (Oświadczenie autora/współautora)*, należy przesłać do redakcji w formie:
a) elektronicznej (e-mail), podpisany za pomocą bezpiecznego podpisu elektronicznego, zgodnie z obowiązującymi przepisami (podpis zaufany),
b) tradycyjnej (przesyłka polecona) na adres redakcji – podpisany czytelnie druk *Listu przewodniego (Oświadczenia autora/współautora)*.

Jeśli pracę współtworzyło kilku autorów, *List przewodni* podpisuje i odsyła każdy współautor oddzielnie.

Adres redakcji:

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ANNALES ACADEMIAE MEDICAE SILESIENSIS

EDITORIAL POLICY AND INFORMATION FOR AUTHORS

"Annales Academiae Medicae Silesiensis" (hereinafter referred to as AAMS) is the official journal of the Medical University of Silesia in Katowice, publishing peer-reviewed review articles, original research works on medicine and pharmacy, as well as basic medical sciences, case studies, letters, book reviews and editorial commentaries in Polish and English. Publications in English are preferred.

Since February 2021, AAMS is published in the open access (OA) system, and articles are made available under the CC BY-SA 4.0 license (Creative Commons Attribution-ShareAlike 4.0 International), specifying the rules for their use.

Articles sent to the Editorial Board via the Editorial System by the end of January 2021 will be published on the old terms (with a copyright notice and the transfer of the copyrights to the Publisher of AAMS, and the articles may be used only under fair use).

The AAMS Editorial Office conforms to the principles provided in the *Declaration of Helsinki* and expects that research on humans has been conducted in accordance with these principles. With regard to the research using animal models, the Editorial Office expects compliance with the principles contained in the *Interdisciplinary Principles and Guidelines for the Use of Animals in Research, Testing and Education*, issued by the New York Academy of Sciences' Ad Hoc Committee on Animal Research. All works relating to humans or animals must be approved by the relevant local ethics committee, which should be indicated in the work.

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Submitted works are evaluated in terms of values such as innovative presentation of the topic, importance for the further development of scientific research and for clinical management.

Works registered in the reviewing system of AAMS journal are automatically forwarded to the anti--plagiarism system used by the Medical University of Silesia in Katowice. The results of the verification procedure in the form of an electronic evaluation report is attached to the work and made available to the reviewer(s), as well as the journal's Editor-in-Chief. In the event the system detects plagiarism, the final decision on whether or not to accept the work rests with the reviewers.

Works are initially evaluated by the AAMS Editorial Office (editorial review): works which do not meet the basic conditions for publication are rejected; works which are incomplete or prepared in a style inconsistent with the journal rules are returned to the authors without any content evaluation; the remaining works are registered and subsequently submitted to two independent reviewers, whose identity is hidden and who are not connected with the institution where the work originated; both the reviewer and author identities are concealed (double-blind peer review).

Works written in English are sent to at least one foreign reviewer for evaluation.

The decision on qualifying the work for publication is sent by the Editorial Office via e-mail to the author responsible for correspondence, together with a reference number which should be used during further contact with the publisher.

The manuscript is approved for publication on the basis of positive opinions of the reviewers.

The reviewers issue their opinion on the basis of a detailed evaluation of the work compared with other papers published on the subject, taking into account the following criteria: originality of the work, significance of the obtained results, quality of the methodology and data, manner of presenting the results, quality of discussions, selection of reference literature.

An opinion on whether the work meets the ethical requirements is also provided by the reviewers.

The conclusions contain information on whether the work may be accepted for publication without changes/accepted after taking into account the corrections suggested by the reviewer/reconsidered after significant corrections and re-review, or whether it should be rejected.

In the final stage, the reviewers provide confidential comments to the Editorial Office, as well as general and detailed (optional) comments to the authors.

The reviewers have the opportunity to submit the content of the amended work in the form of an attachment.

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In the event that both reviews are positive, but the sum of points awarded in one of them amounts to less than 18 (with a maximum of 36 points), the Editor-in-Chief may, after justification, decide to reject the work.

The author familiarizes him/herself with the review, but without the possibility of obtaining information about the reviewer.
The author is obliged to formulate a written response to the review (with a description of the introduced changes) and submit it along with the text of the amended work within the established deadline.
If the author refuses to introduce the recommended amendments, the Editor-in-Chief may decide to reject the work.
After the author sends back the amended version of the work, the final decision on qualifying the paper for publication belongs to the Editor-in-Chief.
The Editorial Office undertakes to publish a list of all the reviewers of a given annual in AAMS once a year.

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Upon submitting the work, the authors of research papers are obliged to disclose any financial obligations, if any, between the authors and the company whose product has significant importance in the submitted work, or a competitor. This information will not be disclosed to the reviewers nor will it affect the decision on publication of the work. After accepting the work, the Editorial Office and authors will decide on the form in which information on the sources of financing should be made available to readers. Any research subsidies or provisions of reagents or analytical tools should be indicated in the "Acknowledgements".
Apart from indicating any possible sources of financing, authors are also obliged to disclose information about any contribution of scientific and research institutions, associations and other entities to the creation of the work.
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