LEKARZ WOJSKOWY
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INSTYTUT MEDYCZNY
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   Calpin C, Macarthur C, Stephens D, et al. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systemic review of the literature. J Allergy Clin Immunol, 1997; 100: 452–457 . doi: 10.1016/s0091-6749(97)70134-9

   Books:
   Rudzki E. Alergia na leki: z uwzględnieniem odczynów anafilaktycznych i idiosynkrazji. Lublin, Wydawnictwo Czelej, 2002

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Letter from the Editor-in-Chief

Dear Readers!

Welcome back after the summer break. I hope the past few months have been a time of health, peace, as well as inspiring professional and personal experiences.

The holiday period has reminded us of the key role medicine plays in ensuring national security and the effective functioning of the armed forces. In this context, modifications in the structure of the military health service have been announced, including the establishment of the Medical Forces.

In light of these changes, the latest issue of our Journal offers a number of articles addressing current issues and trends in military medicine. These include a study on innovative methods for monitoring sunken chemical weapons, as well as an original paper assessing risk factors and preventive implications of cardiovascular diseases in soldiers. Bearing in mind that analyzing the past helps avoid repeating mistakes, we also present a historical account of the Health Center of the State Armament Factory in Radom.

This issue is further enriched by compelling review papers and case reports, including analyses of the harmful effects of e-cigarettes and innovative treatment approaches in erectile dysfunction. A comprehensive compendium on the role of glucocorticoids in managing rheumatic diseases is particularly noteworthy.

In September, we celebrate the 80th anniversary of the Main Medical Library named after its founder, Dr. Stanisław Konopka, who was also a military doctor. This institution holds great importance for us, physicians. On this occasion, we extend our congratulations and gratitude to the entire Library team for their dedicated work to date and wish them continued success in the institution's further development.

I would also like to thank all the authors for their valuable contributions and dedication to the publication process. Your work constitutes the driving force behind the continued growth of our journal.

I wish you an engaging and fruitful reading experience and hope that this issue of Military Physician will inspire further collaboration.

Prof. Bolesław Kalicki, MD, PhD

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ORIGINAL ARTICLE

CASE REPORTS

ANALYSIS OF THE SAFETY PROFILE OF RETATRUTIDE BASED ON PHASE I AND II CLINICAL TRIALS

Analiza profilu bezpieczeństwa retatrutydu na podstawie badań klinicznych fazy I i II

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Abstract

Obesity represents an escalating global public health concern, necessitating the development and implementation of new, more effective intervention strategies. Ongoing research into novel pharmacological treatments for obesity is yielding promising results. The latest advancement in this field is retatrutide, a triple agonist targeting the receptors for glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, and glucagon. This study aims to provide a detailed analysis of the safety profile of retatrutide based on data from available phase I and II clinical trials. Retatrutide demonstrated a favorable safety profile, with gastrointestinal symptoms being the most commonly reported adverse effects. These preliminary findings are promising and warrant further investigation. Although the results are encouraging, further research is needed to elucidate the mechanisms of action of triple agonists and assess their long-term efficacy. Such studies will be crucial for guiding personalized therapeutic strategies and optimizing their clinical utility across various patient groups.

Streszczenie

Otyłość stanowi narastający problem dla zdrowia publicznego na całym świecie. Wymaga to opracowania i wdrożenia nowych, skuteczniejszych strategii interwencyjnych. Obecnie prowadzone badania nad nowymi metodami farmakoterapii w leczeniu otyłości dostarczają obiecujących wyników. Najnowszym osiągnięciem w tej dziedzinie jest retatrutyd, będący potrójnym agonistą receptorów glukozozależnego peptydu insulinotropowego, glukagonopodobnego peptydu oraz glukagonu. Praca ta ma na celu szczegółową analizę profilu bezpieczeństwa retatrutydu na podstawie dostępnych badań klinicznych fazy I oraz II. Retatrutyd wykazywał korzystny profil bezpieczeństwa, a najczęściej obserwowanymi działaniami niepożądanymi były dolegliwości ze strony układu pokarmowego. Wyniki wstępnych badań są obiecujące, co stanowi motywację do dalszego pogłębiania wiedzy na temat tego leku. Pomimo obiecujących rezultatów, niezbędne jest kontynuowanie badań w celu dokładniejszego zrozumienia mechanizmów działania trójagonistów oraz oceny ich długoterminowej skuteczności i bezpieczeństwa. Takie badania będą kluczowe do planowania spersonalizowanych strategii terapeutycznych oraz optymalizacji ich klinicznej użyteczności w różnych grupach pacjentów.

Keywords: obesity; retatrutide; multireceptor agonists

Słowa kluczowe: otyłość; retatrutyd; agoniści wieloreceptorowi

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Introduction

Obesity, according to the definition of the World Health Organization (WHO), is an excessive or abnormal accumulation of fat that adversely affects health. The assessment of obesity typically relies on the body mass index (BMI). A BMI of ≥25 kg/m² indicates overweight, while a BMI of ≥30 kg/m² indicates obesity [1].

Data published by the WHO show that in 2022, one in eight people worldwide was living with obesity. The same report indicated that approximately 2.5 billion adults – representing 43% of the global adult population – were overweight, including 890 million (16%) classified as having obesity. Data from the pediatric population are also deeply concerning. Compared to 1990, the prevalence of obesity among adolescents has quadrupled. Moreover, in 2022, over 390 million children and adolescents aged 5–19 were overweight, including 160 million with obesity [2]. In Poland, according to the Center for Public Opinion Research (CBOS), 21% of adults suffer from obesity, and 38% are overweight. In the Polish pediatric population, 12.2% of boys and 10% of girls are affected by overweight or obesity [3].

According to the World Obesity Atlas 2023, by 2035, an estimated 4 billion people will be living with overweight or obesity. As much as 51% of the adult population will be overweight, including 24% classified as obese. The most dramatic rise in obesity prevalence is expected among children and adolescents. The percentage of obese boys worldwide is projected to increase from 10% in 2020 to 20% in 2035, while that of obese girls is expected to rise from 8% to 18% [4].

Obesity is a chronic disease that does not resolve spontaneously and has a tendency to recur. If left untreated, it can lead to numerous complications, primarily cardiovascular diseases. Excess body fat contributes to the development of hypertension in 60–70% of individuals. Furthermore, approximately 80% of patients with chronic coronary syndrome have an elevated body weight. Excess adipose tissue plays a significant role in the pathogenesis of strokes – it is estimated to be responsible for 64% of ischemic strokes and 24% of hemorrhagic strokes. Furthermore, it increases the risk of venous thromboembolic disease by two- to three-fold. Excess body weight also contributes to the development of osteoarthritis, including of the spinal joints, as well as obstructive sleep apnea, stress urinary incontinence, and type 2 diabetes [5]. According to data from the Organization for Economic Co-operation and Development (OECD), overweight and obese individuals live, on average, four years shorter than those with a healthy body weight. Overweight and obesity increase the risk of death by 22–91%, which indicates their greater clinical significance than previously thought. It is estimated that in the U.S., one in six deaths is attributed to complications related to overweight or obesity [6].

According to the guidelines of the American Association of Clinical Endocrinologists and the American College of Endocrinology, three key strategies are distinguished in the treatment of obesity: lifestyle modification (including diet), pharmacological treatment, and surgical interventions. The foundation of therapy is lifestyle modification, including controlling dietary habits, increasing physical activity, and providing emotional and motivational support. This approach should be recommended to all patients with overweight or obesity. In cases where lifestyle changes fail to produce sufficient results, pharmacotherapy or surgical bariatric options are considered [7].

In recent years, many methods for treating obesity have been developed, including various pharmacological approaches. One of the promising drugs is retatrutide (RTT) – a triple agonist of glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and glucagon receptors. Currently, numerous studies are underway to more precisely assess its efficacy and safety. Favorable results could pave the way for new therapeutic indications for RTT, marking a meaningful step forward in the treatment of obesity.

Aim of study

The aim of this study is to compare clinical trial data concerning the safety profile of RTT. This analysis will enable the assessment of any potential differences in the safety profile of this drug across various study conditions, which may contribute to a better understanding of its potential benefits and limitations in the context of obesity therapy.

Methodology

To accurately assess the safety profile of RTT, a detailed literature review was conducted without restrictions regarding publication date, language, or study type. Searches were carried out in databases including PubMed, IEEE Xplore, ScienceDirect, and Google Scholar using the following keywords: "retatrutide," "retatrutide and obesity," and "triple GIP, glucagon and GLP-1 receptor agonists."

Inclusion criteria encompassed studies addressing at least one of the following topics: retatrutide, obesity, or triple agonists of GIP, GLP-1, and glucagon receptors. Exclusion criteria included non-peer-reviewed publications, duplicates, and articles unrelated to the topic.

Following the preliminary screening, 122 publications were identified for further assessment. The selection process involved the removal of duplicates, detailed analysis, and the selection of the most relevant studies. Ultimately, following the application of the exclusion criteria, 25 publications were included in the analysis. The selected articles comprised various types of studies, including clinical trials, meta-analyses, and systematic reviews, providing comprehensive data on the topic under discussion.

Discussion

Current approach to obesity treatment

All patients with obesity should be advised to modify their diet and increase physical activity. In cases where such measures do not produce the desired results, pharmacological treatment should be considered. In recent years, the Food and Drug Administration (FDA) has approved several medications for obesity treatment: phentermine for short-term use, and five drugs for long-term management – orlistat, phentermine/topiramate, bupropion/

naltrexone, liraglutide, and semaglutide [8]. In a 28-week phase III trial evaluating the efficacy of the naltrexone–bupropion combination, an average weight reduction of 5.7% was observed in the treatment group, compared to 1.9% in the placebo group [8, 9]. In another phase III study evaluating the effect of liraglutide on weight reduction, a 5.7% decrease in body weight was observed in the treatment group, compared to 1.6% in the placebo group [8, 10]. Semaglutide was the first drug in phase III trials to achieve a double-digit body-weight reduction, with the STEP-1 study reporting an average decrease of 14.9% [8, 11]. The newest drug is tirzepatide, which has demonstrated the highest efficacy. In an 88-week phase III study, body weight reduction averaged 25.3% [8, 12].

The main goal of pharmacotherapy for obesity is to reduce the risk of complications and have a beneficial effect on pre-existing conditions. Currently, only semaglutide has a proven beneficial effect on cardiovascular risk, which was confirmed in the SELECT trial [8, 13].

It should be emphasized, however, that bariatric and metabolic surgery remains the most effective method for treating obesity. The guidelines from the American Association of Clinical Endocrinologists and American College of Endocrinology include a concise treatment algorithm, in which the choice of the optimal treatment depends on BMI and the presence of comorbidities [7]. In individuals with a BMI exceeding 27 kg/m^2 and obesity-related complications – such as hypertension, carbohydrate-lipid metabolism disorders, coronary artery disease, or obstructive sleep apnea – pharmacological treatment should be considered. It is also recommended for individuals with a BMI above 30 kg/m^2, regardless of the presence of comorbidities. Bariatric surgery leads to significant and sustained weight loss, as well as improvements in obesity-related conditions in the majority of patients. In an analysis involving 161,756 individuals, the mean reduction in BMI five years after surgery ranged from 12 to 17 units, with a 30-day mortality rate of 0.08% and an overall postoperative mortality rate of 0.31% [14].

Mechanism of action of retatrutide

Retatrutide is an agonist of GIP, GLP-1, and glucagon receptors. GLP-1 is an incretin hormone secreted by the gastrointestinal tract that stimulates pancreatic beta cells to produce insulin. GLP-1 receptors are found in the heart, kidneys, central nervous system, as well as in the lungs, gastrointestinal tract, and pancreas. Studies have shown that GLP-1 delays gastric emptying both after meals and during fasting. It also promotes relaxation of the stomach muscles, allowing for greater gastric distension. This results in lower postprandial blood glucose levels and has a beneficial metabolic effect on the body [15].

The second target of RTT is the GIP receptor, which is located mainly in pancreatic beta cells and in the central nervous system [16]. GIP acts synergistically with GLP-1, influences fat metabolism by promoting lipogenesis, and supports the transport of fatty acids into adipocytes. In addition, it inhibits gastric motility [17]. Both GLP-1 and GIP have incretin properties, meaning that they stimulate insulin secretion in response to the presence of glucose. When glucose levels are low, GLP-1 and GIP do not significantly affect insulin levels [18]. By delaying gastric emptying and stimulating the satiety center, both hormones indirectly promote the reduction of adipose tissue.

The third receptor targeted by RTT is the glucagon receptor. These receptors are located in the liver, kidneys, adrenal glands, spleen, and the central nervous system. Glucagon is a peptide hormone that plays a key role in regulating blood glucose levels. It is secreted by pancreatic alpha cells in response to decreased blood glucose. This hormone stimulates processes such as lipolysis, gluconeogenesis, and glycogenolysis, which leads to an increase in blood glucose levels. It has an effect opposite to that of insulin. Furthermore, glucagon affects other tissues, increasing protein catabolism and releasing amino acids into the bloodstream [19]. By acting on these three receptors, RTT mimics the body's natural hormones, which enables the regulation of blood glucose levels and exerts a beneficial metabolic effect [20].

In vitro and preclinical studies on retatrutide

Retatrutide, also known as LY3437943, is a novel pharmacological agent developed by Eli Lilly for the treatment of obesity. Unlike earlier generations of drugs with similar indications, it acts on three receptors: GIP, GLP-1, and glucagon. The first stage in evaluating this novel compound involved *in vitro* studies of its mechanism of action. Results published in 2019 showed that RTT effectively stimulates glucose synthesis in hepatocytes in a manner similar to the endogenous action of glucagon in human cell models. Moreover, similar to the natural hormones GIP and GLP-1, RTT effectively initiates lipolysis in adipocytes [21, 22].

In 2018, the first studies evaluating the effects of RTT in rodents were published, confirming its triple agonistic activity toward the GIP, GLP-1, and glucagon receptors [21, 23, 24]. In one of these studies, the effects of RTT on body weight, body composition, energy metabolism, and fatty liver were also analyzed. The results showed that administration of the drug led to weight loss and reduced caloric intake, with these effects being dose-dependent (the maximum change in body weight during the study reached up to 59.7%). The mice primarily lost adipose tissue, with minimal impact on muscle mass. For example, in the group receiving 30 mg of RTT, fat mass decreased by 86.8%, while lean body mass was reduced by 31.1% compared to baseline values. A reduction in blood glucose and insulin levels was also observed, which suggests a potential improvement in glycemic control and insulin sensitivity [25].

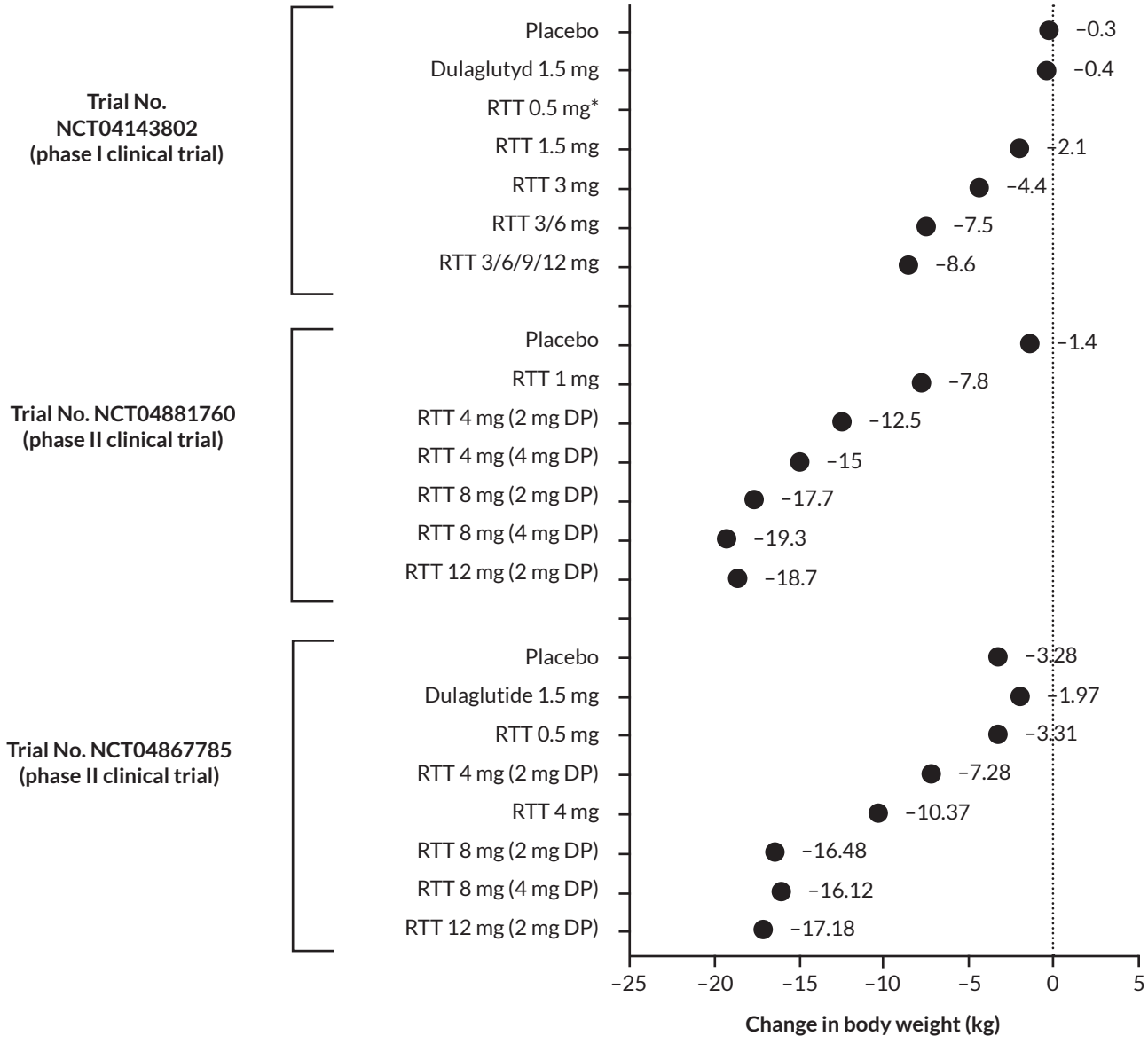
In 2022, a study was conducted comparing the efficacy of tirzepatide and RTT in reducing body weight in obese mice. Tirzepatide, the first dual agonist of GLP-1 and GIP receptors, resulted in a body weight reduction of 21.2%. In contrast, RTT, administered daily at a dose of 10 nmol/kg, led to a body weight loss of 36.9%, which was accompanied by a significant decrease in calorie intake [21].

Phase I clinical trial NCT04143802

Following the promising results of *in vitro* and animal studies, a phase I clinical trial (NCT04143802) was ini-

tiated [26]. The aim was to evaluate the adverse effects of LY3437943 in patients with type 2 diabetes. As part of the study protocol, blood analyses were performed to assess the pharmacokinetic and pharmacodynamic properties of the study drug, as well as its effects on the body. Participants in the study were randomly assigned to groups receiving subcutaneous injections of LY3437943, dulaglutide, or placebo to enable comparison of the study drug's effects with those of the control therapies. The study included patients with diabetes lasting at least 3 months, glycated hemoglobin (HbA1c) ≥7.0% and ≤10.5%, treated with diet or metformin, with stable body weight for three months, and a BMI between 23 kg/m² and 50 kg/m². The study involved 72 volunteers who were administered placebo, dulaglutide, or RTT. Only 42 patients completed the study, largely due to the COVID-19 pandemic. Among the 72 participants, half (37 individuals) were women, with a mean age of 58 years and a mean BMI of 32 kg/m². Phase I clinical trial results showed that RTT significantly reduced daily blood glucose levels by −4.4 mmol/L and HbA1c levels by −1.9% in the three patient groups receiving the highest doses of the drug. Additionally, systolic blood pressure demonstrated an overall decreasing trend from baseline in the groups receiving LY3437943 (RTT), with a reduction of 12 mmHg. A slight downward trend was also observed in diastolic blood pressure, which decreased by approximately 2 mmHg. Additionally, a dose-dependent reduction in body weight was recorded, reaching up to −8.6 kg. The most significant weight loss occurred in the group receiving escalating doses of the drug (3 mg → 6 mg → 9 mg → 12 mg). The dose-dependent weight reduction is illustrated in Figure 1.

Treatment-related adverse events (AEs) were reported in 33 (63%) of 52 participants receiving LY3437943, three (60%) of five participants receiving dulaglutide 1.5 mg, and eight (53%) of 15 participants in the placebo



ID – initial dose; RTT – retatrutide
*Due to COVID-19 pandemic-related constraints, no participants were able to complete the study.

Figure 1. Body weight changes by study drug and dosage in clinical trials NCT04143802, NCT04881760, and NCT04867785

Table 1. Safety profile based on phase I and II clinical trials

Trial	Subgroup	At least 1 AE *n* (%)	Serious AE *n* (%)	AE leading to drug discontinuation *n* (%)	Death *n* (%)
Subgroup	Placebo (*n* = 45)	28 (62)	3 (7)	2 (4)	0
	RTT 0.5 mg (*n* = 47)	26 (55)	3 (6)	1 (2)	0
	RTT 4 mg (2 mg DP) (*n* = 23)	13 (57)	1 (4)	0	0
	RTT 4 mg (*n* = 24)	19 (79)	2 (8)	1 (4)	0
	RTT 8 mg (2 mg DP) (*n* = 26)	19 (73)	2 (8)	3 (12)	0
	RTT 8 mg (4 mg DP) (*n* = 24)	17 (71)	1 (4)	4 (17)	0
	RTT 12 mg (2 mg DP) (*n* = 46)	35 (75)	2 (4)	7 (15)	0
	Dulaglutide 1.5 mg (*n* = 46)	31 (67)	1 (2)	1 (2)	0
	Entire group (*n* = 281)	188 (67)	15 (5)	19 (7)	0
NCT04881760 [20]	Placebo (*n* = 70)	49 (70)	3 (4)	0	0
	RTT 1 mg (n = 69)	58 (84)	3 (4)	5 (7)	0
	RTT 4 mg (2 mg DP) (*n* = 33)	24 (73)	0	2 (6)	0
	RTT 4 mg (4 mg DP) (*n* = 33)	28 (85)	2 (6)	3 (9)	1 (3)
	RTT 8 mg (2 mg DP) (*n* = 35)	28 (80)	1 (3)	5 (14)	0
	RTT 8 mg (4 mg DP) (*n* = 35)	33 (94)	2 (6)	2 (6)	0
	RTT 12 mg (2 mg DP) (*n* = 62)	57 (92)	2 (3)	10 (16)	0
	Entire group (*n* = 337)	277 (82)	13 (4)	27 (8)	1 (<1)
NCT04143802 [19]	Placebo (*n* = 15)	8 (53)	1 (7)	0	1 (7)
	Dulaglutide 1.5 mg (*n* = 5)	3 (60)	1 (20)	0	0
	RTT 0.5 mg (*n* = 9)	3 (33)	1 (11)	1 (11)	0
	RTT 1,5 mg (*n* = 9)	5 (56)	1 (11)	2 (22)	0
	RTT 3 mg (*n* = 11)	5 (46)	0	0	0
	RTT 3/6 mg (*n* = 11)	9 (82)	0	0	0
	RTT 3/6/9/12 mg (*n* = 12)	11 (92)	0	1 (9)	0
	Entire group (*n* = 72)	44 (61)	5 (7)	4 (6)	1 (1)

ID – initial dose; RTT – retatrutide; AE – adverse event

group. Additionally, 23 (44%) of 52 participants treated with LY3437943 experienced adverse events considered related to the study drug. The incidence of these AEs increased with higher drug doses.

The most frequently reported gastrointestinal adverse events were diarrhea and nausea. They occurred in nine (33%) placebo-treated participants, 12 (60%) dulaglutide-treated participants, and 24 (46%) LY3437943-treated patients. Throughout the study, four participants (6%) discontinued treatment due to adverse events, two of which were considered related to the treatment. Four participants reported six serious AEs, none of which were assessed as being associated with the study drug. One death occurred in a participant receiving placebo, resulting from a car accident.

Phase II clinical trial NCT04881760

Following the completion of phase I studies, two separate phase II trials were conducted [27, 28]. The primary objective of the NCT04881760 trial was to evaluate the percentage change in body weight from baseline in adults after 24 and 48 weeks of treatment [28]. The study was a randomized, double-blind, placebo-controlled trial that included adults with a BMI of at least 30 kg/m² or a BMI between 27 kg/m² and 30 kg/m² who had at least one comorbidity related to excess body weight. The participants were randomly assigned to seven groups in a 2:1:1:1:1:2:2 ratio, each receiving different doses of subcutaneously administered RTT (1 mg, 4 mg [with an initial dose of 2 mg], 4 mg [with an initial dose of 4 mg], 8 mg [with an initial dose of 2 mg], 8 mg [with an initial dose of 4 mg], 12 mg [with an initial dose of 2 mg]) or placebo. The drug was administered once weekly for 48 weeks. Secondary endpoints included change in body weight after 48 weeks and the percentage of participants who achieved a weight reduction of at least 5%, at least 10%, or at least 15%. An equally important aspect was the evaluation of the drug's safety profile. The study included 338 patients, 52% of whom were men. The mean body weight was 107.7 kg, and the mean BMI was 37.3 kg/m², with as many as 30% having a BMI >40 kg/m². Body weight changes observed during the study, stratified by administered dose, are shown in Figure 1. Throughout the trial, AEs during the treatment period were reported in 70% of participants in the placebo group and in 73–94% of those receiving RTT. The highest incidence of these events was observed in the groups receiving 8 mg and 12 mg doses. Treatment discontinuation due to adverse events occurred in 6% to 16% of participants receiving RTT, whereas no placebo-group participants discontinued treatment for this reason. The most frequently reported adverse events were gastrointestinal symptoms, including nausea, diarrhea, vomiting, and constipation, which occurred more commonly in RTT-treated patients

Table 2. The most common AEs in phase I and II clinical trials

Test	Subgroup	Nausea *n* (%)	Diarrhea *n* (%)	Constipation *n* (%)	COVID-19 *n* (%)	Vomiting *n* (%)
NCT04867785 [21]	Placebo (*n* = 45)	2 (4)	2 (4)	1 (2)	3 (7)	1 (2)
	RTT 0,5 mg (*n* = 47)	2 (4)	1 (2)	3 (6)	5 (11)	1 (2)
	RTT 4 mg (2 mg DP) (*n* = 23)	2 (9)	2 (9)	2 (9)	3 (13)	1 (4)
	RTT 4 mg (*n* = 24)	6 (25)	6 (25)	4 (17)	1 (4)	0
	RTT 8 mg (2 mg DP) (*n* = 26)	7 (27)	5 (19)	3 (12)	1 (4)	2 (8)
	RTT 8 mg (4 mg DP) (*n* = 24)	10 (42)	7 (29)	2 (8)	1 (4)	4 (17)
	RTT 12 mg (2 mg DP) (*n* = 46)	9 (20)	7 (15)	5 (11)	2 (4)	5 (11)
	Dulaglutide 1,5 mg (*n* = 46)	8 (17)	4 (9)	3 (7)	4 (9)	4 (9)
	Entire group (*n* = 281)	46 (16)	34 (12)	23 (8)	20 (7)	18 (6)
NCT04881760 [20]	Placebo (*n* = 70)	8 (11)	8 (11)	2 (3)	14 (20)	1 (1)
	RTT 1 mg (*n* = 69)	10 (14)	6 (9)	5 (7)	13 (19)	2 (3)
	RTT 4 mg (2 mg DP) (*n* = 33)	6 (18)	4 (12)	5 (15)	4 (12)	4 (12)
	RTT 4 mg (4 mg DP) (*n* = 33)	12 (36)	4 (12)	2 (6)	6 (18)	4 (12)
	RTT 8 mg (2 mg DP) (*n* = 35)	6 (17)	7 (20)	4 (11)	6 (17)	2 (6)
	RTT 8 mg (4 mg DP) (*n* = 35)	21 (60)	7 (20)	4 (11)	12 (34)	9 (26)
	RTT 12 mg (2 mg DP) (*n* = 62)	28 (45)	9 (15)	10 (16)	15 (24)	12 (19)
	Entire group (*n* = 337)	91 (27)	45 (13)	32 (9)	70 (21)	34 (10)
NCT04143802 [19]	Placebo (*n* = 15)	2 (13)	2 (13)	1 (7)	No data	0
	Dulaglutide 1,5 mg (*n* = 5)	2 (20)	3 (60)	0	No data	1 (20)
	RTT 0,5 mg (*n* = 9)	0	1 (11)	0	No data	0
	RTT 1,5 mg (*n* = 9)	0	3 (33)	1 (11)	No data	1 (11)
	RTT 3 mg (*n* = 11)	1 (9)	1 (9)	1 (9)	No data	0
	RTT 3/6 mg (*n* = 11)	4 (36)	2 (18)	1 (9)	No data	0
	RTT 3/6/9/12 mg (*n* = 12)	6 (50)	6 (50)	1 (8)	No data	3 (25)
	Entire group (*n* = 72)	15 (2)	17 (2)	5 (7)	No data	5 (7)

ID – initial dose; RTT – retatrutide

compared to placebo. These adverse events primarily occurred during the dose-escalation phase, were typically mild to moderate in severity, and showed increased frequency in higher-dose groups. Participants who started therapy at a lower initial dose (2 mg compared to 4 mg) reported less severe symptoms. These events were also the most common reason for treatment discontinuation. A detailed analysis of the safety profile is presented in Table 1.

Phase II clinical trial NCT04867785

Between May 13, 2021, and June 13, 2022, a phase II clinical trial (NCT04867785) was conducted in the United States to evaluate the efficacy and safety of RTT at various doses in patients with type 2 diabetes [27]. It was a randomized, double-blind, placebo-controlled study conducted across 42 sites. A total of 281 participants took part, with a mean age of 56.2 years and an average diabetes duration of 8.1 years. Of the study group, 56% (156 individuals) were women, and 84% (235 individuals) were Caucasian. All participants were required to implement lifestyle modifications, including increased physical activity. Eligibility criteria included a diagnosis of type 2 diabetes with an HbA1c level ranging from 7.0% to 10.5%. Prior to the study, participants were managed exclusively with diet and exercise or a stable dose of metformin for at least three months before screening. They were then randomized into eight groups (in a 2:2:2:1:1:1:1:2 ratio) to receive weekly subcutaneous injections of either placebo, 1.5 mg dulaglutide, or RTT at maintenance doses: 0.5 mg; 4 mg (with an initial dose of 2 mg); 4 mg (without dose escalation); 8 mg (with an initial dose of 2 mg); 8 mg (with an initial dose of 4 mg); or 12 mg (with an initial dose of 2 mg). The study results demonstrated that weight loss was significantly greater in groups receiving RTT doses ≥4 mg compared to both the 1.5 mg dulaglutide group and the placebo group. Detailed data on changes in body weight are presented in Figure 1. During the study, at least one treatment-related adverse event was reported by 68% of RTT-treated patients (129 of 190), with incidence increasing dose-dependently – from 55% (26 of 47) in the 0.5 mg group to 79% (19 of 24) in the 4 mg group. In the placebo group, it was 62% [28 out of 45], and in the dulaglutide group – 67% [31 out of 46]. The most commonly reported adverse effects related to RTT involved the gastrointestinal system and occurred more frequently in the RTT groups – from 13% to 50% in the RTT group, compared with 13% in the placebo group and 35% in the dulaglutide group. Gastrointestinal adverse effects were more frequent with higher doses of RTT, particularly in groups where the initial doses were 4 mg compared with 2 mg. Most of them were mild to moderate in severity. A to-

Table 3. Details regarding the methodology, inclusion criteria, and endpoints of the phase III TRIUMPH clinical trials

	TRIUMPH-1 [22]	TRIUMPH-2 [23]	TRIUMPH-3 [24]	TRIUMPH-4 [25]
Placebo	+	+	+	+
Double-blind design	+	+	+	+
Randomization	+	+	+	+
Number of participants	2100	100	1800	405
Inclusion criteria (all must be met)	• ≥18 yo • BMI ≥30.0 kg/m², or ≥27.0 kg/m² with ≥1 of the following conditions: hypertension, dyslipidemia, OSA, or CVD • ≥1 unsuccessful dietary effort to reduce body weight	• ≥18 yo • BMI ≥27.0 kg/m² • T2DM • Stable treatment of T2DM for at least 90 days • ≥1 unsuccessful dietary effort to reduce body weight	• ≥18 yo • BMI ≥35.0 kg/m² • CVD with ≥1 of the following: prior MI, prior ischemic or hemorrhagic stroke, or symptomatic PAD • ≥1 unsuccessful dietary effort to reduce body weight	• ≥18 yo • BMI ≥27.0 kg/m² • ≥1 unsuccessful dietary effort to reduce body weight • Others*
Aim of study	Evaluation of the efficacy and safety of RTT in participants with obesity or overweight, including subgroups with OA and OSA	Evaluation of the efficacy and safety of RTT in participants with T2DM and obesity or overweight, including the subgroup of participants with OSA	Evaluation of the efficacy and safety of once-weekly RTT administration in participants with obesity and CVD	Evaluation of the safety and efficacy of weekly RTT administration in participants with obesity or overweight and OA
Study duration	89 weeks	89 weeks	113 weeks	77 weeks
Intervention model	Equal allocation between placebo and RTT			
Endpoints	• Percentage change in BW relative to baseline • Change from baseline in WOMAC score for the OA subgroup • Change from baseline in AHI for the OSA subgroup	• Percentage change in BW relative to baseline • Change from baseline in AHI for the OSA subgroup	• Percentage change in BW relative to baselinea	• Percentage change in BW relative to baseline • Change from baseline in WOMAC score

OA – osteoarthritis; OSA – obstructive sleep apnea; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; AHI – Apnea-Hypopnea Index; T2DM – type 2 diabetes mellitus; CVD – cardiovascular disease; BW – body weight; MI – myocardial infarction; PAD – peripheral artery disease

* Others:
- Knee pain lasting for >12 weeks prior to screening and knee pain present for >15 days during the past month.
- Knee X-ray showing moderate radiographic changes (grade 2 or 3 on the Kellgren-Lawrence scale).
- Currently meets the American College of Rheumatology criteria (clinical and radiological) for OA.

tal of 16 out of 190 participants (8%) discontinued treatment due to adverse effects, most commonly gastrointestinal (3% of participants). A detailed analysis of the safety profile is presented in Table 1 and Table 2.

Phase III clinical trials: TRIUMPH

After obtaining promising results in phase II studies, four phase III trials were initiated within the TRIUMPH program [29–32]. These studies include patients with class III obesity and – depending on the protocol – individuals with cardiovascular diseases, obstructive sleep apnea, or degenerative joint diseases. The trials aim to assess the efficacy and safety of RTT when administered once weekly. All studies are conducted in a randomized, double-blind, placebo-controlled design. They commenced in May 2023, with completion scheduled for February 2026. Details regarding the methodology, inclusion criteria, and endpoints are presented in Table 3.

Limitations

The present work, being a literature review, aimed to collect, assess, and synthesize available research on a specific topic; however, it does not meet the criteria of a systematic literature review. This type of analysis entails certain limitations that should be taken into account. First, subjectivity in material selection may influence the presented perspective on the issue. Moreover, the lack of original empirical data means that the conclusions are based solely on the interpretation of available publications. The complexity of the topic, combined with the difficulties of synthesizing findings from varied sources, may further limit the ability to draw definitive

conclusions. Therefore, it is important to recognize that a literature review is a valuable but not the only tool in the research process, and it should be complemented by other methods of scientific analysis.

Conclusions

Retatrutide is a novel drug that represents a promising therapeutic option for the treatment of obesity. This review summarizes the available data on its efficacy and safety, based on findings from phase I and II clinical trials. RTT has been shown to not only effectively regulate glycemia but also to induce significant weight loss, while maintaining a relatively favorable safety profile. However, attention should be paid to adverse effects, particularly those involving the gastrointestinal system. Most of them were mild to moderate in severity. Nevertheless, data on the long-term safety of the drug are lacking. Although the results obtained to date are promising, further comparative studies involving larger patient groups are necessary to confirm the therapeutic potential and safety of this novel triple agonist of GLP-1, GIP, and glucagon receptors.

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REVIEW ARTICLE

MANAGEMENT OF LUMBAR DISC HERNIATION – A REVIEW OF CONSERVATIVE AND SURGICAL TREATMENT

Postępowanie w przepuklinie dysku lędźwiowego – przegląd leczenia zachowawczego i chirurgicznego

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Abstract

Lumbar disc herniation is considered one of the leading causes of disability worldwide, with a lifetime risk of occurrence as high as 30%. A common initial symptom is pain in the sacro-lumbar region, which may radiate to the buttocks or lower extremities. The management of patients with lumbar disc herniation includes both conservative and surgical treatments. Conservative treatment involves medications, physical therapy, traction and appropriate exercises, and often yields good clinical results in 60–90% of patients. Surgical options include various techniques, such as open discectomy, microdiscectomy, percutaneous laser disc decompression, and percutaneous microscopic discectomy, among others. The purpose of this article is to present therapeutic methods used in the conservative and surgical treatment of lumbar disc herniation and to assess these methods in terms of clinical outcomes.

Streszczenie

Przepuklina dysku lędźwiowego jest zaliczana do jednej z głównych przyczyn niepełnosprawności na świecie. W ciągu całego życia ryzyko jej wystąpienia wynosi nawet 30%. Częstym pierwszym objawem jest ból w okolicy krzyżowo-lędźwiowej, który może promieniować do pośladków czy kończyny dolnej. W postępowaniu u pacjentów z przepukliną dysku lędźwiowego stosuje się leczenie zachowawcze oraz chirurgiczne. Leczenie zachowawcze składa się z leków, fizykoterapii, trakcji oraz odpowiednich ćwiczeń. Takie postępowanie często przynosi dobre efekty kliniczne u 60–90% pacjentów. W leczeniu chirurgicznym stosuje się różne techniki, takie jak otwarta dyskektomia, mikrodyskektomia, przezskórna laserowa dekompresja dysku, przezskórna mikroskopowa dyskektomia i wiele innych. Celem niniejszej pracy jest przedstawienie metod terapeutycznych używanych w leczeniu zachowawczym i chirurgicznym przepukliny dysku lędźwiowego oraz ich ocena w kontekście wyników klinicznych.

Keywords: disc herniation; LDH management; discectomy; disc; spinal surgery

Słowa kluczowe: przepuklina dysku; postępowanie w LDH; dyskektomia; dysk; operacja kręgosłupa

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Introduction

Lumbar disc herniation (LDH) is a common cause of patient complaints of back pain and radiculopathy. It predominantly occurs in patients between the ages of 24 and 45, with a male-to-female ratio of 2:1. Over 95% of lumbar herniations occur at the L4–L5 or L5–S1 levels in patients aged 25 to 55. LDH is considered one of the leading causes of disability worldwide, with a lifetime risk of approximately 30% [1–4].

Intervertebral disc herniation refers to a situation where the nucleus pulposus protrudes or extrudes through the fibrous ring beyond the intervertebral space. This may result in compression of the spinal nerve roots and the meningeal sac, leading to radiculopathy. Low back pain is a common initial symptom of LDH. It can radiate to the buttocks or lower extremities, typically unilaterally. Symptoms often worsen with physical exertion, sedentary lifestyle, squatting, and tend to subside after rest. Root symptoms, on the other hand, may be increased by activities such as sneezing, coughing, standing, or walking [3, 4].

In the diagnosis of LDH with radiculopathy, assessment of sphincter function, evaluation of muscle strength and sensory disturbances, as well as Lasegue's sign and crossed Lasegue's sign, may be useful. The gold standard in suspected LDH is MRI, which has a diagnostic accuracy of up to 97% [4].

The basis of treatment is conservative management focused on exercise and pain control with pharmacological agents. Nearly 60–90% of patients experience clinical improvement or even spontaneous regression already at this stage of treatment. If conservative treatment fails, surgical intervention with discectomy is indicated [1, 5, 6]. Advances in technology have contributed to the development of various surgical techniques aimed at removing herniated intervertebral discs with minimal tissue damage and, at the same time, the best possible clinical outcomes [7]. Especially important is the development of endoscopic techniques, which allow surgery to be performed under local anesthesia [3].

The traditional technique that finds application in LDH is open discectomy (OD) (with or without fusion surgery), but other surgical approaches can also be employed, such as microdiscectomy (MD), tubular discectomy (TD) (a subtype of microdiscectomy), and percutaneous laser disc decompression (PLDD) [8].

In addition, endoscopic spine surgery can be divided by the characteristics of the endoscopes into percutaneous endoscopic (PED) (or full-endoscopic), microendoscopic (MED), epiduroscopic, and biportal endoscopic techniques [7, 9].

Historical overview

The first true discectomy surgery took place in 1932 and is attributed to Mixter and Barr. Barr's published results (1947) indicated better clinical outcomes for LDH patients treated with surgical decompression and fusion than those treated with discectomy alone. In the 1970s, these surgeries became so popular that they were even offered to patients with very early, acute symptoms of lumbar disc herniation [10].

In 1977, Caspar and Ya□argil introduced the concept of microsurgical techniques in lumbar disc surgery. The smaller incision and tissue-sparing surgical approach made them superior to open discectomy. This marked the origin of microendoscopic discectomy, which has been improved over the years [11]. Percutaneous decompression surgery was inspired by Hijikata's theory developed in 1975, whose premise was "Reducing intradiscal pressure reduces the irritation of the nerve root and the pain receptors in the annulus and peridiscal area." [12].

Percutaneous endoscopic lumbar discectomy (PELD) through the intervertebral foramen emerged around 1980. It quickly became popular and a common technique, along with percutaneous endoscopic interlaminar discectomy (PEID) [9]. Seventeen years later, Smith and Foley described microendoscopic discectomy for the first time. The treatment of LDH patients using an endoscope and a minimally invasive transmuscular approach quickly became widespread [13]. In a short period, other minimally invasive surgical procedures such as PED and PLDD also emerged [3]. Tubular retractors combined with endoscopes became the foundation of the MED surgical technique, which was described in 1999 by Foley and Smith [14]. In the United States alone, approximately 200,000 discectomies were performed per year in the mid-1990s [10].

Conservative treatment

The foundation of conservative treatment is a combination of physical therapy and pharmacological management. However, there is a difference of opinion regarding the use of pharmacotherapy in the management of LDH. For instance, the American College of Physicians (ACP) recommends that pharmacological therapy should be introduced only when there is an unsatisfactory response to non-pharmacological therapy [15]. Some of the pharmacological agents commonly used in the conservative treatment of patients with LDH are described below.

Nonsteroidal anti-inflammatory drugs (NSAID)

NSAIDs are a well-known group of medications commonly used in clinical practice, including in the treatment of patients with LDH. However, study findings differ regarding the improvement of function and pain relief in such patients. Jung Hwan Lee et al. recommend the use of NSAIDs. A slightly different consideration is described in the article by Jo Jordan et al., who report that these medications have a comparable effect to placebo, since no significant difference was found in overall improvement after 5–30 days of use. It is important to note that NSAID therapy is not without side effects. These may include abdominal pain, gastrointestinal bleeding/perforation, cardiovascular incidents, headaches, and dizziness. Therefore, consideration should be given to the appropriate use of these medications so that their potential side effects do not outweigh the benefits. According to United Kingdom guidelines, the lowest effective dose should be used for the shortest possible time [2, 15–17].

Opioids

Opioid medications may also be used in LDH therapy, especially in combination with other drugs (antiepileptic, analgesic). This approach is very commonly used in the United States and Canada. Opioids have helped to reduce pain and improve patient functionality. However, with their use, vomiting and addiction, among others, may occur as adverse effects [2, 15].

Antidepressants and antiepileptic drugs

NICE (which provides evidence-based recommendations for health and care in England and Wales) recommends antidepressants and antiepileptic drugs as first-line treatment for neuropathic pain. These medications help improve function and reduce pain. Popular among these are amitriptyline, duloxetine, gabapentin, and pregabalin [2, 15].

Steroids

In clinical practice, epidural corticosteroid injections and systemic steroids are often used. However, if patients do not experience improvement after 4–8 weeks, surgical treatment is indicated [2, 5].

According to the article by Jung Hwan et al., epidural steroid injections are recommended for patients with LDH. They have demonstrated a high level of evidence and strength of recommendation for relieving pain and improving function. These injections can be administered via transforaminal, caudal, or interlaminar approaches. Although the caudal and interlaminar approaches were preferred for years, this trend has been reversed with the increasing use of transforaminal epidural injections. This is reflected in studies that are inconclusive, but point to the clinical benefit of the transforaminal approach over the mentioned above. In these interventions, the use of nonparticulate steroids is recommended, while particulate steroids are not advised [16, 18]. It is worth mentioning, however, that discectomy provides better results after 1–3 months in terms of functional improvement and pain reduction compared to epidural injections [17].

The effect of systemically administered steroids remains inconclusive. Significant pain reduction was experienced by patients with acute lumbosacral pain after systemic administration of dexamethasone. However, this improvement diminished after six months. Also, 14 days of oral triamcinolone therapy provided better pain control than oral anticonvulsant drug therapy. The clinical benefit of systemic steroid use is rated as clinically favorable, which supports its recommendation [16].

Other treatments

Non-pharmacological conservative treatments such as acupuncture or electroacupuncture of the spine do not show a significant difference compared to pharmacological treatment during the intervention period. Kim Doori et al. compared the treatment methods used above. The results demonstrated that non-pharmacological conservative treatment showed a significant improvement in the LDH patient's condition compared to pharmacological treatment, but only after 14 weeks of follow-up (difference: −0.56, 95% CI −1.62 to 0.50, $p = 0.003$). A meta-analysis by Shujie Tang et al. showed that acupuncture in the treatment of LDH has a more favorable clinical effect than NSAIDs and lumbar traction [15, 19].

A meta-analysis by Jung Hwan Lee et al. presented functional improvement and pain reduction in LDH patients suffering from root pain who used manual therapy, exercise and traction. In addition, patients who underwent traction therapy showed favorable changes on magnetic resonance imaging (MRI) in just two months, although no reduction in pain was observed [16].

A common practice recommended by physicians for patients with LDH-induced back pain is bed rest. However, studies have shown that this practice is not advisable and may even slightly worsen the patient's clinical condition. In such a case, the patient should be encouraged to return to daily physical activity with restriction to activities that do not cause pain [16, 20].

Surgical treatment

Patients with LDH are generally recommended to start with conservative treatment. If this proves ineffective, surgical intervention may be considered. However, some clinical situations require the implementation of surgical treatment first. Among these are severe neurological motor deficits, cauda equina syndrome, sphincter dysfunction, or insufficient pain control [21]. The surgeon, therefore, has to consider many factors in selecting the most appropriate surgical method. Some of the available techniques are described below.

Open discectomy

Open discectomy is a traditional surgical procedure used to treat patients with LDH. However, it is being performed less frequently, with minimally invasive surgeries becoming more popular. Compared to other surgical approaches, it is a technique associated with greater blood loss, prolonged hospitalization, and the formation of scarring and adhesions, which may contribute to decreased activity of the lumbar spine. This has led to the development of less invasive surgical approaches. A more modern approach – with shorter recovery times and lower surgical costs – is minimally invasive surgery (MIC) [3, 22].

Percutaneous laser disc decompression

Percutaneous laser disc decompression (PLDD) is a procedure that can be performed under local anesthesia. It involves percutaneously accessing the nucleus pulposus and then vaporizing it using the photothermal effect of laser energy. This reduces intradiscal pressure, allowing the disc to return to its normal position and relieving compression of the nerve root. In addition, the photochemical effect of the laser causes the destruction of pain mediators (neurokinins, cytokines). The study by Ivan Radoš et al. showed satisfactory pain reduction in LDH patients and a low risk of complications after the PLDD procedure [22, 23].

Percutaneous endoscopic lumbar discectomy

Percutaneous endoscopic lumbar discectomy (PELD) is a minimally invasive alternative to microdiscectomy

surgery. It is currently the most commonly used technique in endoscopic spine surgery. It is usually equated with percutaneous endoscopic interlaminar discectomy (PEID) and percutaneous endoscopic transforaminal discectomy (PETD). PELD is becoming an increasingly routine surgical approach. In comparison with open discectomy, it offers shorter operative times, with less soft tissue damage, fewer post-operative complications, and faster recovery. The main difference between the above-mentioned procedures is the surgical approach: PEID is performed between the lumbar vertebral arch laminae, while PETD is performed through the intervertebral foramen [7, 24, 25]. PEID is a well-suited surgical approach for subarticular disc herniations and concurrent stenosis of the lateral recess. In contrast, spinal disc herniations in the foramen but also in the lateral recess ventral to the traversing nerve root are a suitable indication for PETD. Notably, both surgical approaches are particularly appropriate for the lower lumbar spine – L4/5 and L5/S1 for PEID, and L5/S1 for PETD [5]. In the study results, PETD was characterized by better postoperative improvements in pain and function, but longer surgery times than PEID at the L5–S1 level. However, when comparing both surgical techniques, the clinical outcomes were very similar in terms of patient satisfaction, days of hospitalization, postoperative complications, blood loss, VAS (visual analog scale), and ODI (Oswestry Disability Index). Also, the PETD procedure was found to expose patients to higher levels of radiation than PEID [12, 26, 27]. A meta-analysis by Lu Qin et al. compared the effectiveness of PELD and microendoscopic discectomy to open discectomy. The minimally invasive procedures had better short-term outcomes based on VAS and ODI scores, but the difference at six months after surgery was not significant [3].

Microdiscectomy

Microdiscectomy is considered the gold standard in LDH surgery. The technique involves a small incision (up to a maximum of 2 cm), relatively little muscle damage, and faster recovery [9, 22]. However, it can lead to postoperative back pain or spinal instability. This is mainly caused by incision of the midline ligament and separation of the spinal muscles from the spinous process. A retrospective study by Konsta Koivunen et al. of 353 patients revealed that the level of pain decreased within a year after microdiscectomy but slightly worsened thereafter [14, 28].

Tubular microdiscectomy (TMD) is not based on standard subperiosteal muscle dissection, but rather the insertion of small tubes and dilators through a small incision to create a working corridor for the operation. This approach results in less tissue damage and supports faster recovery [14].

A meta-analysis by Tingxin Zhang et al. showed that tubular microdiscectomy achieved better ODI rates than conventional microdiscectomy. However, there were no significant differences in surgical blood loss, length of hospitalization, VAS score, reoperation rates, and operation time. The results show similar clinical effects of both surgical methods. In addition, the results of a meta-analysis by Shichao Liu et al. comparing TMD to PETD revealed no significant differences in clinical outcomes between these two techniques [14, 29].

Also worth mentioning is unilateral biportal endoscopic discectomy (UBED), which is similar to open MD. It combines endoscopic spine surgery and standard open surgery. UBED produced similar clinical results in terms of patient satisfaction and pain control compared to PELD. However, UBED was associated with increased blood loss, longer hospitalization, and higher costs [9, 30].

Discussion

Treatment of symptomatic LDH patients should be approached individually. The goal of treatment is to reduce or completely eliminate pain and to improve or restore limb function [29]. Correct diagnosis is a crucial element in further management. Lumbar pain should be differentiated from facet joint, discogenic, or sacroiliacal joint pain. In addition to diagnostic manual testing, current guidelines recommend magnetic resonance imaging (MRI) whenever symptoms persist for more than six weeks to confirm the presence of LDH. MRI should be performed as soon as possible if neurological deficits are present. In patients in whom MRI cannot be performed, or if the results are inconclusive, CT (computed tomography) or CT myelography is recommended [4]. Therapeutic management should begin with conservative treatment, which leads to improvement in 60–90% of patients. Pharmacological agents, physical therapy procedures, and physiotherapy exercises should be selected on an individual basis. It should be noted that for some conservative treatments, the question of clinical improvement is still unclear and requires further research.

If there is no improvement with conservative treatment, surgical intervention is indicated. Patients with insufficient pain control, symptoms of sphincter dysfunction, neurological motor deficits, or cauda equina syndrome require urgent surgery [21]. Patients should be cautiously qualified for surgical treatment. The risk of LDH recurrence is approximately 9.1%, of which 38% cases recur within the first year after surgery. In addition, postoperative pain may be worse in some patients than before surgery. While patients usually blame the operator for such outcomes, the predominant factor is actually the patient's individual predisposition – particularly the formation of scar tissue after surgery, which presses on the nerve root. This issue is the most important factor in failed spinal surgeries due to LDH. It is important to note that reoperations in such patients tend to worsen their clinical outcomes [4, 22]. When selecting a surgical method, minimally invasive spinal surgery techniques should be the main consideration, as studies have shown that they produce better clinical outcomes than open discectomy. In 2024, a meta-analysis by Qin Lu et al. was published, comparing standard open discectomy, microdiscectomy, microendoscopic discectomy, PELD, PLDD, TMD, and chemonucleolysis. It showed that microendoscopic discectomy is the best surgical intervention for back and leg pain, based on VAS scores [3]. However, it is important to note that each of the listed surgical methods has its own indications and contraindications, which are often individual. Therefore, the final choice of surgical technique is made by the surgeon, who looks at the patient on an individual basis and selects the most appropriate surgical method.

In addition to the aforementioned surgical treatment methods, risk factors for LDH are also worth highlighting. A prospective study conducted in Copenhagen on thousands of men found that heavy physical activity at work was a strong risk factor for LDH. On the other hand, physical activity outside of work did not correlate with the occurrence of LDH. This suggests that different types of physical and ergonomic loads at work influence the development of lumbar disc herniation. Sørensen et al. additionally described body height as a predictor associated with lumbar herniated discs, while body weight was only slightly associated with LDH [31]. In a surprising finding, Mirza Pojskic et al. indicated an increased relative risk of LDH in cigarette smokers [4]. Risk factors that may contribute to lumbar spinal herniation should be avoided whenever possible.

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REVIEW ARTICLE

UNMANNED MARINE SYSTEMS FOR MONITORING CHEMICAL WEAPONS SUNK IN THE BALTIC SEA – AN INNOVATIVE TOOL FOR PROTECTING HUMAN HEALTH AND THE ENVIRONMENT

Bezzałogowe systemy morskie w monitorowaniu broni chemicznej zatopionej na dnie Bałtyku – innowacyjne narzędzie dla ochrony zdrowia ludzi i środowiska

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Abstract

The Baltic Sea, one of the most congested seas in Europe, is particularly vulnerable to pollution due to its shallow depth and enclosed nature. After World War II, tons of German chemical weapons were dumped there on the orders of the Allied forces. It is estimated that around 40,000 tons of these weapons and munitions – including dangerous chemical agents such as sulfur mustard, tabun, and phosgene – now lie on the sea floor. These substances pose a serious threat to both marine life and human health, especially if leaks occur as a result of corrosion in the shells or containers in which the chemicals are stored. Regular monitoring of the condition of these containers is therefore essential. In this context, unmanned maritime systems – including underwater, surface, and aerial vehicles – play a crucial role in monitoring and neutralizing the threats posed by chemical weapons on the Baltic Sea floor. Working in collaboration, these systems can be used for detection, mapping, and environmental analysis to help minimize the risks associated with these substances.

Streszczenie

Morze Bałtyckie jest zbiornikiem wodnym szczególnie narażonym na zanieczyszczenia ze względu na swoją niewielką głębokość i zamknięty charakter. Po II wojnie światowej, w ramach operacji alianckich, została zatopiona w nim niemiecka broń chemiczna. Szacuje się, że na dnie znajduje się około 40 tysięcy ton chemikaliów, w tym niebezpieczne środki bojowe, jak iperyt siarkowy, tabun czy fosgen. Zatopione substancje stanowią poważne zagrożenie dla środowiska morskiego i zdrowia ludzi, zwłaszcza w przypadku uwolnienia ich np. na skutek korozji korpusów amunicji czy pojemników, których stan powinien podlegać stałej kontroli. W tym kontekście rosnące zainteresowanie bezzałogowymi systemami morskimi, w szczególności pojazdami podwodnymi, powierzchniowymi oraz powietrznymi, staje się kluczowy w monitorowaniu i neutralizacji zagrożeń związanych z zatopioną bronią chemiczną. Współdziałanie tych systemów może być wykorzystywane do wykrywania, mapowania oraz analizy środowiskowej w celu zminimalizowania ryzyka związanego z tymi substancjami.

Keywords: Baltic Sea; ecological safety; civil protection; chemical weapons; unmanned maritime systems

Słowa kluczowe: Morze Bałtyckie; bezpieczeństwo ekologiczne; ochrona ludności cywilnej; broń chemiczna; bezzałogowe systemy morskie

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Introduction

The history of chemical weapons sunk in the Baltic Sea is closely linked to the military operations of World War I and World War II. During that time, vast quantities of toxic agents were produced for filling aerial bombs, artillery shells, grenades, mines, and metal containers. It is estimated that between 1914 and 1918, around 180,000 tons of chemical warfare agents (CWAs) were produced [1]. The widespread deployment of chemical weapons during this period resulted in the poisoning of approximately 1.2 million people, with about 100,000 fatalities [2]. In the interwar period and during World War II, the production and development of chemical weapons continued. Previously used agents, such as sulfur mustard (yperite), lewisite, and adamsite, remained in military use, while new, more toxic organophosphorus compounds – including tabun and sarin – were developed. During the military operations in Europe, not all of the stockpiled weapons were used, which, after the war, created the problem of disposing of both chemical munitions and the CWAs themselves [1]. Various methods were employed to eliminate them: some were buried, others incinerated or neutralized, while vast quantities were dumped into seas and oceans. It was a widely accepted practice from the early 20th century until the 1970s, considered at the time to be the safest and cheapest way to dispose of chemical weapons. A key turning point in this matter was the Potsdam Conference in 1945, where the disposal of chemical weapons in the Baltic Sea was officially approved as part of Germany's demilitarization process [1, 3]. Today, it is estimated that within Poland's exclusive economic zone (EEZ), the risk of human exposure or contamination of ships by submerged chemical weapons exists across an area of approximately 340 km² (Fig. 1). The EEZ is an area of maritime waters under Poland's jurisdiction, granting it broad sovereign rights over resources and economic activities within 200 nautical miles from the

Figure 1. Official and unofficial chemical weapons transport routes and dumping sites within the Polish exclusive economic zone [1]

coastline. Within the Polish EEZ, Polish maritime authorities have designated six hazardous zones, which include: the area near Bornholm – at the border with the Danish EEZ, covering approximately 220 km² – as well as regions close to Dziwnów (88 km²), Kołobrzeg (8 km²), Darłowo (8 km²), Hel (8 km²), and the Gdańsk Deep (approximately 8 km²) [4, 5]. The estimated quantity of chemical munitions in these areas ranges between 10,000 and 12,000 units [4, 6].

In Polish maritime areas, the largest quantities of chemical weapons were dumped in the Gdańsk Deep. They were deposited there as a result of actions by Weimar Germany, Nazi Germany, Soviet forces, the GDR, and the USSR. It is estimated that around 60 tons of chemical munitions, mainly containing sulfur mustard (mustard gas), were dumped in these areas. An additional hazard comes from conventional munitions that were disposed of alongside chemical weapons [4]. Table 1 presents the characteristics of the areas within Polish maritime waters where there is a risk of contact with CWA, as well as the types of chemical weapons recovered from these areas.

Chemical munitions lying on the Baltic Sea floor become particularly hazardous if toxic substances are released into the water. This can occur due to the corrosion of metal containers or as a result of explosions during research, recovery, or operational activities. Such events can cause the rapid dispersal of CWAs in the form of an aerosol, suspension, or colloid, leading to environmental contamination [2]. Health risks to humans include direct exposure of fishermen to chemical munitions, consumption of contaminated fish, and beach pollution from containers washed ashore [7, 8].

In the first half of the 1950s, reports began to emerge of containers with sulfur mustard being washed ashore along the Polish coast, southwest of Bornholm, and along shipping routes leading to dumping sites in the Gotland Deep and Bornholm Deep [4]. Until 2012, incidents involving chemical weapons in the Baltic Sea were recorded by the Danish Navy on behalf of the Helsinki Commission (HELCOM). However, since 2013, Denmark has discontinued this practice, resulting in a lack of official data on such incidents after that date. Nevertheless, several incidents are still reported each year. Analysis of recorded events shows a decline in their number since 2000 (with the exception of 2003). Experts suggest this trend may be attributed to shifts in local fish stocks, reduced fishing activity in high-risk zones, and the use of modern fishing gear. Additionally, underreporting remains an issue – fishermen often fail to report retrieved hazardous objects if no one was harmed, which may skew the statistics downward [4].

It can be concluded that chemical weapons are dispersed over a much wider area than indicated in the reports prepared by the HELCOM CHEMU Working Group based on available archival documentation. Numerous cases of encounters with chemical weapons and leaked chemical warfare agents outside designated disposal zones suggest that weapons were frequently dumped *en route* to their intended sites, and that unauthorized disposal occurred in undesignated areas, many of which remain largely unmapped to this day. In light of the intensive exploitation of the Baltic Sea, which plays a key role in the European economy, there is a growing need to implement modern technologies, including unmanned marine systems, for monitoring and neutralizing contamination. Therefore, effective management of this issue requires not only a thorough analysis of existing threats, but also the implementation of innovative technological solutions that can safeguard this precious ecosystem from the consequences of past chemical weapons disposal activities.

Unmanned maritime systems

Unmanned vehicles, including aerial and maritime systems, are seeing increasingly widespread applications [9, 10]. Their potential is particularly evident in marine research and monitoring, where these advanced technologies offer new possibilities for both exploring and protecting the marine environment [11]. Unmanned maritime sys-

Table 1. Risk zones for chemical warfare agent exposure in Polish marine waters. Source: Fabisiak [4]

Region	Hydrogeological characteristics	Type of ammunition
Bornholm	• depth: 70–105 m • salinity: 7–16 PSU • temperature at the seabed: 5–6°C	bombs, artillery ammunition, mines, containers, and canisters with mustard gas and arsenic compounds
Dziwnów	• depth: 10–16 m • salinity: 7.5 PSU • temperature at the seabed: 5–6°C	artillery shells containing mustard gas and arsenic compounds
Kołobrzeg	• depth: 65 m • salinity: 7–16 PSU • temperature at the seabed: 5–6°C	bombs, artillery ammunition, mines, containers, and canisters with mustard gas and arsenic compounds
Darłowo	• depth: 90 m • salinity: 7–16 PSU • temperature at the seabed: 5–6°C	mustard gas bombs
Hel	• depth: to 117 m • salinity: low • temperature at the seabed: 5–6°C	bombs, artillery ammunition, mines, containers, and canisters with mustard gas and arsenic compounds
Gdańsk Deep	• depth: 80–110 m • salinity: 7–16 PSU • temperature at the seabed: 5–6°C	mustard gas bombs; conventional munitions were also dumped in the area.
PSU – practical salinity unit		

tems encompass a broad range of technologies. Based on their operational characteristics, they can be classified into three main categories: unmanned underwater vehicles (UUVs) [12], unmanned surface vehicles (USVs) [13], and unmanned aerial vehicles (UAVs) [14] used for maritime operations. Each of these systems offers distinct advantages and limitations, while their integrated operation can ensure optimal mission effectiveness.

Unmanned underwater vehicles are capable of operating in challenging deep-sea conditions where manned vessels cannot function, enabling the monitoring and exploration of otherwise inaccessible locations. Additionally, their long endurance allows them to carry out missions lasting many hours, or even days, without the need to return to the surface [12]. Equipped with advanced sensors and imaging systems, UUVs provide high-precision seabed mapping data, facilitating the identification of shipwrecks [15] and hazardous objects like chemical weapons [16]. On the other hand, their limitations arise from the challenges of underwater communication, which necessitate autonomous operation. This can lead to delays in responding to dynamic or rapidly changing situations. In addition, depth and variable conditions may limit the effectiveness of sensors, adversely affecting the quality of the collected data [12].

In contrast, unmanned surface vehicles maintain continuous contact with the base, allowing real-time data exchange and swift responses to changing conditions [17]. They also serve as support platforms for other unmanned systems, such as underwater vehicles and aerial systems, providing power and communication points. Their lower operating cost, compared to manned units, makes them more cost-efficient [10, 12, 14, 15]. However, USVs are vulnerable to changing weather conditions, which may impede their operation, and they offer limited mobility compared to aerial systems – a significant drawback when operating over large water areas [13, 17].

Unmanned aerial vehicles, on the other hand, are distinguished by their speed and agility, enabling them to rapidly cover long distances [10, 14]. This makes them particularly well-suited for immediate reconnaissance, large-scale monitoring, and rapid response to emerging threats. Equipped with advanced cameras and sensors, they provide real-time imagery and data to support decision-making processes in maritime operations. Additionally, their operational flexibility enables rapid deployment and retrieval of units as needed. However, limited flight time due to battery capacity necessitates frequent recharging or swaps, and their effectiveness can be significantly reduced by harsh weather conditions such as strong winds and rain, posing a major challenge during prolonged open-sea missions.

Each of the aforementioned unmanned systems has distinct strengths and limitations, but their combined deployment creates an optimal support framework. UUVs provide valuable deep-sea data, USVs serve as communication hubs and surface support platforms, while UAVs deliver real-time aerial surveillance.

Unmanned surface vehicles conduct detailed surface water monitoring and perform measurements in coastal zones. Aerial platforms provide extensive airborne surveillance coverage, enabling wide-area monitoring and identification of potential hazard zones. Meanwhile, diving drones conduct deep-water investigations, collecting direct seabed data and profiling threat-source environments. Data collected by these three types of platforms is transmitted in real time to a central analytical system. Leveraging advanced computing technologies such as artificial intelligence algorithms and 3D spatial modelling, the system performs multi-layered data analysis. Based on the obtained results, operational decisions are made in accordance with previously developed safety protocols. Thanks to this integrated architecture, the system enables precise mapping of sunken chemical weapons, assessment of potential threats, and rapid implementation of protective measures, minimizing the risk to the environment and humans (Fig. 2).

When integrated, these three categories of unmanned maritime systems complement one another, forming a comprehensive solution capable of addressing even the most demanding operational challenges.

Applications of unmanned maritime systems

The use of unmanned systems for monitoring and neutralizing chemical weapons sunk in the Baltic Sea includes:

- **Detection and mapping.** Unmanned underwater vehicles are equipped with advanced sensors, such as sonars, magnetometers, and imaging systems, which enable precise seabed mapping and identification of objects that may pose a potential threat.
- **Monitoring and environmental analysis.** Unmanned underwater and surface vehicles can be deployed to collect water and seabed sediment samples for chemical analysis and contamination assessment. Regular measurements allow for continuous monitoring of potential leaks and their impact on the ecosystem. Currently, due to technological limitations, direct on-site sample analysis is not feasible. Consequently, collected sediments, water, or fragments of objects must be transported to specialized laboratories for examination However, research is underway to develop sensors capable of performing direct analysis in the surveyed area. One promising innovation is a neutron analyzer, which would enable on-site identification of hazardous substances.
- **Threat neutralization.** Unmanned systems can also take part in threat neutralization operations, for example by precisely placing explosive charges for the controlled destruction of corroded chemical weapon containers.

Challenges related to the use of unmanned vehicles for monitoring the Baltic Sea floor

The advancement of unmanned maritime systems undoubtedly offers significant benefits, particularly in mitigating or eliminating hazards posed by dangerous submerged objects – such as chemical weapons – in seas and oceans. However, these systems also present certain limitations that should guide future technological developments. A primary concern is the safety of unmanned vehicle operations. Operations in chemical weapon dumping zones – characterized by highly dynamic conditions – are

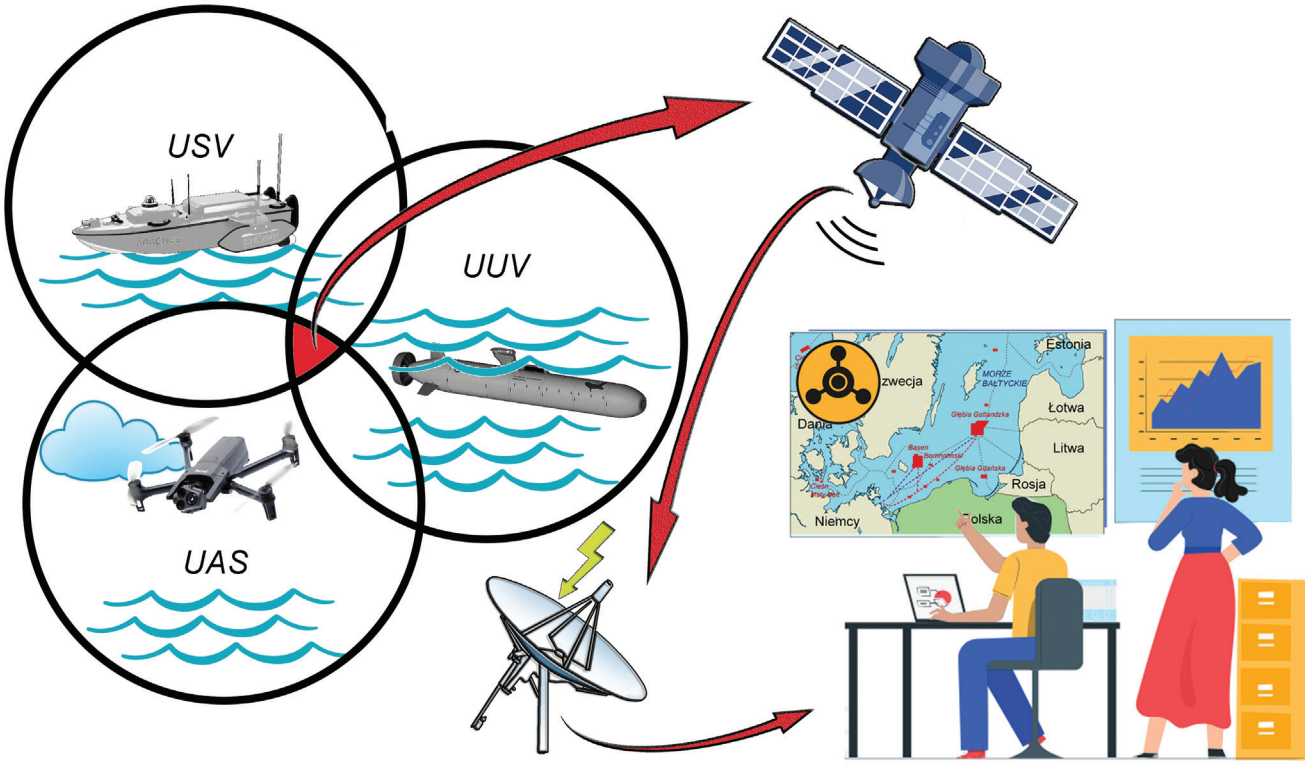

Figure 2. Integrated support system using unmanned platforms for monitoring chemical weapons hazards on the Baltic seafloor. USV – unmanned surface vehicles; UUV – unmanned underwater vehicles; UAS – unmanned aircraft system

extremely hazardous, require rapid response capabilities, and carry a high risk of serious accidents if mistakes occur [18]. Moreover, operations in the Baltic Sea often require cooperation between multiple countries, which can be complicated due to differences in legal regulations, operational procedures, and levels of technological advancement [19]. To minimize risks associated with such operations, several preventive measures should be considered. First and foremost, before commencing operations, a detailed risk analysis should be conducted to identify potential hazards and develop contingency plans. Drone operators should undergo regular training, including crisis simulations, to prepare for various scenarios. It is also essential to ensure that personnel operating unmanned maritime vehicles are well-trained in data analysis and in carrying out activities without endangering or obstructing traffic in the Baltic Sea. This type of training should cover topics related to hazard identification, procedures for handling emergency situations, operation of specialized equipment, evacuation protocols, as well as principles for minimizing the impact of operations on the marine environment and navigational safety. Therefore, it is essential to develop and implement strict safety procedures for working with unmanned maritime systems, particularly in areas classified as hazardous.

Another challenge lies in the technological limitations associated with operating equipment in the difficult conditions of the Baltic Sea, such as high pressure, low temperature, limited visibility, and the presence of other vessels [20–22]. For this reason, it is essential to develop an information system that integrates and supports the operation of various types of unmanned vehicles – including underwater, surface, and aerial systems. The development of such systems should deliver comprehensive and complementary data, enabling precise detection and mapping, as well as facilitating environmental analyses related to chemical weapons and toxic agents located on the Baltic Sea floor.

Another factor that should not be overlooked is the high cost of purchasing, maintaining, and operating advanced unmanned systems, which can be a barrier to their widespread adoption. The Baltic Sea is an international body of water, which is why the development of a monitoring program and the sharing of its costs should be a shared responsibility among all Baltic states. It is necessary to agree on a joint financing strategy for unmanned maritime systems to monitor threats related to submerged chemical weapons.

The role of Polish science and numerous academic centers in Poland, which monitor and study the ecological safety of the Baltic seabed, is also very important. Adequate funding for Polish science is essential, as it can drive significant progress in developing information systems that enhance the ergonomics, performance, and energy efficiency of unmanned vehicles. Equally important is the involvement of biologists analyzing ecological changes caused by chemical weapons submerged on the Baltic seabed [23, 24].

Conclusions

Unmanned maritime systems hold significant potential for enhancing the mapping, monitoring, and neutralization of hazards related to chemical weapons in the Baltic Sea. The development of advanced technologies can significantly improve ecological and health safety in this region. Further efforts are needed to integrate individual

unmanned systems and improve cooperation between them. This requires investment in technology development and the creation of comprehensive strategies and procedures to enable effective and safe management of the threat elimination process.

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REVIEW ARTICLE

INNOVATIVE TREATMENT METHODS FOR ERECTILE DYSFUNCTION

Innowacyjne metody terapii zaburzeń erekcji

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Abstract

Erectile dysfunction is a common sexual disorder among men. The complexity of its aetiology, problems with therapeutic efficacy and convenience prompt the search for new solutions that could improve the existing treatment approaches. The article presents a set of innovative surgical, physiotherapeutic and pharmacological solutions for erecqtile dysfunctions, including stem cell therapy, platelet-rich plasma therapy, low energy shock wave therapy, as well as pharmacological innovations using amorphous solid dispersions of phosphodiesterase-5 inhibitors.

Streszczenie

Zaburzenia erekcji są częstym problemem z zakresu dysfunkcji seksualnych mężczyzn. Złożoność ich przyczyn, ograniczenia skuteczności i wygody obecnych metod leczenia, a także powszechność występowania sprawiają, że konieczne jest nieustanne poszukiwanie nowych rozwiązań, które mogłyby ulepszyć dotychczasowe formy leczenia. W artykule przedstawiono przegląd innowacyjnych metod terapii zaburzeń erekcji, które podzielono na metody zabiegowe, fizjoterapeutyczne oraz farmakologiczne. Omówiono m.in. terapię komórkami macierzystymi, terapię osoczem bogatopłytkowym, terapię falą uderzeniową o niskiej energii oraz innowacje farmakologiczne z wykorzystaniem amorficznych stałych dyspersji inhibitorów fosfodiesterazy-5.

Keywords: erectile dysfunction; Li-ESWT; amorphous solid dispersions; phosphodiesterase-5 inhibitors; platelet-rich plasma

Słowa kluczowe: zaburzenia erekcji; Li-ESWT; amorficzne stałe dyspersje; inhibitory fosfodiesterazy-5; osocze bogatopłytkowe

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Introduction

Erectile dysfunction (ED) is the most common type of sexual dysfunction in men. Treatment options include both symptomatic and causal approaches, with differential diagnosis playing a key role in causal treatment [1]. Erectile dysfunction is defined as the inability to achieve or maintain an erection adequate for satisfactory sexual intercourse. Multiple mechanisms may be involved in its pathophysiology. These include vascular, neurogenic, anatomical, hormonal, drug- or substance-induced, and psychogenic factors, which may coexist and mutually exacerbate ED [2]. Since effective ED treatments are still lacking, novel, more effective therapeutic modalities are being explored, including surgical, physiotherapeutic, behavioural, and pharmacological approaches. This prompted us to summarize the latest innovations in ED therapy.

Pharmacological treatments for ED aim to temporarily improve sexual performance rather than address the underlying cause or provide a permanent outcome. Regenerative therapies that may reverse changes leading to EDs include platelet-rich plasma (PRP) injections, low-intensity extracorporeal shockwave (LI-ECSW), and stem cell therapy [3].

Stem cell therapy

Injection of mesenchymal stem cells (stem cell therapy, SCT) or stromal vascular fractions derived, among oth-

ers, from adipose tissue, is one of medical interventions used to treat ED.

To date, most studies have been conducted in rodents. A recent systematic review identified five human studies on SCT for erectile dysfunction. These phase I and II trials included a total of 61 patients. Importantly, none of the studies reported serious adverse events (AEs), and their results were indicative of a positive therapeutic effect. However, the authors of the review emphasize that the limited data in this area warrant further in-depth clinical trials to assess the efficacy and safety of this therapy, particularly in patients with prostate cancer [3].

Platelet-rich plasma

Platelet-rich plasma (PRP) is a natural blood-derived product containing biologically active platelets, which release growth factors such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF-1), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), which stimulate cell growth, proliferation, and differentiation, as well as collagen and elastin production, promoting tissue regeneration and faster wound healing. Growth factors also stimulate angiogenesis, giving rise to new blood vessels. PRP is obtained by centrifuging the patient's venous blood, typically collected from the ulnar vein (approximately 10 mL), using an FDA-approved separation process. The resulting PRP is then injected into corpora cavernosa. Contraindications include blood disorders, cancer, skin lesions at the injection site, and poorly controlled diabetes mellitus [4].

The first randomized, double-blind, placebo-controlled clinical trial was conducted among 60 sexually active patients with mild to moderate ED, forming two equal groups (n = 30): one receiving 10 mL of PRP, and one receiving placebo intracavernosal injections. Participants did not use any other ED treatments during the study. Erectile function was assessed at 1, 3, and 6 months after treatment completion. The results were very promising with improved erectile function in 69% of the study group vs 27% in the placebo group at 6 months. These patients were also more satisfied with the treatment. The results observed at 1 and 3 months were consistent with the final results. No adverse events were reported during the study [5].

Another clinical trial, conducted in a group of 34 patients, showed that PRP intracavernosal injections were particularly beneficial for smokers [6].

According to a 2015–2020 study, PRP injections can be a beneficial addition to low-intensity extracorporeal shock wave therapy (Li-ESWT) in ED patients who had not responded to at least 3 months of treatment with phosphodiesterase type 5 inhibitors (tadalafil at 5 mg daily). The patients were randomised into two groups: Li-ESWT alone and Li-ESWT combined with PRP. Although the increase in IIEF-EF (International Index of Erectile Function – Erectile Function domain) was similar in both groups, the PRP plus Li-ESWT group experienced a 1.5- to 3.5-fold longer duration of vaginal penetration. No adverse events were reported, with all patients on the combination therapy expressing a desire to continue PRP injections [7].

In conclusion, although PRP intracavernosal injections seem to be a potentially safe, innovative and promising treatment approach for ED and improving sexual function in men, further clinical trials are needed to confirm these reports.

Low-intensity extracorporeal shock wave therapy

Low-intensity extracorporeal shock wave therapy (Li-ESWT) is a first-line treatment for erectile dysfunction [8].

Li-ESWT is a form of acoustic wave with unique properties: it generates a sudden rise in pressure that rapidly decreases to a negative value, with propagation speed higher than that of typical sound waves. Li-ESWT energy, generated by electrohydraulic, electromagnetic, or piezoelectric sources, is delivered through an applicator placed on the penis, which is coated with gel to eliminate the air layer. Key treatment parameters include energy density (<0.2 mJ/mm^2), frequency (Hz), and number of pulses. Their selection impacts the therapeutic effect [9]. It is worth noting that there is currently no standardised protocol for Li-ESWT in the treatment of ED, as emphasized in 2018 during the 20th Congress of the European Society for Sexual Medicine (CESSM) and the 21st World Meeting of the International Society for Sexual Medicine (WMISSM) [10].

Research on the use of Li-ESWT in patients with ED was initiated by Gruenwald et al. [11], who described and defined metabolic and tissue processes involved in the formation and development of blood vessel networks. Several mechanisms are thought to underlie the beneficial effects of Li-ESWT in ED, including stimulation of penile tissue mechanoreceptors, reduction of inflammation, recruitment and activation of endothelial progenitor cells (EPCs), and both neuroprotective and neuroregenerative effects [12]. In their studies in rats, Lin et al. [13] demonstrated increased stem cell proliferation in penile tissue after 48 hours and 1 week of Li-ESWT (*in-situ*), with stronger therapeutic effects in young animals compared to middle-aged ones, and higher doses producing greater benefits. In turn, Scorpo et al. [14] demonstrated improved penile microcirculation in men undergoing Li-ESWT (based on Doppler flow analysis).

The beneficial effects of Li-ESWT in ED are observed at 6 and 12 months, but gradually deteriorate, reaching a plateau of about 40% at 5 years post-treatment (according to patients' subjective assessments) [15–17]. It is also noteworthy that Li-ESWT is a non-invasive, safe procedure, and precise targeting of the treatment site helps protect surrounding tissues. However, it is important to note that Li-ESWT for ED may cause discomfort due to the nature of the procedure, and patients should be adequately informed beforehand. A review of available studies showed virtually no adverse reactions to Li-ESWT for ED. Furthermore, our clinical experience indicates that patients describe the procedure as well-tolerated and even relaxing.

Unfortunately, Li-ESWT treatments for ED are not reimbursed in Poland and can be quite costly. This, combined with limited awareness of the method's effectiveness among both patients and medical personnel, as well as the small number of centres offering this treatment in our country, makes Li-ESWT poorly accessible. Based on current research findings, we believe that it is worth promoting Li-ESWT in the treatment of ED.

Innovative pharmacological treatments for ED

Phosphodiesterase-5 inhibitors (PDE5Is) are currently used as the first-line treatment for ED and represent the most common form of pharmacotherapy. In later phases (second-line treatment), other agents such as alprostadil or papaverine may be used, administered either as an intraurethral gel or via intracavernosal injection. PDE5Is are widely tolerated by patients due to their convenient oral formulations (tablets, films, and powders for oral suspension). However, discontinuing PDE5I therapy is very common. Studies indicate poor compliance with PDE5I treatment, despite its high efficacy [18]. Therefore, new pharmacological treatments are being explored, using known substances with improved performance parameters that may enhance compliance.

The mechanism of action of PDE5Is is based on the selective inhibition of phosphodiesterase type 5, an enzyme found in various tissues, including the corpus cavernosum of the penis. As a result, the breakdown of cyclic guanosine monophosphate (cGMP) is inhibited. The accumulated cGMP induces a decrease in smooth muscle calcium ions, leading to relaxation of vascular and cavernous smooth muscle, increased blood flow, and erection. However, nitric oxide (NO), released locally during sexual stimulation as the primary mediator of erection, with cGMP acting as a secondary mediator, is a key factor. Consequently, the effectiveness of PDE5I depends on adequate release of NO, which activates guanylate cyclase to produce cGMP. PDE5Is act only by increasing cGMP levels through inhibition of its degradation [19].

The PDE5I class includes five drugs: sildenafil, tadalafil, vardenafil, avanafil, and udenafil. Udenafil is not approved for use in Poland, the United States, and many other countries. These medications vary in efficacy, as confirmed by a recent meta-analysis of systematic reviews on PDE5Is and erectile dysfunction. Their efficacy as compared to placebo was often dose-dependent in the general population [20]. All five inhibitors have specific dosage ranges. In Poland, the available doses are 25 mg, 50 mg, and 100 mg for sildenafil; 5 mg, 10 mg, and 20 mg for tadalafil; 5 mg, 10 mg, and 20 mg for vardenafil; and 50 mg, 100 mg, and 200 mg for avanafil. The choice of appropriate dose depends on the patient's response. In some cases, physicians may prescribe the maximum dose. In recent years, 10 mg tadalafil has also become available over the counter in Poland. All PDE5Is discussed in this paper belong to the second class of the Biopharmaceutics Classification System (BCS). The second group comprises substances that are poorly soluble in water, but easily penetrate biological membranes, which makes their absorption rate similar to their dissolution rate in water [21–25]. Due to possible adverse reactions, the need for optimal formulations, and the possibility of improving bioavailability while reducing treatment costs, efforts are being made to enhance the water solubility of these compounds.

Amorphous solid dispersions (ASDs) are systems where the amorphous form of a pharmacologically active substance is molecularly dispersed within a carrier matrix that, due to its physicochemical properties, effectively stabilizes the amorphic substance. Their role in stabilization is crucial, as the commercial crystalline forms of active substances such as sildenafil, tadalafil, avanafil, and vardenafil have poor water solubility. Converting them into the more soluble amorphous form improves dissolution but reduces physical stability, necessitating appropriate stabilization. Achieving a physically stable amorphous form of the drug improves bioavailability, which may allow for lower doses of the active substance while maintaining efficacy. Enhanced solubility can also accelerate drug action by facilitating membrane penetration and delivery to the target site [26–28].

The amorphous state of the substance is beneficial due to its improved water solubility and the resulting increase in bioavailability. The process of converting a crystalline form into an amorphous one is referred to as a phase transition as the elemental composition, molecular formula, and structural formula of the molecule remain unchanged. Only the crystal structure changes. The presence of different crystallographic forms of a given substance results from the different spatial arrangement of its molecules. Unlike the crystalline form, the amorphous form exhibits only short-range order, meaning that the molecular positions are not precisely defined. As a result, it shows variable molecular mobility and exists in a less stable, higher-energy state than the crystalline form. This leads to crystallization, resulting in reduced water solubility and bioavailability of the drug. Therefore, efficient stabilization of amorphous forms is essential. In ASDs, stabilization can be achieved by using a carrier with suitable physicochemical properties. Key criteria for carriers include a high glass transition temperature and an amorphous form. Efficiency can be further improved by employing an appropriate excess of carrier [26].

Amorphous solid dispersions of sildenafil

Studies on the formation of sildenafil ASDs with glycyrrhizin and polymeric solubilizer Soluplus, using spray drying as the amorphization method, demonstrated satisfactory performance and an optimal particle size (0.710 µm for a 1:1 drug-to-stabilizer weight ratio). Furthermore, the ASD form showed higher drug release efficiency compared to the pure substance. These results were confirmed in a rat model, where sildenafil ASD led to improved sexual activity compared to its crystalline counterpart [23].

Similar studies on the impact of a stabilizing polymer on the physicochemical stability of sildenafil ASD were published in 2021. In these studies, the substance was amorphized by solvent evaporation using a rotary evaporator. Among the three polymers tested (Kolliphor® P188, Kollidon® 30, and Kollidon® VA64), all improved the solubility of sildenafil ASD compared to its crystalline form. The ASD system with Kollidon® VA64 was selected for

further research as it showed the greatest improvement in dissolution rate compared to crystalline sildenafil. The amorphous nature of the systems was confirmed by X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC). For ASDs with Kolliphor® P188 and Kollidon® 30, the authors observed powder diffraction patterns indicative of a partially crystalline form of the drug, as noted in their study results. The ASD formulation of sildenafil with Kollidon® VA64 was considered amorphous as it lacked the characteristic peak reflections around 20° of 2-theta. However, the diffraction pattern did not include the fully amorphous 'halo' typically seen in a completely amorphous form. This may suggest that the amorphization method is less efficient than, for example, spray drying. When tested in a rat model, the formulation significantly improved male sexual activity [29]. Furthermore, recent research from a Polish centre highlighted the use of a carrier with plasticizing properties, which has (unlike previous studies) a glass transition temperature significantly lower than that of the amorphous substance. This was achieved by using polyvinyl acetate polymer at high concentrations (75% by weight). This led to the conclusion, suggesting areas for further research, that plasticizers may also stabilize ASD systems when used at concentrations at which they no longer accelerate recrystallization, but instead have the opposite effect [30].

Amorphous solid dispersions of tadalafil

Tadalafil was also investigated for physical stability in an ASD prepared by spray drying, using glycyrrhizin as a stabilizing carrier. This resulted in a significant increase in the dissolution rate of tadalafil in the ASD with glycyrrhizin compared to its crystalline form. A significant improvement in sexual parameters was also observed in rats for the formulation with a 1:2 tadalafil-to-glycyrrhizin weight ratio. It maintained physicochemical stability in studies conducted after one month [23].

Other studies have also confirmed the improved solubility of tadalafil in ASD formulations with polymeric carriers compared to its pure crystalline form. This was important as it allowed for comparing various amorphization methods, including solvent evaporation using a rotary vacuum evaporator, spray drying, and melt extrusion. Regardless of the approach used, the dissolution rate increased, although the release profiles differed depending on a given method. The highest dissolution rate was consistently observed in the formulation prepared by solvent evaporation using a rotary vacuum evaporator. Differences in release rates and the amount of drug released likely resulted from the distinct morphologies of particles formed during the individual amorphization processes. Furthermore, the researchers observed that the molecular weight of the polymer carrier affected drug release efficiency: tadalafil release decreased with increasing polymer molecular weight [31].

Amorphous solid dispersions of vardenafil

Vardenafil was also amorphized to explore its physicochemical stability, this time using lyophilization. Formulations were prepared with β-cyclodextrin and hydroxypropylmethylcellulose in various proportions. Optimal solubility in a formulation containing cyclodextrin was achieved with a 1:5 weight ratio of vardenafil to cyclodextrin. All amorphous vardenafil systems, regardless of the polymer used, showed an improved dissolution profile compared to pure crystalline vardenafil. Additionally, the formulation with β-cyclodextrin at a 1:5 ratio exhibited enhanced permeability across biological membranes [32].

Amorphous solid dispersions of avanafil

Avanafil was amorphized to create an ASD incorporated into a self-emulsifying drug delivery system (SEDDS). This formulation (containing lipids, surfactants, cosurfactants, and the drug itself) rapidly formed an oil-in-water (O/W) nanoemulsion. The resulting high-surface-area globules, combined with peristaltic mixing, enhanced the drug's solubility in water. The development of SEDDSs using amorphous avanafil gave rise to formulations that remained stable for six months and exhibited a 3.2-fold increase in bioavailability compared to the commercial crystalline form of the drug [33].

An amorphous form of avanafil was also produced using a three-step process involving solvent precipitation, ultrasound, and high-pressure homogenization, resulting in avanafil stabilized with polyvinyl alcohol. However, this approach was less effective in enhancing solubility compared to nanoparticle sonoprecipitation [34].

The discussed studies on amorphous solid dispersions of PDE5Is highlight a promising research direction focused on enhancing pharmacotherapy by modifying existing, well-known substances. This strategy not only reduces the substantial costs associated with bringing new drugs to market, which can reach billions of dollars, but also improves the bioavailability of existing medications, allows for lower dosages, reduces certain adverse effects, lowers production costs, and ultimately prices for patients. Furthermore, research in this area may alter the drug's release kinetics, potentially resulting in a more rapid onset of action – a factor that could be crucial for improving sexual comfort and quality of life in men with erectile dysfunction.

Conclusions

The innovative ED treatment methods described in this paper are often still at the preliminary preclinical stage. The complexity and prevalence of EDs prompt researchers worldwide to explore increasingly advanced pharmacological and surgical strategies. In the coming years, we can expect a dynamic rise in interest in these approaches, potentially leading to the establishment of new standards for ED treatment.

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REVIEW ARTICLE

HISTORY OF NEUROMUSCULAR JUNCTION MONITORING IN ANAESTHESIOLOGY

Historia monitorowania przewodnictwa nerwowo-mięśniowego w anestezjologii

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Abstract

The history of monitoring neuromuscular conduction dates back to the 16th century when studies were conducted on curare, a plant-derived toxin used by Native Americans to poison arrows. Later studies made it possible to describe the concept of the neuromuscular junction, but it was not until the 20th century that the mediator acetylcholine was isolated. Measurement of neuromuscular transmission gained clinical importance when it became apparent that almost half of the patients who received a long-acting muscle relaxant were admitted to the post-operative room with incomplete resolution of neuromuscular block. Today, neuromuscular junction measurement devices using acceleromiography are becoming standard equipment in the operating theatre.

Streszczenie

Historia monitorowania przewodnictwa nerwowo-mięśniowego sięga XVI wieku, kiedy prowadzono badania nad kurarą, używaną przez Indian do zatruwania strzał. Późniejsze analizy umożliwiły opisanie zjawiska złącza nerwowo-mięśniowego, jednak dopiero w XX wieku udało się sprecyzować rolę mediatora, jakim jest acetylocholina. Pomiar przewodnictwa nabierał coraz większego znaczenia klinicznego, gdy okazało się, że prawie połowa pacjentów, którzy otrzymali długodziałający środek zwiotczający mięśnie, trafiała na salę pooperacyjną z niepełnym ustąpieniem blokady nerwowo-mięśniowej. Obecnie urządzenia do pomiaru przewodnictwa nerwowo-mięśniowego wykorzystujące akceleromiografię stają się standardowym wyposażeniem bloku operacyjnego.

Keywords: history of neuromuscular junction measurement; curare; acceleromiography; train of four (TOF); post tetanic count (PTC)

Słowa kluczowe: historia pomiaru złącza nerwowo-mięśniowego; kurara; akceleromiografia; train of four (TOF); liczba potężcowa (PTC)

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What is neuromuscular transmission and why is it assessed?

Neuromuscular transmission is the process of converting an electrical impulse conducted by a nerve into muscle contraction [1]. Skeletal muscles are primarily innervated by motor neurons (α-motoneurons) located in the anterior horns of the spinal cord. As they approach muscle fibres, motor neuron axons branch into fine nerve endings, become covered by Schwann cells, lose their myelin sheath, and form the neuromuscular junction [2]. The neuromuscular junction (NMJ) is a specialized connection that enables the conversion of a nerve impulse into muscle contraction through the action of the neurotransmitter acetylcholine (ACh). NMJ is composed of three primary components: the presynaptic terminal, the postsynaptic membrane, and the synaptic cleft, which is the space between the axon terminal and the muscle cell membrane [3].

When a nerve impulse (action potential) reaches the axon terminal of a motor neuron, the presynaptic membrane depolarizes, opening voltage-gated calcium channels and causing a rapid influx of calcium ions (Ca^{2+}) into the nerve terminal. The rise in calcium ion levels in the axoplasm triggers fusion of synaptic vesicles with the presynaptic membrane, mediated by the SNARE protein complex (synaptobrevin, SNAP-25, and syntaxin), which results in the release of ACh into the synaptic cleft. ACh molecules diffuse across the synaptic cleft and bind to nicotinic acetylcholine receptors (nAChRs) found on the postsynaptic membrane of the muscle fibre. These receptors are ligand-gated ion channels that open upon binding two ACh molecules, allowing sodium ions (Na^+) to enter and potassium ions (K^+) to exit the muscle cell. This generates a local depolarization of the postsynaptic membrane. If the depolarization reaches the threshold, voltage-gated sodium channels open, initiating an action potential in the muscle cell membrane. The action potential propagates along the muscle fibre and into the transverse tubules (T-tubules), where it activates dihydropyridine receptors (DHPRs). These receptors are mechanically coupled to ryanodine receptors (RyR1) in the sarcoplasmic reticulum. Activation of RyR1 leads to the release of Ca^{2+} into the cytoplasm. The increased cytoplasmic Ca^{2+} allows its binding to troponin C, causing tropomyosin to move away from the actin binding sites and enabling actin-myosin interactions. Muscle contraction is directly mediated by cross-bridge cycling. For the process to occur, acetylcholine must first be removed from the synapse. This task is carried out by acetylcholinesterase (AChE), which breaks down ACh into choline and acetic acid. The choline is then reabsorbed by the nerve ending and used to resynthesize ACh, enabling continuous transmission of nerve impulses [1–3]. Figure 1 illustrates the motor end plate function.

Neuromuscular blockers (NMBs) inhibit the mechanism described above, producing muscle relaxation. They are widely used in anaesthesiology, particularly to facilitate intubation and to maintain muscle relaxation during surgical interventions [4].

Depolarizing neuromuscular blockers, such as succinylcholine, activate nicotinic cholinergic receptors in the postsynaptic membrane of the motor end plate. Due to their structural similarity to acetylcholine, they bind to these receptors and trigger depolarization of the postsynaptic membrane. This causes transient muscle fasciculations. Succinylcholine has a short duration of action as

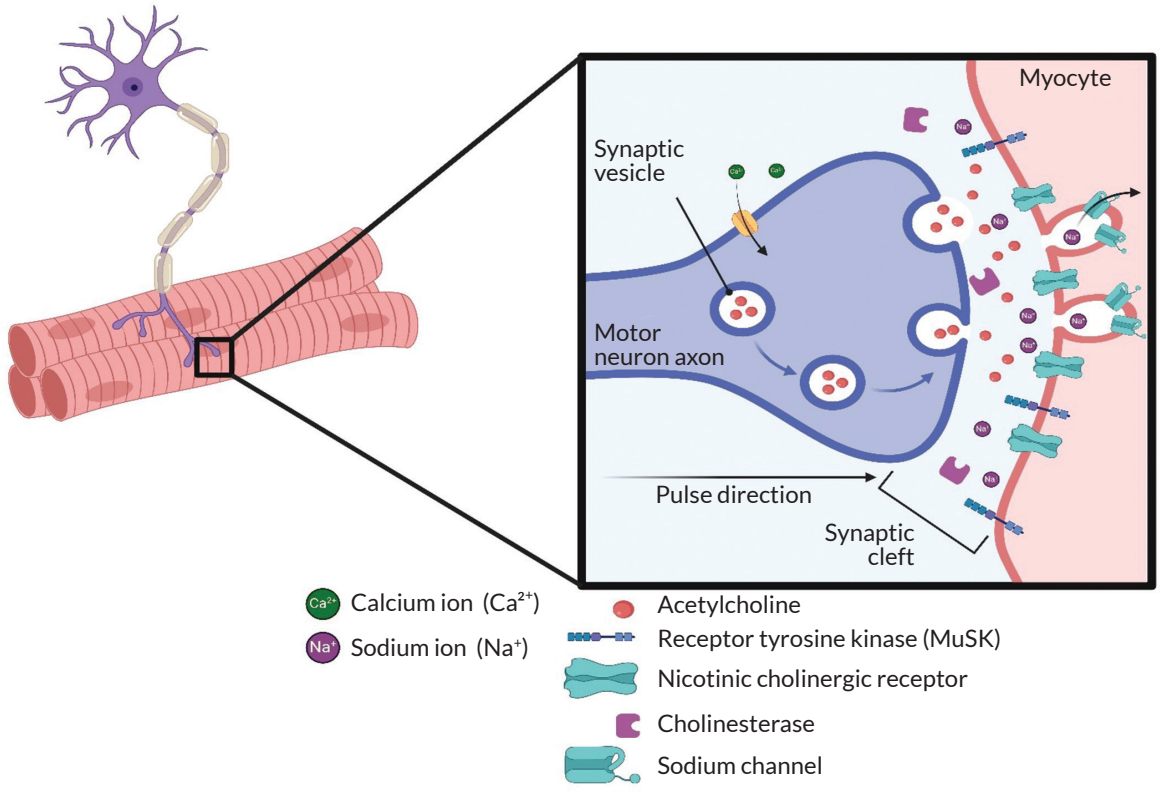

Figure 1. The mechanism of action of neuromuscular junction

it is rapidly hydrolysed by plasma cholinesterase, allowing neuromuscular function to be quickly restored once the drug is discontinued [5].

Non-depolarizing muscle relaxants, such as aminosteroids (vecuronium, rocuronium) and benzylisoquinoline derivatives (atracurium, cisatracurium), act as competitive antagonists of nicotinic cholinergic receptors, producing relaxation without depolarization [5].

Monitoring muscle relaxation helps assess the depth of neuromuscular block, enhancing anaesthetic safety. It also allows precise adjustment of muscle relaxant doses and prevents patients from leaving the operating room with residual paralysis. The importance of complete recovery from neuromuscular block was already highlighted in 1979 by Viby-Mogensen et al., who showed that about 40% of patients receiving intraoperative long-acting, non-depolarizing muscle relaxants entered the postoperative recovery room without full blockade resolution [6]. Monitoring the effects of these drugs enhances patient safety while also reducing treatment costs [7].

The history of the discovery and use of curare

First references to a muscle relaxant date back to 1516, when the Italian scholar Peter Martyr d'Anghera (1457–1526), living in Spain, documented the use of curare, a substance used by South American peoples to coat their hunting implements such as arrowheads. According to his accounts, curare was so potent that even its vapours could kill those preparing it [5, 8–10]. One of the first Europeans to encounter curare directly was likely the Spanish conquistador and explorer Francisco de Orellana, who during his Amazon River expedition (1541–1542) observed indigenous peoples using arrows soaked in the substance [11]. Alonso Pérez de Tolosa, who in 1548 explored the Lake Maracaibo region in present-day Venezuela, was another European to encounter the poison [12]. In 1745, Charles Marie de La Condamine described in his Mémoires de l'Académie des Sciences curare and its production from *Strychnos* and *Chondrodendron* species, and also brought some samples to Europe [12].

In 1780, the Italian researcher Gasparo Ferdinando Felice Fontana (1730–1805) commented on the reports describing curare's extreme toxicity in a presentation to the Royal Society, noting that although its fumes had an unpleasant odour, they did not cause death in those who inhaled them [8, 9]. Charles Waterton (1782–1865), an English naturalist and explorer who, in the early 19th century, travelled to Demerara (now Guyana) to oversee his family's sugarcane plantation, was the first person to experiment with curare. He conducted his first experiment on an injured dog, which did not survive the injection. Subsequent trials on poultry and oxen showed that its effects depended on the dose administered. After returning to England in 1814, he continued his research with a series of experiments on donkeys. One donkey given curare was kept alive through tracheotomy-assisted ventilation for four hours and went on to survive for another 25 years. Waterton also appreciated curare's medicinal potential, suggesting that it might be useful in treating rabies [13, 14]. Dr. William Sewell (1781–1853), an English veterinarian, tested this theory by administering curare with simultaneous ventilation to horses afflicted with rabies. In 1811, Benjamin Brodie (1783–1862), an English philosopher and surgeon, presented to the Royal Society a study suggesting that an animal could survive curare administration if resuscitated long enough. A year later, he supported this claim by administering curare to a cat and ventilating it for 160 minutes. After ventilation ended, the animal initially remained paralyzed, but soon regained mobility and stood up on its own. Although unaware of the substance's exact mechanism, Brodie concluded that the poison likely acted centrally [10, 13, 14]. Research into curare's mechanism of action began in the 1850s with the French physiologist Claude Bernard (1813–1878), who conducted a series of experiments on frogs. He administered the substance subcutaneously and dissected the animal immediately after death. He discovered that the muscles retained normal contractility under direct stimulation but failed to respond to motor nerve stimulation [13, 14]. He performed the same experiment on birds and mammals, with identical findings. Based on this, he concluded that curare disrupts the connection between motor nerves and muscles while sparing the sensory nerves [15]. These experiments laid the foundation for the later description of the motor end plate by Claude Bernard's colleagues Wilhelm Kühne and Wilhelm Krause (1833–1910) [16]. The definitive explanation of curare's mechanism of action emerged only in the first half of the 20th century. In his paper published in the Journal of Pharmacology and Experimental Therapeutics (1914), British physiologist and pharmacologist Professor Henry Dale (1875–1968) demonstrated that acetylcholine functions as a neurotransmitter in neuromuscular junctions [9]. In 1921, Otto Loewi described the function of acetylcholine as a neurotransmitter in his work "Über humorale Übertragbarkeit der Herznervenwirkung". In 1936, both scientists were awarded the Nobel Prize in Physiology or Medicine for their discoveries concerning the "chemical transmission of nerve impulses" [13, 14].

L. A. Sayers was first to use curare in human medicine. In 1858, he administered the substance locally to a wound on the thumb, which unfortunately resulted in the patient's death. In 1932, West used curare to treat spastic states such as Parkinson's disease, tetany, and hemiplegia. However, treatment outcomes were inconsistent as the preparation he used was not standardized [8]. Curare entered clinical practice in 1940, when Abram Elting Bennett (1898–1985) used it to treat metrazol-induced convulsive seizures. Curare was introduced into the operating room in 1942 by Canadian anaesthesiologists Harold Griffith (1894–1985) and Enid Johnson (1909–2001), who employed its muscle relaxant properties during surgeries.

Measurement of neuromuscular block

Efforts to assess the degree of neuromuscular block did not begin until 1949 [17], when English anaesthesiologist Geoffrey Organe (1908–1989) and colleagues explored human sensitivity to muscle relaxants and investigated whether their effects paralleled those observed in animals. Three volunteers participated in the study. The drug's efficacy was assessed based on clinical measurements. They assessed leg lifting, standing ability,

grip strength, as well as abdominal and eyelid muscle tone. Graphs were presented showing hand strength as a percentage relative to the time elapsed after drug administration [18]. That same year, Professor William W. Mushin (1910–1993) and colleagues explored the effects of Flaxedil, a gallamine-based nondepolarizing muscle relaxant widely used in the mid-20th century. They used several tests to monitor its effects on the body. They measured finger flexion strength with a dynamometer and assessed abdominal muscle contraction strength. The latter was measured in a volunteer laying supine with their legs attached to a couch. A device with a pointer and spring was placed over the centre of the rectus abdominis, which was pushed out by the muscle during an attempt to raise legs on the doctor's command. Breathing was recorded with a spirometer, along with blood pressure and the plantar reflex [19].

The methods described above were the first attempts to objectify the effects of muscle relaxants. While simple, they had a major limitation: they could not be applied to anaesthetized patients, who were unable to follow commands. Thus, assessing neuromuscular block in unconscious patients requires alternative approaches, such as direct stimulation of muscle contractions [7].

The first reported use of nerve stimulation in anaesthetized patients to assess muscle relaxant–induced relaxation likely dates to 1952 [17]. Finnish pharmacology professor Stephen Thesleff (1924–2020) described the effects of succinylcholine in his publication. To measure the degree of muscle relaxation, the patient's right hand was mounted on a Brown-Schuster myograph. An electrode connected to a stimulator delivering discharges at 0.1 Hz was fixed to the right elbow, above the ulnar nerve. Stimulation caused contraction of the fourth and fifth fingers, and their movements were recorded by the myograph. The responses were then traced with a kymograph (a pen on a paper cylinder rotating at a constant speed). In his study, Thesleff also monitored patients' respiratory muscle activity using two pneumographs and a Marey's tambour. The pneumographs were placed in the middle of the sternum and halfway between the umbilicus and the xiphoid process. Volume changes detected by the pneumographs were transmitted to the Marey's tambour and recorded on a kymograph [20]. Electromyography was introduced into clinical practice by Fritz Buchthal, and later adopted in anaesthesiology by Thomas Hildred Christie (1927–2017) and Harry Cunningham Churchill-Davidson (1922–1995). In 1958, a description of a user-friendly neuromuscular conduction stimulator designed for anaesthesiologists for use in the operating room was published in the Lancet. The authors highlighted its potential for diagnosing the causes of incomplete postoperative recovery of muscle strength. This device allowed for determining whether incomplete recovery was caused by muscle relaxants, analgesics, or anxiolytics. It generated a stimulating current at 3 Hz or 50 Hz, with adjustable intensity. The study recommended using maximum intensity in unconscious patients to ensure a distinct contraction of all muscle fibres supplied by a given nerve [21]. Figure 2 schematically illustrates the device described above.

Churchill-Davidson gradually improved the device he had developed, presenting the first small, battery-powered stimulator in Anesthesiology in 1965. The device allowed voltage regulation from 0 to 250 V, generated pulses of fixed 0.3 ms duration, and could deliver them individu-

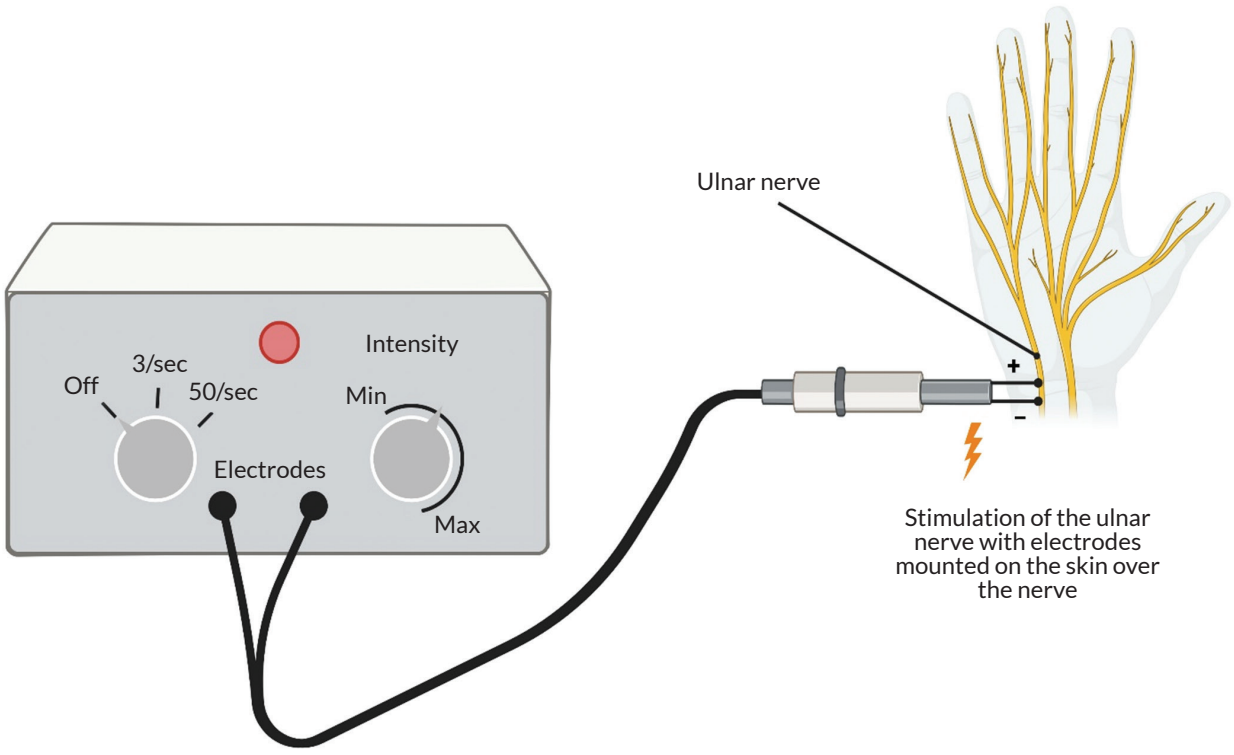

Figure 2. A representative diagram of the St. Thomas Hospital Nerve Stimulator [15]. Illustration created with BioRender.com

ally or in series at a frequency of 50–60 Hz. Interestingly, while developing this device, he discovered a method to differentiate between depolarizing and nondepolarizing block based on muscle responses to stimuli. He noted that cessation of contractions after, typically, four consecutive single pulses or following tetanic stimulation, is a hallmark of nondepolarizing blockade [22].

Similar observations were made by Roberts and Wilson, who in 1968 described a gradual decrease in muscle responses after four twitches when a 4 Hz current was applied in patients with myasthenia gravis. In 1970 and 1971, Hassan H. Ali et al. (1931–2022) published a series of articles in the British Journal of Anaesthesia describing the use of train-of-four (TOF) monitoring to assess the degree of curarization in humans. Based on their experience, they concluded that the TOF monitoring was superior to using frequency shifts between 0.1 and 10 Hz for quantitative assessment of nondepolarizing block. They also noted that this test could help evaluate individual sensitivity to muscle relaxants and determine dose requirements for specific procedures. In a 1971 publication, the same authors reported similar studies involving 26 patients given muscle relaxants preoperatively. They introduced the concept of the TOF ratio, expressing the amplitude of the fourth muscle twitch (T4) to the first muscle twitch (T1), thereby providing an indicator of the degree of neuromuscular block. According to the authors, limiting the stimuli to four at 2 Hz was intended to ensure maximum depletion of acetylcholine stores. Subsequent studies evaluated the practical utility of the TOF ratio, comparing it to clinical manifestations signalling cessation of muscle relaxant action. They found that a patient's ability to raise the head for at least three seconds (a clinical indicator of recovery) was only possible with a TOF ratio greater than 0.6 [17].

The 1979 study conducted by Viby-Mogensen et al. convinced the authors of the need to measure the degree of relaxation in operating rooms to reduce the incidence of residual curarization in postoperative recovery rooms [6]. In their 1980 paper entitled 'A New Nerve Stimulator (Myotest)', they presented a new device measuring 90 × 45 × 165 mm, weighing approximately 400 g, and powered by four 1.5 V alkaline batteries, and able to operate for about 200 hours. The device offered several functions, including single contractions at varying frequencies and a TOF programme, which delivered a series of four pulses every 10 seconds at 0.5-second intervals. The authors noted that their stimulator differed from that of Christie and Churchill-Davidson by precisely generating unipolar pulses at constant voltage, enhancing result reproducibility. They also found it more practical due to its multiple functions, as demonstrated by their year-long use of the Myotest [23].

In 1981, Viby-Mogensen et al. introduced the term 'post-tetanic count' (PTC). In one of their papers, the authors reported results of assessing neuromuscular block during the period of no response to single or TOF stimulation and first described using PTC to monitor deep neuromuscular block [24].

In 1989, Engbaek et al. sought an approach superior to TOF for assessing residual neuromuscular block after muscle relaxant administration. They suggested that TOF might fail to reliably detect residual curarization because the two middle responses complicate comparison between the first and last twitch. Their study aimed to investigate a new diagnostic system for residual NMB: double-burst stimulation (DBS). DBS consisted of two short 50-Hz tetanic stimuli separated by a 750-ms pause. This stimulation pattern produced two single muscle contractions, with the second being less pronounced than the first one during the non-depolarizing NMB. The DBS version with three impulses in each burst (DBS3i3) was found to be the most sensitive and least painful, thus most suitable for clinical use. It was also more sensitive than TOF for manual detection of residual block [25].

In 1988, Jensen et al. introduced Accelograph®, the first device for objectively measuring NMB. It used two electrodes placed on the thumb and near the ulnar nerve. Finger movement in response to nerve stimulation generated a voltage difference between the electrodes, which was then measured and recorded. The inventors of the device noted that since, according to Newton's law ($F = m \times a$), force (F) is directly proportional to acceleration (a), the latter one could be used to quantify NMB, assuming that mass (m) remains constant. Measuring acceleration is more convenient than measuring contractile force, as it requires no additional device to stabilize the hand. It also allowed an assessment of both TOF and PTC [26]. Table 1 summarizes key discoveries and milestones in neuromuscular transmission monitoring.

The newly developed TOF-Cuff® neuromuscular transmission monitor, which utilizes compressomyography, is a product of RGB Medical Devices. It integrates electrode

Table 1. Chronology of major discoveries and advances in neuromuscular monitoring

Year	Discovery	Description/Achievements
1516	First mentions of curare	Peter Martyr d'Anghiera's description of the substance used by the Indians to poison their arrows
1811	Benjamin Brodie's Research	Suggesting the possibility of survival after administration of curare with appropriate resuscitation
1932	The first use of curare for therapeutic purposes	West's Attempts to use curare in the treatment of spastic states
1942	The first use of curare in anaesthesiology	Harold Griffith and Enid Johnson use curare to achieve muscle relaxation during surgery
1970–1971	Introduction of TOF	Hassan H. Ali describes the use of train of four (TOF) for monitoring neuromuscular block

Table 2. Types of devices used to monitor neuromuscular conduction

Type of device	Description	Clinical use	Benefits	Limitations
Electromyography (EMG)	Measuring muscle electrical activity in response to nerve stimulation	Precise assessment of NMB	High accuracy	Requires precise electrode placement
Acceleromyography	Measuring the acceleration of muscle contraction following nerve stimulation	Used to assess the degree of NMB	Mobility, ease of use	Requires precise electrode installation EMG
Mechanomyography	Recording the strength of muscle contraction after nerve stimulation	Mainly research use	High precision	Not very clinically available, requires special equipment

stimulation into a blood pressure monitoring cuff. The device can be used to stimulate the brachial plexus and assess the degree of neuromuscular block based on changes in cuff pressure. Compared to conventional NMB monitors, it can offer both neuromuscular block assessment and non-invasive blood pressure measurement on the upper arm or lower leg, the latter being less affected by patient positioning and medical personnel interventions [27].

Future directions in the development of NMJ monitoring

Acceleromyography remains one of the most effective and widely used methods for monitoring neuromuscular transmission, with devices such as TOF-Scan, TOF Watch SX, and its predecessor TOF Watch known and commonly employed in hospital settings. Other approaches are also being developed, including mechanomyography, electromyography, kinematography, phonomyography, and the newest, informally known as 'compressomyography'. Table 2 summarizes the types of devices used to monitor neuromuscular transmission.

Future research is focusing on integrating these technologies with hemodynamic and respiratory monitoring systems to enable comprehensive, real-time assessment of patient status. Additionally, artificial intelligence and machine learning algorithms may predict individual responses to muscle relaxants, allowing personalized dosing and reducing the risk of complications. Implementing these advanced monitoring approaches in clinical prove the quali care and patient safety [28].

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VITAMIN E ACETATE – A POTENTIAL FACTOR IN E-CIGARETTE OR VAPING PRODUCT USE-ASSOCIATED LUNG INJURY (EVALI)

Octan witaminy E jako potencjalny czynnik wywołujący ostre uszkodzenie płuc związane z używaniem e-papierosów (EVALI)

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Abstract

E-cigarettes are gaining popularity as an alternative to traditional cigarettes, especially among young people. However, their use is associated with severe health consequences, such as e-cigarette or vaping product use-associated lung injury (EVALI), a lung injury linked to e-cigarette use or vaping. The objective of this study was to discuss the health consequences of using e-cigarettes, with particular emphasis on the negative effects of vitamin E acetate. Google Scholar, PubMed and SpringerLink databases were used for the literature review. The search terms in English included: „EVALI," „lung injury," „pulmonary," „respiratory," „e-cigarette," „vitamin E acetate," „vaping," and „vape." Articles published from 2019 onwards were included. Recent studies focus on the role of vitamin E acetate in the pathophysiology of EVALI. The mechanism by which this substance can cause lung injury remains unknown, but its potential harmfulness may result from its decomposition during heating into toxic substances such as formaldehyde, acetaldehyde, acrolein, and ketenes. Tocopherol acetate, as a surface-active substance, damages the pulmonary surfactant, leading to acute respiratory failure. Despite the increasing popularity of e-cigarettes, their negative health effects are still poorly described. In particular, determining long-term consequences is challenging due to the short observation period for e-cigarette users. EVALI is diagnosed based on the exclusion of other conditions and a positive history of e-cigarette use.

Streszczenie

E-papierosy zyskują na popularności jako alternatywa dla tradycyjnych papierosów, szczególnie wśród młodych ludzi. Jednakże ich używanie wiąże się z poważnymi konsekwencjami zdrowotnymi, takimi jak uszkodzenie płuc związane z używaniem e-papierosów lub tzw. wapowaniem (EVALI). Celem niniejszej pracy jest omówienie konsekwencji zdrowotnych wynikających z korzystania z e-papierosów, ze szczególnym uwzględnieniem negatywnych skutków działania octanu witaminy E. Przeglądu piśmiennictwa dokonano z wykorzystaniem bazy Google Scholar, PubMed oraz SpringerLink. Wyszukiwane frazy w języku angielskim: „EVALI", „lung injury", „pulmonary", „respiratory", „e-cigarette", „vitamin E acetate", „vaping" oraz „vape". Włączono artykuły opublikowane od 2019 roku. Najnowsze badania koncentrują się na roli octanu witaminy E w patofizjologii EVALI. Mechanizm, w którym substancja ta może wywołać uszkodzenie płuc, pozostaje nieznany, ale potencjalna szkodliwość tego związku chemicznego może wynikać z jego rozkładu podczas podgrzewania do toksycznych substancji, takich jak formaldehyd, aldehyd octowy, akroleina oraz keteny. Octan tokoferolu jako substancja powierzchniowo czynna uszkadza surfaktant, co prowadzi do ostrej niewydolności oddechowej. Pomimo rosnącej popularności e-papierosów, negatywne skutki zdrowotne są nadal niewystarczająco opisane. W szczególności trudność sprawia określenie długofalowych konsekwencji z powodu krótkiego czasu obserwacji osób korzystających z e-papierosów. EVALI jest rozpoznaniem stawianym po wykluczeniu innych schorzeń oraz na podstawie dodatniego wywiadu w kierunku stosowania e-papierosów.

Keywords: youth; pneumonia; nicotine; vaping; e-cigarette

Słowa kluczowe: młodzież; zapalenie płuc; nikotyna; wapowanie; e-papieros

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Introduction and aim

With the growing popularity of e-cigarettes, the incidence of acute respiratory failure due to interstitial pneumonia has increased among their users. In 2019, the United States saw a sharp rise in such cases, primarily among young individuals without comorbidities. This prompted researchers to investigate the etiopathogenesis, identifying vitamin E acetate, an ingredient in some e-cigarette liquids, as a potential contributing factor.

The aim of this study is to describe e-cigarette or vaping product use-associated lung injury (EVALI) and to identify potential risk factors. Special attention should be paid to vitamin E acetate, as it is considered a key trigger of pneumonia among e-cigarette users and individuals exposed to passive vaping.

Review methods

The literature review was conducted using the PubMed, Google Scholar, and SpringerLink databases. Only papers published in English since 2019 were considered. In order to obtain precise results, the following English-language search terms were used: „EVALI", *„lung injury"*, *„pulmonary"*, *„respiratory" „e-cigarette"*, *„vitamin E acetate"*, *„vaping"* and *„vape"*. The literature review was expanded to include data obtained from the websites of the Ministry of Health and the Institute of Economic Forecasts and Analysis. A total of 95 publications were identified. After excluding duplicates and incomplete, irrelevant, unreliable, or methodologically inadequate works, as well as those containing outdated medical data, 28 scientific publications were ultimately included in the review.

The state of knowledge

Definition and epidemiology of EVALI

EVALI is an acute lung injury resulting from the inhalation of substances heated by e-cigarettes or other devices. In August 2019, the United States reported a sharp rise in hospital admissions for acute respiratory distress syndrome of unknown origin, primarily among young people without chronic illnesses [1]. This has been linked to the use of e-cigarettes, with 2,807 documented cases and 68 deaths. Several similar clinical cases had been reported in the United States before 2019. The number of cases rose so rapidly in 2019 that it met the criteria for an epidemic in the United States.

In the early stage of identifying the etiological factor, vitamin E acetate (tocopherol acetate) was considered, as it was used as a thickening agent in e-liquids, particularly those enriched with tetrahydrocannabinol (THC) [3]. Although vitamin E acetate is widely used in the food and cosmetics industries, its presence in e-cigarette aerosol likely contributed to the development of EVALI [4, 5].

Composition of e-cigarette liquids

The composition of e-cigarette liquids remains controversial, with nicotine concentrations ranging from 15 to 50 mg/mL. In their study on the negative effects of e-cigarette use, Bhave and Chadi reported the actual nicotine content in these liquids. Assuming a liquid volume of 2 mL and a nicotine concentration of 5%, the total nicotine content can reach 100 mg [6]. This amount of liquid is typically inhaled within about 1 hour. The intake of such a high dose of nicotine over a short period is toxic [7]. In addition to nicotine and water, e-liquids also contain multiple toxic and carcinogenic chemicals, heavy metals, and contaminants. These substances include propylene glycol, acetaldehyde, formaldehyde, tobacco alkaloids, nitrosamines, free radicals, polycyclic aromatic hydrocarbons, benzene, phthalates, caffeine, volatile organic compounds, acrolein, isoprene, nickel, phenol, chrysene, cadmium, toluene, butanone, and various flavouring compounds [8].

Diagnosis of EVALI

EVALI is often diagnosed by exclusion, as its nonspecific symptoms resemble those of infection. A thorough medical history is essential, including respiratory symptoms (such as dyspnoea, cough, chest pain, respiratory distress, and hypoxia), other systemic symptoms, and a history of e-cigarette use within the past 90 days [1, 8]. Physical examination often shows fever or low-grade fever, tachycardia, tachypnoea, and hypoxemia, with clinical severity ranging from mild illness to the need for intubation and mechanical ventilation [8]. A chest X-ray should be performed in patients with suspected EVALI. If the X-ray is abnormal or inconclusive, non-contrast computed tomography (CT) is recommended. CT angiography may also be considered as an alternative. EVALI can occur in many forms of lung damage, such as organizing pneumonia, acute eosinophilic pneumonia, diffuse alveolar damage, and lipoid pneumonia [9]. Organizing pneumonia, which presents radiographically as bilateral, patchy ground-glass opacities with peripheral and perilobular

consolidations, is the most common type. An inverted halo sign, also known as the "atoll sign" because of its resemblance to a coral atoll, is a hallmark of organizing pneumonia [10, 11]. The inverted halo sign is a distinctive radiological CT finding, defined by a dense ring of complete opacification surrounding a central area of ground-glass opacity [11].

Diffuse alveolar damage, which appears on chest X-ray and CT as volume loss, predominantly lower-lobe consolidations, and ground-glass opacities, is yet another most common type of lung injury. Radiological findings of organizing pneumonia and diffuse alveolar damage may overlap, with both showing interlobular septal thickening and the cobblestone sign [9]. Imaging plays a crucial role in the early diagnosis of EVALI and treatment initiation.

The role of vitamin E acetate in the pathophysiology of EVALI

Vitamin E acetate is a synthetic ester of tocopherol and acetic acid, added in e-cigarette liquids as a thickening agent [12, 13]. It is a common and well-studied ingredient in cosmetics and dietary supplements, exhibiting antioxidant effects when administered orally or applied topically to the skin [13]. However, data on the safety of its inhaled form (via e-cigarettes) is still limited, with studies suggesting that vitamin E acetate plays an important role in the pathophysiology of EVALI.

Blount et al. collected bronchoalveolar lavage fluid (BALF) from patients hospitalized for EVALI and from healthy individuals (controls). Vitamin E acetate was detected in 94% of samples from EVALI patients and none of the control samples [12]. EVALI patients had elevated BALF tocopherol acetate, with a median value of 21.9 ng/mL [14]. Duffy et al. found that tocopherol acetate was present in 60.5% of e-cigarette liquids used by EVALI patients [4].

The mechanism by which vitamin E acetate causes EVALI remains unknown and is still under investigation. The harmful effects of this compound may arise from its loss of chemical stability when heated, leading to decomposition into toxic substances such as formaldehyde, acetaldehyde, acrolein, and ketenes [15, 16]. Ketenes are unsaturated ketones that cause cytotoxic damage to the pulmonary alveoli and surrounding capillaries. They are considered a potential contributor to chemical pneumonia in EVALI [16]. Animal studies suggest a possible pathophysiological mechanism by which vitamin E acetate causes lung damage. Vitamin E acetate–exposed mice were found to have lipid-laden macrophages in their lungs, accompanied by signs of lung injury [5]. Lipid-laden macrophages, indicative of pulmonary surfactant damage, were also detected in the BALF of EVALI patients [5, 17, 18]. Vitamin E acetate has also been reported to exert harmful effects on pulmonary surfactant and type II pneumocytes [19]. As a surface-active substance, tocopherol acetate increases surface tension in the pulmonary alveoli, disrupting the dynamics of alveolar compression and expansion during the respiratory cycle. This results in hypoxia and, ultimately, acute respiratory failure [20].

Van Bavel et al. conducted a study to assess the effects of e-cigarette liquids on pulmonary surfactant function using a bovine surfactant model. The study showed that, among e-liquid additives, vitamin E acetate was the strongest disruptor of the lipid bilayer in surfactant, leading to impaired alveolar ventilation [21]. The *in vitro* study exposed human airway progenitor cells to e-cigarette aerosol containing tocopherol acetate. Exposure of *in vitro*–cultured airway mucosa to vitamin E acetate resulted in the formation of lipid droplets on its surface, accompanied by an increase in the number and dilation of goblet cells in response. Although goblet cells synthesize and secrete mucus in response to pollutants entering the respiratory tract, insoluble tocopherol acetate may be difficult to eliminate, leading to its accumulation in the body. The analysed cells exhibited increased synthesis of inflammatory factors, including interleukin-6 (IL-6), chemokine ligand 15 (CCL15), soluble interleukin-6 receptor (IL-6sR), and chemokine ligand 2 (CCL2) [22]. Vitamin E acetate is therefore considered a potentially harmful ingredient in e-cigarette liquids. Further research identifies mechanisms through which it can cause respiratory damage and contribute to EVALI.

Pharmacotherapy

Outpatient treatment is recommended for individuals without comorbidities or respiratory disorders, with oxygen saturation above 95%, access to medical care, and follow-up within 24–48 hours. If the patient's condition worsens, immediate medical attention is required. Hospitalization is recommended for patients with suspected EVALI, particularly those with comorbidities such as chronic obstructive pulmonary disease (COPD) or asthma, which can reduce respiratory reserve and arterial oxygen saturation, increasing the risk of respiratory complications [23].

According to current guidelines, glucocorticoids (GCCs) may be beneficial in treating EVALI. A study conducted among patients in Illinois and Wisconsin reported improved respiratory function in 65% of those receiving GCC therapy. Improvement has also been observed in patients with exogenous lipoid pneumonia (ELP) following steroid therapy, suggesting an inflammatory aetiology of both conditions [24]. It is important to rule out an infectious cause of lung damage, as steroid use in such cases may aggravate the disease [25].

In 2019, the University of Rochester Medical Center (USA), in collaboration with the New York State Department of Health, published a report presenting an algorithm for the rapid identification of patients with suspected EVALI. The algorithm is based on clinical data, including dyspnoea, fatigue, chest pain, tachypnoea, and fever; chest imaging showing bilateral airspace opacification; and a history of e-cigarette or vaping device use within 30 days prior to hospital admission.

According to the report, 12 patients with suspected EVALI were admitted between June 1 and September 15, 2019. Initially, 11 patients received empirical antibiotic therapy for community-acquired pneumonia, with 8 out of 12 patients requiring admission to the intensive care unit for advanced respiratory support. Corticosteroids were given to 67% of patients, with 40 mg of intravenous methylprednisolone given every 6–12 hours and gradually tapered. The total treatment duration was approximately three weeks. However, some patients received prednisone for five days and also experienced symptom resolution, suggesting that therapeutic success may be achieved in less than three weeks [26]. Nonetheless, cessation of e-cigarette use remains the cornerstone of treatment.

Conclusions

E-cigarette sales, and consequently their use, continue to rise each year. Easy availability and prevailing trends have boosted their growing popularity, especially among young people. Curiosity about new flavours appears to be another factor contributing to the growing popularity of e-cigarettes among young people. Despite widely available diagnostic tools, diagnosing EVALI remains a challenge due to its nonspecific symptoms. Medical history, recent use of e-cigarettes in particular, is one of the most important factors in diagnosing EVALI. Although the direct cause of lung damage has not been identified, all patients report using e-cigarettes or vaping products. Vitamin E acetate is considered the primary factor responsible for the development of EVALI, as it decomposes into harmful compounds when heated, causing chemical pneumonia. In addition to symptomatic treatment, systemic corticosteroids are commonly used, with therapeutic efficacy typically assessed after about three weeks.

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REVIEW ARTICLE

WEILL-MARCHESANI SYNDROME: A COMPREHENSIVE REVIEW OF PATHOGENESIS, CLINICAL FEATURES, AND MANAGEMENT

Zespół Weilla-Marchesaniego: kompleksowy przegląd patogenezy, cech klinicznych i postępowania

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Abstract

Weill-Marchesani syndrome is a rare genetic connective tissue disorder, with an estimated prevalence of approximately 1 in 100,000 individuals. It is characterized by a pleiotropic set of manifestations, including short stature, brachydactyly, joint stiffness, ocular abnormalities, and cardiovascular complications. The syndrome follows either an autosomal recessive or autosomal dominant inheritance pattern, with pathogenic variants identified in the FBN1, ADAMTS10, ADAMTS17, and LTBP2 genes. This review examines the current understanding of Weill-Marchesani syndrome pathogenesis, clinical presentation, diagnostic approaches, and treatment strategies. Diagnosis relies on a combination of genetic testing and clinical evaluation. The autosomal dominant form, primarily associated with FBN1 mutations, is typically characterized by lens ectopia and joint stiffness. In contrast, the autosomal recessive form, resulting from mutations in ADAMTS10, ADAMTS17, or LTBP2, is predominantly linked to microspherophakia and cardiovascular abnormalities. Ophthalmological manifestations, including severe myopia and an increased risk of angle-closure glaucoma, are crucial for diagnosis. Management requires a multidisciplinary approach, incorporating ophthalmological interventions such as iridotomy or lensectomy, cardiological monitoring, and orthopedic care. This review synthesizes findings from literature published between 2015 and early 2025, highlighting the ongoing challenges in establishing definitive diagnostic criteria. The analysis underscores the need for further research into the molecular mechanisms underlying Weill-Marchesani syndrome and the development of targeted therapeutic strategies.

Streszczenie

Zespół Weilla-Marchesaniego to rzadka genetyczna choroba tkanki łącznej, występująca z częstością 1:100 000 osób. Charakteryzuje się plejotropowym spektrum objawów, obejmujących niskorosłość, brachydaktylię, sztywność stawów, wady wzroku oraz powikłania sercowo-naczyniowe. Choroba dziedziczona jest autosomalnie recesywnie lub dominująco, z różnymi mutacjami w genach FBN1, ADAMTS10, ADAMTS17 i LTBP2. W pracy omówiono patogenezę, obraz kliniczny, diagnostykę oraz leczenie zespołu Weilla-Marchesaniego. Diagnostyka opiera się na badaniach genetycznych oraz ocenie klinicznej. Wariant autosomalny dominujący związany jest głównie z mutacjami w FBN1 i objawia się ektopią soczewki oraz sztywnością stawów. Wariant recesywny wynika z mutacji w ADAMTS10, ADAMTS17 lub LTBP2 i wiąże się z mikrosferofakią oraz nieprawidłowościami kardiologicznymi. Objawy okulistyczne są kluczowe dla rozpoznania i obejmują m.in. wysoką krótkowzroczność oraz ryzyko jaskry zamkniętego kąta. Leczenie wymaga interdyscyplinarnego podejścia – okulistycznego (np. irydotomia, lensektomia), kardiologicznego i ortopedycznego. W pracy przedstawiono aktualny stan wiedzy na temat zespołu Weilla-Marchesaniego na podstawie przeglądu literatury z lat 2015–2025. Wyniki wskazują na brak jednoznacznych kryteriów diagnostycznych oraz konieczność dalszych badań nad patogenezą i terapią tej choroby.

Keywords: Weil-Marchesani syndrome; FBN1 mutation; fibrillins; Marfan syndrome

Słowa kluczowe: zespół Weilla-Marchesaniego; mutacja FBN1; fibryliny; zespół Marfana

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Introduction

Weill-Marchesani syndrome (WMS, spherophakia-brachymorphia syndrome) is a rare genetic connective tissue disorder, with an estimated prevalence of approximately 1 in 100,000 individuals. It is characterized by short stature, brachydactyly, joint stiffness, cardiovascular complications, and ocular abnormalities, including microspherophakia, lens ectopia, severe myopia, and secondary glaucoma [1]. First described in the early 20th century by Weill and later by Marchesani [2], the syndrome follows both autosomal recessive (more common) and autosomal dominant inheritance patterns. The autosomal recessive form is primarily associated with microspherophakia and cardiovascular abnormalities, whereas the autosomal dominant variant is predominantly linked to lens ectopia and joint stiffness [1].

This study aims to review current knowledge and recent discoveries regarding Weill-Marchesani syndrome, with a focus on its pathogenesis, clinical presentation, diagnostic approaches, and treatment strategies.

Materials and methods: A systematic literature review was conducted using PubMed, analyzing case reports and studies published between 2015 and early 2025.

Etiology

The genetic basis of Weill-Marchesani syndrome is attributed to pathogenic variants in the *FBN1*, *ADAMTS10*, *ADAMTS17*, and *LTBP2* genes. There are two primary modes of inheritance: autosomal dominant, associated with pathogenic variants in *FBN1*, and autosomal recessive, linked to mutations in *ADAMTS10*, *ADAMTS17*, and *LTBP2*. Regardless of the inheritance pattern, these mutations exhibit complete penetrance (100%). However, the severity of clinical manifestations varies significantly, even among individuals carrying the same mutated gene, including members of the same family [3]. In cases of autosomal dominant inheritance, at least one parent is typically affected, although the mutation may also arise de novo. The exact proportion of individuals who inherit the disorder from an affected parent versus those in whom it results from a de novo mutation remains unknown. However, the autosomal recessive form is more frequently inherited [1, 4]. In this inheritance pattern, both parents may be affected, one parent may have WMS while the other is a heterozygous carrier, or both parents may be heterozygous carriers of pathogenic variants in *ADAMTS10*, *ADAMTS17*, or *LTBP2*. It is important to note that heterozygous individuals do not exhibit any clinical symptoms of the disease [1, 5, 6].

Genetics

The autosomal dominant form of WMS is caused by mutations in the *FBN1* gene, which encodes fibrillin-1 [7, 8]. Fibrillins are structural proteins that constitute microfibrils within the extracellular matrix of both elastic and non-elastic tissues [9]. Three types of fibrillins have been identified: fibrillin-1, encoded by the *FBN1* gene on human chromosome 15; fibrillin-2, encoded by the *FBN2* gene on chromosome 5; and fibrillin-3, encoded by the *FBN3* gene on chromosome 19 [10]. Microfibrils exhibit a distinctive morphology, characterized by alternating light and dark – or hollow – regions, giving them a railroad track-like appearance. They are found as large microfibril bundles, as single short microfibrils (often near basement membranes, such as in glomerular endothelial cells), and as a peripheral microfibrillar sheath surrounding elastin in elastic fibers. Microfibrils serve as scaffolds that adapt to the functions of specific tissues to maintain their integrity. For example, in the skin, elastic fiber microfibrils form a loose network of interconnected pathways. In the dermis, they run parallel to the epidermis, with branches extending perpendicularly upwards – from the deeper elastic fiber layers to the basement membrane at the dermo-epidermal junction, where microfibril bundles cross the lamina densa. In tendons and the perichondrium, elastic fibers align parallel to the longitudinal axis, whereas in muscular arteries, they encircle the vascular lumen [11]. Additionally, microfibrils regulate the bioavailability of potent growth factors from the TGF-β superfamily.

In contrast, the autosomal recessive form of WMS is associated with mutations in the *ADAMTS10*, *ADAMTS17*, or *LTBP2* genes. The ADAMTS (A Disintegrin-like and Metalloproteinase with Thrombospondin motifs) family consists of extracellular matrix metalloproteinases capable of degrading matrix proteins. ADAMTS proteins participate in various biological processes, including angiogenesis, coagulation, morphogenesis, and development, as well as pathological conditions such as cancer, arthritis, and extracellular matrix disorders. *ADAMTS10*, in particular, is crucial for microfibrillar fiber organization: it accelerates microfibril assembly in fibroblast cultures, facilitates cell-cell adhesion in epithelial tissues, binds heparan sulfate, and supports focal adhesion formation [12]. Dysfunction of fibrillin or ADAMTS family proteases in WMS results in connective tissue abnormalities, which clinically manifest as the characteristic syndrome [1].

Symptoms

Weill-Marchesani syndrome is characterized by a pleiotropic spectrum of clinical manifestations affecting multiple organ systems. According to the available literature, no clear genotype-phenotype correlation has been established. The disorder involves musculoskeletal, ocular, cardiovascular, and psychiatric abnormalities. Typical features include short stature (average height 142–169 cm in males and 130–157 cm in females), brachydactyly (short fingers), joint stiffness, and ocular anomalies [1]. Ophthalmologic complications often present in childhood, with key manifestations including microspherophakia, high myopia, and angle-closure glaucoma, which can lead to vision loss. Additional ocular findings may include lens dislocation, cataracts, and a recently described feature – corneal thickening. The spherical, subluxated lens appears as a "golden ring" under slit-lamp examination [4, 13–15]. Some patients with WMS also exhibit cardiovascular anomalies such as patent ductus arteriosus, pulmonary valve stenosis, aortic valve stenosis, and mitral valve regurgitation. Less common but clinically significant features include restricted mouth opening and difficulties with intubation, highlighting the need for thorough preoperative assessment. Intellectual disability has been reported in a subset of patients. Rare cases in the literature describe severe supravalvular pulmonary artery stenosis, mitral supravalvular stenosis, and subaortic stenosis. In mildly symptomatic individuals, Weill-Marchesani syndrome type 4 (WMS4) may be diagnosed. Awareness of these clinical features is crucial for pediatricians to ensure early referral for further evaluation and timely diagnosis. Interestingly, most pathogenic variants in *FBN1*, the gene encoding fibrillin-1, are associated with Marfan syndrome, which in many aspects presents as a phenotypic opposite of Weill-Marchesani syndrome [6]. Table 1 provides a comparative overview of the clinical features and genetic mutations observed in WMS and Marfan syndrome [1, 7, 16, 17].

Diagnosis

There are no official, widely accepted diagnostic criteria for WMS, unlike Marfan syndrome (e.g., Ghent criteria). Diagnosis is primarily based on clinical evaluation, imaging studies, and genetic testing. WMS does not present a pathognomonic sign that allows for definitive diagnosis; genetic testing remains the only reliable method. In cases where the autosomal dominant form is suspected, serial testing of a single gene, including sequential analysis of *FBN1*, is performed. Genetic testing including *ADAMTS10*, *ADAMTS17*, *FBN1*, *LTBP2*, and other relevant genes helps identify the condition and exclude uncertain variants. Commonly used diagnostic methods include sequence analysis, deletion analysis, and duplication testing [1]. The primary symptoms of WMS that prompt patients to seek medical consultation, such as short stature, brachydactyly, and musculoskeletal abnormalities, are diagnosed using standard radiographic imaging. This allows for the identification of shortened long bones, delayed bone age, and widening of the proximal phalanges, as well as the assessment of skeletal dysplasia [1]. Ophthalmological examination is critical, as WMS affects the lens and supportive structures of the eye. Techniques such as biomicroscopy help detect lens ectopia, as well as changes in the cornea and anterior chamber. Tonometry is used to assess the risk of glaucoma, while gonioscopy aids in identifying anatomical abnormalities in the filtration angle. Ultrasound biomicroscopy is a valuable tool for detailed analysis of Zinn's ligaments and the degree of lens subluxation. Furthermore, due to the high prevalence of significant myopia in WMS patients, keratometry and skiascopy are also essential [18, 19]. In the evaluation of cardiovascular symptoms, electrocardiography may reveal a prolonged QT interval, while echocardiography helps identify valvular heart diseases [20]. For the differential diagnosis, other connective tissue disorders, such as Marfan syndrome, as well as acromelic dysplasias, which are a group of genetic bone dysplasias, should be considered. These dysplasias are characterized by abnormalities in bone development, especially in the distal parts of the body, including the hands, feet, and face, leading to characteristic deformities [1]. Among the conditions to be considered in the differential diagnosis of WMS are gelatinous-physical dysplasia (GD), acromicrodysplasia (AD), and Myhre syndrome [21, 22]. A comparison of common and distinguishing features is presented in Table 2.

Table 1. Comparison of clinical features between Marfan syndrome and Weill-Marchesani syndrome [1, 7, 16, 17].

Feature	Weill-Marchesani syndrome	Marfan syndrome
Genetic cause	Mutations in *FBN1* (less common than in Marfan syndrome), *ADAMTS10*, or *LTBP1*	*FBN1* gene mutation encoding fibrillin-1
Phenotypic features	Short stature, short fingers and toes (brachydactyly), joint stiffness	Tall stature, long and slender limbs (arachnodactyly), joint hypermobility
Height	Below average	Above average
Digits (fingers/toes)	Short and broad (brachydactyly)	Long and slender (arachnodactyly)
Joint involvement	Restricted mobility, joint stiffness	Increased joint flexibility (hypermobility)
Ocular manifestations	Downward lens dislocation, severe myopia, secondary glaucoma	Upward lens dislocation, myopia
Cardiovascular involvement	Less frequently associated with severe cardiac abnormalities	Aortic aneurysm, aortic dissection, mitral valve prolapse
Cognitive function	Typically normal, although learning difficulties may occur	Typically normal
Additional features	Small, spherical lenses, accommodation difficulties	Chest wall deformities (pectus excavatum or carinatum), skin laxity, striae distensae

Table 2. Comparative features of Weill-Marchesani syndrome (WMS), gelatinous-physical dysplasia (GD), acromicrodysplasia (AD), and Myhre syndrome

Common features of WMS, GD, AD	Short stature, short hands and feet, joint restrictions, thickened skin, mild facial anomalies, and specific radiological findings including delayed bone age, shortened long bones, oval-shaped vertebral bodies
Characteristic features of WMS	Lenticular myopia, lens ectopia, glaucoma, spherophakia
Characteristic features of GD	Valvular heart abnormalities, progressive hepatomegaly, tracheal stenosis
Characteristic features of AD	Progressive hepatomegaly and tracheal stenosis
Common features of WMS and Myhre syndrome	Intrauterine growth restriction (IUGR), short stature, brachydactyly, joint stiffness, thickened skin, heart disease
Characteristic features of Myhre syndrome	Hearing loss, characteristic facial features, varying degrees of cognitive dysfunction, absence of lens abnormalities

Treatment

Following the diagnosis of WMS, it is essential to conduct comprehensive and interdisciplinary evaluations to assess potential manifestations of the disease. Such an approach allows monitoring of disease progression, detection of complications, and initiation of appropriate treatment. Ophthalmic management in WMS is complex and requires an individualized approach, taking into account the unique characteristics of each case. In the early stages of WMS, glaucoma prophylaxis is crucial. Peripheral iridotomy is recommended as a preventive measure to avert closure of the drainage angle. However, closed-angle glaucoma represents a severe complication of WMS, and is often resistant to standard treatments. Available studies indicate that although laser iridotomy is commonly used, it may prove ineffective in deepening the anterior chamber and opening the drainage angle in WMS patients. In such cases, more invasive interventions are necessary. For advanced, chronic closed-angle glaucoma, the following combined procedures may be effective:

- **Lensectomy:** Removal of the lens, which often exhibits abnormal structure and positioning in WMS, contributing to closure of the drainage angle.
- **Anterior vitrectomy:** Removal of the vitreous body from the anterior chamber to improve aqueous humor flow.
- **Combination of vitrectomy and lensectomy:** A combined approach to address the underlying issues.
- **Intraocular lens (IOL) implantation:** Implantation of an artificial intraocular lens following lensectomy.
- **Molteno tube shunt implantation:** Use of a drainage system to reduce intraocular pressure.
- **ExPress shunt implantation:** Another method to reduce intraocular pressure.

In addition to essential ophthalmologic care, patients with WMS require the involvement of specialists from various medical fields. Given the broad range of symptoms and complications associated with this syndrome, the multidisciplinary management team should include a pediatrician, cardiologist, endocrinologist, orthopedist, and physiotherapist [1, 15, 23–26].

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GLUCOCORTICOIDS IN RHEUMATIC DISEASES. PART I

Glikokortykosteroidy w leczeniu chorób reumatycznych. Część I

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Abstract

The discovery of glucocorticoids represented a crucial moment in the history of medicine, particularly in the treatment of rheumatic diseases. These powerful hormonal substances revolutionized therapeutic approaches, enabling effective management of severe diseases that previously resulted in disability or even death. Glucocorticoids remain an essential part of emergency treatment. The first section of this work presents the history of research on adrenal hormones, biochemical and pharmacological aspects of their action, as well as the general principles of glucocorticoid therapy in rheumatic diseases. The paper also discusses detailed expert recommendations and guidelines from recognized rheumatological organizations regarding the use of glucocorticoids in the treatment of arthritis and systemic connective tissue disorders. This review presents the current and systematic knowledge on the role of glucocorticoids in the therapy of rheumatic diseases, with particular emphasis on their use in daily clinical practice.

Streszczenie

Odkrycie glikokortykosteroidów stanowiło przełomowy moment w historii medycyny, zwłaszcza w leczeniu chorób reumatycznych. Substancje te, o silnym działaniu hormonalnym, zrewolucjonizowały możliwości terapeutyczne, pozwalając na skuteczne leczenie schorzeń o ciężkim przebiegu, które wcześniej prowadziły do niepełnosprawności lub nawet śmierci pacjentów. Glikokortykosteroidy nadal pozostają niezastąpione w stanach nagłych. W pierwszej części pracy przedstawiono historię badań nad hormonami nadnerczy, biochemiczne oraz farmakologiczne aspekty ich działania, a także ogólne zasady leczenia glikokortykosteroidami w chorobach reumatycznych. Omówione zostały również szczegółowe rekomendacje ekspertów oraz uznanych organizacji reumatologicznych dotyczące stosowania glikokortykosteroidów w leczeniu zapaleń stawów i chorób układowych tkanki łącznej. Opracowanie to ma na celu przedstawienie aktualnej i usystematyzowanej wiedzy na temat roli glikokortykosteroidów w terapii chorób reumatycznych, ze szczególnym uwzględnieniem wykorzystania ich w codziennej praktyce klinicznej.

Keywords: rheumatic diseases; pharmacotherapy; glucocorticoids

Słowa kluczowe: choroby reumatyczne; farmakoterapia; glikokortykosteroidy

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Introduction

Despite the rapid advances in pharmacology over the past several decades, few classes of drugs have achieved such broad application in medicine as glucocorticoids (GCs). Their widespread use stems from their diverse effects on physiological and pathological processes, as well as the absence of therapeutic alternatives with comparable mechanisms of action. Today, GCs are used across nearly all fields of clinical medicine. Although decades of clinical experience with GCs have provided a thorough understanding of their pharmacological proper-

ties, further research is still needed. The development of optimal treatment regimens that balance therapeutic efficacy with the risk of adverse effects remains a major challenge.

Among the various effects of GCs, their ability to inhibit inflammatory and immune responses has been particularly valuable in the treatment of autoimmune disorders. For this reason, GCs hold a special place in rheumatology, and are frequently introduced as first-line therapy due to their relatively rapid therapeutic effects. Consequently, they are commonly used in remission-inducing protocols and, in selected cases, as part of maintenance therapy. In addition, their rapid action makes them valuable as emergency treatment in acute, life-threatening situations.

Our paper summarizes and compares current principles for the use of GCs in treating different rheumatic diseases, based on the latest recommendations and research data.

Historical outline

In 1929, Philip Showalter Hench, head of the Rheumatology Department at the Mayo Clinic, observed that symptoms of rheumatoid arthritis (RA) improved during jaundice or pregnancy. However, potential causes of this condition, such as hyperbilirubinemia or increased release of female hormones, do not occur simultaneously with pregnancy and jaundice. He therefore postulated that a naturally occurring, unidentified substance, later referred to as "Factor X" or "Substance X," was responsible for this symptomatic relief [1]. The temporary remission of RA symptoms observed in the postoperative period, together with knowledge of the adrenal response to surgical stress and the fatigue seen in Addison's disease, similar to that in RA, led Hench to consider the adrenal glands as a possible source of substance X. In 1935, he began cooperation with Edward Kendall, a professor of physiological chemistry at the Mayo Clinic, who had been the first to isolate crystalline thyroxine and, in 1930, had initiated research on the adrenal glands. At the same time, Tadeusz Reichstein, a Polish-born professor of organic chemistry conducting research in Switzerland, attempted to isolate adrenal hormones. By 1940, 28 substances had been isolated from the adrenal glands, four of which showed effects in animal testing. One of these was dehydrocorticosterone, referred to as 'Compound E' (cortin) by Kendall and 'Substance Fa' by Reichstein. Compound E appeared to have a life-saving effect in animals after adrenalectomy, leading Kendall and Hench to conclude that it might be the 'Substance X' they were seeking. At that time, however, isolating adrenal hormones was ineffective [2].

During World War II, reports surfaced that German scientists had isolated an adrenal hormone, which enhanced combat pilots' tolerance to low oxygen levels and was used in treating post-traumatic shock. In 1941, the progression of the war led the National Research Council, a U.S. government organization, to fund three initiatives: the development of antimalarial medications, the production of penicillin, and isolation and synthesis of cortin, with the latter one given highest priority.

In 1942, Lewis Sarett of Merck Pharmaceuticals completed a research fellowship at the Mayo Clinic and began close collaboration with Edward Kendall. By December 1944, Sarett had synthesized Compound E from ox bile, and by November 1948, with Kendall's assistance, he had improved a 37-step process for producing the hormone, making commercial use possible [3].

The first recipient of Compound E was a 29-year-old woman with severe RA unresponsive to treatment for four and a half years. She was admitted to the Mayo Clinic on July 26, 1948, with complaints of stiffness, pain, and oedema involving multiple joints. Imaging revealed destructive joint changes and elevated erythrocyte sedimentation rate (ESR) of 109 mm/h. Oral lactoferrin produced neither jaundice nor clinical improvement. The patient's symptoms worsened over hospital stay, making the patient bedridden. On September 21, 1948, the first intramuscular injection of 100 mg of compound E was administered. Gradual improvement was initially observed, but morning stiffness had nearly resolved by day 3, allowing the patient to walk. Joint pain and oedema decreased after a week of receiving compound E. At 8 days, the dose was reduced to 50 mg/day for 4 days, followed by 25 mg/day for 10 days. However, the symptoms recurred, accompanied by a further increase in ESR. Since the fall of 1948, compound E had been administered to 14 patients with moderate to severe disease. Two of these patients also received adrenocorticotropic hormone (ACTH). A water-based cholesterol solution was used as a control, administered either in place of or several days before compound E. Both patients and researchers were blinded to the timing of its replacement with compound E. Compared to the control solution, all patients treated with the active substance showed significant improvement in joint stiffness and pain, as well as increased mobility, and a lower ESR. Some patients experienced first adverse reactions. On June 1, 1949, Hench and his team published a paper reporting the efficacy of compound E and ACTH in treating RA [1].

In 1950, Edward Calvin Kendall, Tadeusz Reichstein, and Philip Showalter Hench were jointly awarded the Nobel Prize in Physiology or Medicine "for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects".

Endogenous synthesis of steroid hormones

The adrenal gland is made up of medulla, which releases catecholamines, and cortex, which is histologically and endocrinologically divided into three layers. The outer layer (zona glomerulosa) secretes aldosterone, the middle layer (zona fasciculata) releases cortisol, and the inner layer (zona reticularis) secretes a sex hormone precursor - dehydroepiandrosterone (DHEA) and its derivative, dehydroepiandrosterone sulfate. Each layer releases hormones upon stimulation by ACTH, whose release is regulated by hypothalamic corticotropin-releasing hormone (CRH). The outer layer secretes aldosterone, whose primarily role is to regulate water and electrolyte balance. In addition to ACTH stimulation, its secretion is also mediated by extracellular potassium levels and angiotensin II. Therefore, this layer does not undergo atrophy in the absence of ACTH stimulation. The two inner layers of the

adrenal cortex, however, are more dependent on ACTH. Increased levels of this hormone cause their hypertrophy and up-regulate the secretion of GCs and androgen precursors, whereas decreased ACTH levels result in their hypotrophy.

At the cellular level, ACTH binds to the MC2 receptor (MC2R), activating the adenylate cyclase pathway and promoting the translation of multiple enzymes required for steroid hormone synthesis in the adrenal cortex [4].

The effects of corticosteroids on the body

The adrenal cortex synthesizes two classes of steroid hormones: corticosteroids (glucocorticoids and mineralocorticoids), which have 21 carbon atoms, and androgens, which have 19 carbon atoms. Corticosteroids affect the metabolism of carbohydrates, proteins, and lipids. They also play a role in regulating the immune, cardiovascular, excretory, nervous, musculoskeletal, and endocrine systems. They help the body cope with stressors such as trauma, infections, and extreme temperatures. Corticosteroids are classified into mineralocorticoids and glucocorticoids, based on their roles in regulating water, electrolyte, and carbohydrate metabolism. Their effects on glucose metabolism typically correlate with anti-inflammatory properties, without significantly influencing sodium retention. This results from stimulation of different target sites and variations in ligand selectivity [4].

GCs bind to receptors in specific tissues, altering the expression of target genes and, consequently, affecting the production of specific proteins. The genomic response is delayed, becoming apparent after at least 30 minutes, usually several hours. Glucocorticoid receptors (GCRs or GRs) are members of the nuclear transcription factor family. In the cytoplasm, they remain inactive, bound to other proteins. Binding to corticosteroids activates the receptor and translocates it to the nucleus, where it interacts with specific DNA sequences called glucocorticoid response elements (GREs), which confer specificity in gene transcription. Genes can be activated or suppressed in this way, thereby altering protein production. A key mechanism by which GCs exert their ant-inflammatory action is by inducing the production of lipocortin 1, which inhibits phospholipase A2, affecting the arachidonic acid cascade and reducing the synthesis of inflammatory mediators. GCs also reduce the synthesis of various cytokines, including TNF-alpha and interleukins 2 and 6 (IL-2, IL-6). Some inhibitory effects of GCs, such as reduced expression of genes encoding cytokines, collagenases, and metalloproteinases, are mediated by protein-protein interactions between GRs and other transcription factors (e.g., NF-kB and AP-1). GCs also influence mRNA stability, translation, and secretion. For example, they can limit the production of cyclooxygenase-2 mRNA, which is normally stimulated by interleukin 1 (IL-1). Furthermore, GCs have rapid, not fully understood non-genomic effects on specific cell membrane receptors. A possible physicochemical mechanism has also been described, whereby GCs directly affect membrane channel activity, thereby interfering with lymphocyte activation induced by elevated intracellular calcium. Summarising, the genomic effects of GCs develop gradually at low doses, while non-genomic effects appear almost immediately but require much higher doses [4, 5].

Molecules used in rheumatology

For therapeutic use, synthetic GCs with high anti-inflammatory activity and minimal or no mineralocorticoid effects are preferred. The anti-inflammatory potency of different preparations is expressed in milligrams of prednisone-equivalent dose. Prednisone is used as a reference for historical reasons, being the first synthetic, pharmacologically relevant glucocorticoid introduced into clinical practice. This conversion applies when equivalent doses do not exceed 100 mg of prednisone, as genomic effects predominate at these levels. At higher doses, non-genomic effects emerge, and the relative potency of different GCs may vary [6].

To achieve a rapid therapeutic effect during rheumatic disease exacerbations, intravenous methylprednisolone is often preferred over prednisone. While both agents share similar genomic effects, methylprednisolone exhibits more than three times the non-genomic effect [6]. The therapeutic effect and the risk of adverse effects are directly proportional to both the dose and the duration of GC therapy. This is due to GCR saturation and the enhanced non-genomic effects at high doses. It was proposed in 2002 that daily glucocorticoid doses be divided into:

- low: ≤7.5 mg prednisone equivalent;
- medium: >7.5 mg but ≤30 mg prednisone equivalent;
- high: >30 mg but ≤100 mg prednisone equivalent;
- very high >100 mg prednisone equivalent.

Another treatment approach, referred to as 'pulse therapy', involves intravenous doses of ≥250 mg prednisone equivalent per day administered for up to five days [6].

General principles of GC treatment in rheumatology

In 2007, the European League Against Rheumatism (EULAR), renamed the European Alliance of Associations for Rheumatology in 2021, issued recommendations for the use of GCs in rheumatic diseases [7]. Initial dose, dose reduction and long-term dosing depend on the underlying rheumatic disease, its activity, risk factors, and the patient's individual responsiveness. The timing of GC administration can also affect their effectiveness, as symptoms (such as morning stiffness in RA) and pro-inflammatory cytokine levels follow a circadian rhythm, peaking in the morning. The lowest effective dose should be used due to the pharmacodynamic properties of GCs. The therapy should be tapered or discontinued during remission or low disease activity. Before starting treatment, risk factors for adverse effects need to be assessed, and comorbidities such as glaucoma, diabetes mellitus, and hypertension should be taken into account, implementing appropriate prophylaxis and treatment where needed. Potential adverse effects should be discussed with patients, and the benefits of therapy should be clearly explained.

During treatment, regular patient monitoring is recommended, including body weight, blood pressure, and relevant laboratory parameters, along with lifestyle guidance

to prevent undesirable metabolic changes [7]. Vitamin D and calcium supplementation is recommended for patients receiving prednisone at ≥7.5 mg/day for more than three months to prevent secondary osteoporosis. Indications for antiresorptive therapy are based on risk factors, including bone mineral density measurements. When GCs and nonsteroidal anti-inflammatory drugs (NSAIDs) are used concurrently, co-administration with a proton pump inhibitor (PPI), misoprostol (synthetic analogue of prostaglandin E1), or a selective COX-2 inhibitor is recommended. Conventional NSAIDs combined with PPIs are less likely to cause dyspepsia than selective NSAIDs alone [7].

Patients on corticosteroids for longer than 1 month, who will undergo surgery, need perioperative management with adequate GC replacement to overcome potential adrenal insufficiency. For minor procedures, 100 mg of hydrocortisone is recommended preoperatively. For major surgery, supplementation should continue postoperatively with four doses given every 8 hours, followed by a gradual taper over the subsequent days [7].

GC therapy poses no additional risks to the pregnant woman or foetus, but it may increase the risk of pregnancy-related conditions such as hypertension, diabetes, and osteoporosis. Dexamethasone may be used when a glucocorticoid effect in foetal tissues is required, as it is poorly metabolized by the placenta. Prednisone, prednisolone, or methylprednisolone are a preferred option in pregnant women with exacerbations of chronic diseases, since only about 10% of the administered dose reaches the foetus. Prednisone and methylprednisolone are classified as FDA Category B, as there is no evidence of teratogenicity in humans. Exposure to GCs in utero does not increase the risk of neonatal infection. Breastfeeding by women on low-dose GC therapy is not contradicted, but it should be avoided during the first 4 h after GC intake. Children receiving GCs should be monitored for linear growth and considered for growth-hormone replacement if necessary. In rheumatology, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, azathioprine, and cyclosporine A are commonly used to shorten GC therapy and reduce patient exposure to adverse effects [7, 8].

Intra-articular corticosteroid injections may be considered for aseptic arthritis, although their local mechanism of action remains unclear. Possible mechanisms include reduced permeability of periarticular vessels and synovial membrane blood flow, decreased synovial fluid volume and synovial membrane size, increased pain threshold, and lower joint temperature. Additionally, removing excess synovial fluid during arthrocentesis can be therapeutic by eliminating leukocytes and crystals and improving joint mobility. Indications include mono- or oligoarthritis and cases where systemic therapy is ineffective or contraindicated. GCs can also be injected into other synovial spaces, such as bursae and tendon sheaths [9].

Arthritis

In rheumatoid arthritis, GCs are used to rapidly control symptoms before DMARDs start to take effect. As set out in the 2022 EULAR recommendations, short-term GCs should be considered when initiating or changing DMARDs. When starting GCs, it is important to plan for a gradual tapering as soon as possible, aiming for complete discontinuation, ideally within three months. The need to continue GC therapy beyond four months should be considered a sign of DMARD inefficacy and prompt treatment modification [10].

The American College of Rheumatology (ACR) recommends initiating RA therapy without routine GCs, both short-term (<3 months) or long-term (≥3 months), in treatment-naïve patients with moderate-to-high disease activity. Short-term GCs are acceptable if symptom relief is needed before DMARDs take effect. GC therapy can only be continued if the maximum DMARD dose has been already reached or DMARD type switch fails to produce satisfactory outcome [11]. A systematic review by Bergstra et al., which evaluated a two-year follow-up of high-dose GCs in combination with DMARDs in early RA, found that clinical improvement and radiographic progression at moderate doses (≤30 mg/day) were comparable to those achieved with higher doses (60 mg/day) [12]. The Steroid Elimination in Rheumatoid Arthritis (SEMIRA) study investigated the effects of GC discontinuation in RA patients [12]. In patients with stable, low disease activity receiving tocilizumab (a monoclonal antibody targeting the IL-6 receptor, used in the treatment of arthritis and other rheumatic diseases) prednisone dose reduction was associated with an increase in Disease Activity Score 28 (DAS28) and a lower likelihood of maintaining remission. No increase in disease activity was observed in patients who continued prednisone at 5 mg/day [12].

In psoriatic arthritis (PsA), GCs can be used as initial supportive therapy, either as local injections or systemically at the lowest effective dose [13]. They are also used as first-line treatment for limited disease (mono- or oligoarthritis) and enthesitis. Systemic GCs should not be used in axial PsA. The risk of psoriasis exacerbation should be evaluated when systemic GCs are used. In ankylosing spondylitis (AS), involvement may extend beyond the axial skeleton to peripheral joints, tendon attachments, and the uvea. The 2022 joint recommendations of the Assessment of Spondyloarthritis International Society (ASAS) and EULAR permit the use of local GC injections into inflamed musculoskeletal sites, despite limited clear scientific evidence [14]. Few studies confirm the benefits of GC injections into the sacroiliac joints (SIJ), particularly under ultrasound guidance, which provides pain relief with a low risk of adverse reactions [14]. The authors of the recommendations advise against long-term systemic GC therapy solely for axial disease, due to insufficient evidence of its efficacy. However, some data suggest that moderate benefit may be achieved with short-term systemic therapy at 50–60 mg/day, tapered over six months [14].

According to ACR recommendations, intra-articular GCs are more effective than NSAID monotherapy in patients with isolated sacroiliac arthritis. Systemic GCs are not recommended for AS [15]. Local GCs are also recommended for patients with controlled axial disease but active inflammation in peripheral joints or entheses. However, injections into the Achilles tendon, patellar

ligament, and quadriceps tendon should generally be avoided, as these structures are at high risk of rupture, a potential complication of GC treatment [15].

GCs also play an important role in treating uveitis, which often accompanies AS. In such cases, topical GCs are used to control acute inflammation. Delaying treatment increases the risk of a chronic, corticosteroid-resistant disease. Prompt GC administration also reduces the risk of posterior synechiae [15]. In the absence of poor prognostic factors, such as prior visual impairment, ocular hypotony, glaucoma, cataracts, macular oedema, or vitreous tortuosity, intensive topical treatment should be initiated, administering 1% prednisolone acetate drops every 1–2 hours. If, however, these factors are present, systemic prednisone should be added at an initial dose of 1 mg/kg/day, gradually tapered, and limited to no more than three months. Periocular injections of methylprednisolone acetate or triamcinolone acetate may also be used. If symptoms persist beyond three months or the patient's condition worsens, DMARDs should be added to the local corticosteroid therapy [16].

GCs are also used for inflammatory bowel disease (IBD) and its extraintestinal manifestations. Local injections are preferred for the involvement of individual peripheral joints. However, the few available publications do not specify doses. GCs are generally not effective for axial arthritis and enthesitis in IBD [17].

Intra-articular GC injections should be considered for oligoarticular reactive arthritis [18]. In more severe cases with multiple joint involvement, short-term oral prednisone at 30–40 mg/day, which is further gradually tapered, may be used. Some symptoms of reactive arthropathies, such as uveitis, may require topical GCs in the form of eye drops [18]. According to EULAR recommendations, intra-articular (IA) corticosteroid injections should be considered for early undifferentiated arthritis to control local inflammation. Limited literature data prevent precise determination of doses and systemic treatment strategies. Nevertheless, systemic treatment is considered safe when used at the lowest effective dose for the shortest duration (up to six months) and can effectively relieve symptoms and limit disease progression [19]. It is also emphasized that GCs should always be used alongside DMARDs, never as monotherapy, in patients with early undifferentiated arthritis. This is particularly important because GCs alone may mask disease activity, leading to misdiagnosis, inadequate treatment, or a more challenging prognosis [19].

ACR recommendations for the treatment of juvenile idiopathic arthritis (JIA) base the approach on predominant clinical symptoms. Eight disease subtypes have been distinguished according to these symptoms [20–22]:

- oligoarthritis;
- polyarthritis;
- sacroiliitis;
- enthesitis;
- temporomandibular joint inflammation;
- active systemic JIA with or without macrophage activation syndrome (MAS);
- inactive systemic JIA with or without MAS;
- uveitis.

Due to the risk of impaired bone growth in children, GC treatment should be given at the lowest effective dose, for the shortest possible duration, and in combination with DMARD [20, 21]. Treatment of active oligoarthritis (involving ≤ 4 joints, without systemic symptoms) includes, among others, intra-articular GC injections [20]. Systemic GCs are not recommended for initial therapy. However, they may be used when intra-articular treatment is not possible, symptoms are severe and need rapid relief, or when conventional DMARDs are ineffective. IA corticosteroids may be used in polyarthritis to achieve faster disease control, particularly when arthritis causes patient's dysfunction. However, frequent or multiple IA injections can be burdensome for children. In such cases, systemic therapy may be less likely to cause unpleasant treatment-related experiences [21].

Oral corticosteroids may be used when starting DMARD therapy or during flares. Treatment with intra-articular GCs may be intensified in polyarthritis with low disease activity (JADAS ≤ 2.5) but exacerbation in at least one joint that limits daily activities [21]. Oral corticosteroid therapy is recommended for up to three months, either at disease onset or during flares in JIA with active sacroiliac arthritis unresponsive to NSAIDs. This approach may be useful when high disease activity is difficult to control (severe symptoms, limited mobility). Injections directly into the sacroiliac joints may also be considered, although supporting research is limited [21].

For enthesitis unresponsive to NSAIDs and associated with high, mobility-limiting disease activity, short-term (<3 months) systemic GCs at the lowest effective dose are recommended. IA glucocorticoids are used in addition to NSAIDs in JIA with temporomandibular joint involvement. However, injections should be reserved for the most severe cases due to the risk of complications, heterotopic ossification and growth disturbances in particular. Routine oral GCs are not recommended, and if necessary, the dose should be minimized [20].

In most cases, oral GCs should not be used as monotherapy in patients with systemic JIA without MAS. Systemic treatment may be considered when access to other therapies, such as biological DMARDs, is limited, in the initial stages of treatment or in cases of severe joint symptoms. Corticosteroids are an important component of initial therapy in JIA with MAS. The benefits of corticosteroids outweigh the risks, even in infection-induced MAS. High-dose systemic corticosteroids are warranted to control severe symptoms, although no exact dosing has been specified in the recommendations [20]. Regardless of MAS, once JIA remission is achieved, gradual GC tapering aiming at complete discontinuation is recommended, as the risks of long-term use (even at low doses) outweigh the risk of flare [20].

Prednisolone acetate 1% (1–2 drops daily) or an equivalent corticosteroid is the first-line treatment for chronic anterior uveitis (CAU). Prompt initiation is crucial to prevent complications such as cataracts, glaucoma, elevated intraocular pressure (IOP), infections, and vision loss. It is essential to exclude other causes of elevated IOP or cataracts and to ensure regular, close ophthalmologic monitoring before initiating prednisolone monotherapy [22].

If CAU flares despite systemic treatment, the dose of 1% prednisolone acetate should be added or increased to a maximum of three drops daily. If topical treatment is used alongside systemic therapy for more than three months without improvement, the systemic strategy should be modified, and the topical treatment gradually tapered to discontinuation [22]. Acute anterior uveitis (AAU) is associated with the HLA-B27 antigen and may occur in children with enthesitis or psoriatic arthritis. In these cases, topical GC drops are usually sufficient, without modifying the primary JIA therapy [22].

Systemic connective tissue diseases

According to the 2023 update of EULAR recommendations for the management of systemic lupus erythematosus (SLE), GCs should be used for flares and tapered as quickly as possible, while still allowing for maintenance therapy. Dosage depends on the type and severity of organ involvement. The recommended maintenance dose is up to 5 mg/day of prednisone equivalent [23]. Available data indicate it is relatively safe to use GCs at this dose. Patients at cardiovascular risk, in whom doses of 5–10 mg/day carry an uncertain risk, while doses above 10 mg/day significantly increase the risk of adverse effects, are an exception [24].

The initial oral dose depends on disease activity. Moderate to severe SLE may require intravenous methylprednisolone pulses at 125–1000 mg/day for 1–3 days. Specific indications include severe active neuropsychiatric involvement, lupus nephritis, and severe thrombocytopenia. Topical and systemic corticosteroids are a first-line treatment for cutaneous lupus erythematosus (CLE), and should be discontinued as soon as possible. Pharmacotherapy is discontinued once sustained remission is achieved, which is more easily reached when DMARDs are added [23].

The 2019 EULAR recommendations for antiphospholipid syndrome (APS) limit corticosteroid use to catastrophic or obstetric cases. Low-dose prednisolone may be used in obstetric APS, particularly in the first trimester for women experiencing recurrent pregnancy complications despite first-line therapy [25].

GCs are also effective for haemolytic anaemia and severe thrombocytopenia in APS patients. In such cases, intravenous methylprednisolone at 250–1000 mg/day for three days is recommended [26].

Polymyalgia rheumatica requires long-term GC therapy. According to the 2015 EULAR recommendations, treatment should last at least 12 months, starting with 12.5–25 mg of prednisone equivalent per day. Single daily dosing is preferred over divided doses except in cases of prominent night pain when tapering below 5 mg daily. Higher doses may be considered in patients at high risk of relapse, while lower doses are advisable in cases with comorbidities such as glaucoma, diabetes mellitus, or osteoporosis. Intramuscular methylprednisolone may be considered when cumulative dose reduction is desired. Dose tapering should be individualized, though the recommended regimen suggests reducing the oral dose to 10 mg daily within the first 4–8 weeks of therapy. In the event of a flare, the previous dose should be reinstated and then tapered over 4–8 weeks to the relapse level. Once remission is achieved, the prednisone dose should be reduced by 1 mg every four weeks. For a 10/7.5 mg every-other-day regimen, a 1.25 mg reduction is possible. Sustained remission allows for gradual tapering until treatment discontinuation [27].

The efficacy of corticosteroids in primary Sjögren's syndrome has not been confirmed due to the lack of randomized clinical trials. The 2019 EULAR recommendations include corticosteroids as a treatment option for active systemic Sjögren's syndrome. In severe cases, induction therapy includes methylprednisolone pulses, followed by prednisone at doses ≤0.5 mg/kg/day. Doses <0.5 mg/kg/day are used in mild to moderate cases. GCs should be discontinued once remission is achieved. If no remission is achieved, the dose should be maintained at 5 mg/day or lower, or additional immunosuppressants should be introduced. Detailed recommendations for tapering GCs in these patients have not yet been established. EULAR recommends GCs for patients with specific organ involvement in Sjögren's syndrome, including:

- acute involvement of salivary glands, after excluding infection and inefficacy of NSAIDs used for 3–5 days – prednisone 0.3 mg/kg/day;
- arthritis involving > 5 joints or simultaneous extensive, severe tenosynovitis if the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is moderate or high – prednisone 0.5 mg/kg/day with hydroxychloroquine (HCQ);
- arthritis in fewer joints or limited tenosynovitis, moderate to high ESSDAI scores and no response to NSAIDs or HCQ – GCs 0.5 mg/kg/day in combination with hydroxychloroquine;
- cutaneous vasculitis with moderate ESSDAI scores and limited purpura – prednisone 0.3 mg/kg/day, high ESSDAI score, and diffuse purpura – GCs 0.5–1 mg/kg/day;
- limited annular erythema – local GCs, diffuse annular erythema – prednisone 0.3 mg/kg/day, in monotherapy or in combination with HCQ;
- bronchial involvement resistant to inhaled treatment with moderate ESSDAI score – prednisone 0.5 mg/kg/day;
- interstitial lung disease (ILD) with moderate ESSDAI score – prednisone 0.5 mg/kg/day; the dose should be increased to 0.5–1 mg/kg/day if there is no response to treatment;
- ILD with high ESSDAI score – prednisone from 0.5 to 1 mg/kg/day;
- glomerulonephritis or interstitial nephritis, after excluding SLE and the presence of anti-neutrophil cytoplasmic antibodies (ANCA), if the ESSDAI score is low and despite correction of metabolic acidosis and potassium levels, the symptoms have not subsided and if the ESSDAI score is moderate – prednisone 0.5 mg/kg/day; 0.5–1 mg/kg/day in patents unresponsive to treatment and with high ESSDAI score;
- peripheral neuropathy after exclusion of vasculitis unrelated to cryoglobulinemia and axonal polyneuropathy associated with vasculitis – prednisone 0.5–1 mg/kg/day as first-line treatment;
- central nervous system vasculitis, neuromyelitis optica, and lymphocytic meningitis unresponsive

to symptomatic treatment or with cerebral involvement – prednisone 0.5–1 mg/kg/day;
- neutropenia <500/mm^3 that does not respond to granulocyte colony-stimulating factor (G-CSF) – GKS 0.5–1 mg/kg/day;
- platelets <20,000/mm^3 or haemoglobin 8–10 g/dL – prednisone 0.5–1 mg/kg/day; no treatment response or haemoglobin <8 g/dL requires the inclusion of intravenous immunoglobulins.

Corticosteroids are not recommended for pharmacological stimulation in xerostomia. However, they may be used for dry eye treatment, but only in combination with artificial tears and lubricating ointments. Treatment duration should not exceed 2–4 weeks due to the risk of infection, cataract, and increased IOP. Fluorinated GCs are recommended for neonatal lupus (NL) with anti-Ro antibodies, depending on the degree of congenital heart block [28].

Dermatomyositis, polymyositis, necrotizing autoimmune myositis, and inclusion body myositis are considered the major types of idiopathic inflammatory myopathies (IIMs). According to the 2022 British Society for Rheumatology recommendations, high-dose GCs are advised as initial treatment for skeletal myositis, typically 0.5–1 mg/kg/day of oral prednisolone. Once clinical response is achieved, the dose should be gradually tapered. If a rapid therapeutic effect is needed, intravenous methylprednisolone pulses may be considered [29]. According to some authors, the initial prednisone dose of 1–2 mg/kg/day should be maintained for 4 weeks, followed by tapering to the lowest effective dose, with treatment continued for 6–12 months [30]. Specific indications for GC therapy include joint and skin involvement, dysphagia, and chronic progressive interstitial lung disease [29, 30].

The use of GCs in scleroderma (also known as systemic sclerosis) remains controversial. According to the 2017 EULAR recommendations, they may be considered for interstitial lung disease or skin and musculoskeletal manifestations, despite limited supporting evidence. However, their use is associated with an increased risk of scleroderma renal crisis, which requires careful consideration [31].

In eosinophilic fasciitis, GC therapy is initiated with prednisone at 1 mg/kg/day, followed by gradual tapering. Higher doses may be needed if clinical symptoms or eosinophilia persist. In cases of inadequate response after 3 months of prednisone at 1.5 mg/kg/day, other immunosuppressive or immunomodulatory agents should be considered [32]. The optimal duration of treatment has not been established; therapy typically lasts from several months to several years. Observational data suggest that patients who initiate treatment with methylprednisolone pulses (0.5–1 g/day for three consecutive days) are more likely to achieve full remission and less likely to require additional immunosuppressive therapy [33].

The treatment of mixed connective tissue disease (MCTD), including corticosteroids, involves managing specific conditions that define its clinical picture. It should be noted that no specific treatment guidelines for MCTD have been established to date. GCs are used to manage symptoms such as refractory synovitis, myositis, myocarditis, pleurisy, aseptic meningitis, and oesophageal involvement. They also play a role in the initial management of thrombocytopenia and haemolytic anaemia [34].

According to the 2024 EULAR recommendations, systemic idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD) should be jointly referred to as "Still's disease". High-dose GCs (prednisone equivalent >1 mg/kg/day) are indicated in cases of severe disease, defined by symptoms such as high fever, VAS pain intensity score >6–7/10, pericarditis, and extensive inflammation involving multiple joints. The risk of MAS, which may present with elevated ferritin, triglycerides, and transaminases, along with decreased fibrinogen and thrombocytopenia, is another indication. Treatment is initiated intravenously and then continued orally, combined with an IL-1 or IL-6 inhibitor.

Medium- or low-dose GCs (≤0.1 mg/kg/day of prednisone), used either as monotherapy or in combination with IL-1 or IL-6 inhibitors, represent one of the treatment options for patients with lower disease activity. Dose tapering should be started as early as possible. The recommended regimen assumes resolution of clinical symptoms by month 3 of low-dose GC therapy, and complete discontinuation by month 6.

In MAS, intravenous pulses of methylprednisolone are recommended at doses of 15–30 mg/kg/day (maximum 1 g per infusion). In cases with CNS involvement, dexamethasone should be considered due to its superior ability to cross the blood–brain barrier (BBB). Nevertheless, current recommendations strongly emphasize the early initiation of IL-1 and IL-6 inhibitors, highlighting their role in reducing or even eliminating the need for GCs [35].

The principles of GC therapy can vary significantly depending on the disease entity and the goal of therapy, which should be remission or low disease activity. This is particularly important in cases that are refractory to treatment or pose a threat to health or life. It should be noted that the presented standards of practice do not preclude the use of GCs in other regimens, tailored to the individual patient's needs.

The principles of GC treatment discussed above apply to arthritis and collagenoses. The next part of the paper will summarize the recommendations and expert opinions on the use of GCs in vasculitis and other rheumatological conditions.

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REVIEW ARTICLE

MRI OF LYMPHOMAS THROUGH CLINICAL CASES

Obrazowanie chłoniaków metodą rezonansu magnetycznego na podstawie analizy przypadków

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Abstract

Lymphomas are a diverse group of lymphoid neoplasms that can develop in various parts of the body. This paper discusses four clinical cases of patients with lymphomas of the brain, orbit, mesentery and bone, with special emphasis on their morphology on magnetic resonance imaging, emphasizing the importance of this technique in diagnosis and assessment of disease progression. In each case, despite the different histological types, the characteristic imaging features of lymphomas, i.e. signal homogeneity in T1-weighted images, absence of cystic elements, intense contrast enhancement and diffusion restriction, were identified before treatment. Attention is given to the therapeutic implications of early suspicion of lymphoma and the importance of biopsy in confirming the diagnosis. The paper emphasizes that skillful interpretation of MRI images in the context of the overall clinical picture can significantly shorten the diagnostic process and accelerate the implementation of targeted treatment in the affected patients.

Streszczenie

Chłoniaki to zróżnicowana grupa nowotworów limfatycznych, które mogą występować w organizmie w różnych lokalizacjach. W pracy omówiono cztery przypadki kliniczne pacjentów z chłoniakami mózgowia, oczodołu, krezki oraz kości, ze szczególnym uwzględnieniem ich morfologii w obrazowaniu rezonansu magnetycznego, podkreślając znaczenie tej techniki w diagnostyce i ocenie zaawansowania choroby. W każdym przypadku, pomimo różnych typów histologicznych, zidentyfikowano charakterystyczne cechy obrazowe chłoniaków przed rozpoczęciem leczenia, tj. jednorodność sygnału w obrazach T1-zależnych, brak elementów torbielowatych, intensywne wzmocnienie kontrastowe oraz ograniczenie swobodnej dyfuzji wody. Zwrócono uwagę na implikacje terapeutyczne wynikające z wczesnego podejrzenia chłoniaka oraz znaczenie biopsji w ostatecznym potwierdzeniu diagnozy. Praca podkreśla, że umiejętna interpretacja obrazów MRI w kontekście pełnego obrazu klinicznego może znacząco skrócić czas do postawienia diagnozy i przyspieszyć wdrożenie leczenia celowanego u pacjentów z chłoniakami.

Keywords: lymphoma; MRI

Słowa kluczowe: chłoniak; obrazowanie metodą rezonansu magnetycznego

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Introduction

Lymphomas are a heterogeneous group of malignancies arising from lymphocytes, with diverse clinical presentations that can involve any part of the body. They account for approximately 4% of all malignancies diagnosed worldwide [1,2], with this proportion increasing to 15% in the paediatric population [3]. Depending on their site of origin, lymphomas are classified as primary or secondary. Non-invasive imaging techniques, magnetic resonance imaging (MRI) in particular, play a key role in diagnosing and assessing the initial extent of the disease. Knowledge of typical radiological features of lymphomas facilitates timely diagnosis and the initiation of appropriate treatment [3, 4].

Case reports

Case 1

A 39-year-old man presented to the Emergency Department (ED) with a head MRI report indicating an intra-axial mass in the left parietal-occipital region. The imaging had been performed due to headaches and hearing impairment persisting for one month. He also had a history of hypertension, temporarily managed with captopril. A head computed tomography (CT) scan taken on the same day revealed a focal lesion in the left parietal lobe, another in the region of the left lenticular nucleus, as well as soft tissue lesions surrounding the left auditory ossicles and causing their complete destruction.

After excluding the need for urgent neurosurgical intervention, the patient was admitted to the Neurology Clinic for further diagnostic evaluation. Neurological examination found right-sided hemianopia and mild weakness of the right upper limb. The patient received dexamethasone, 20% mannitol, and furosemide, with the head of the bed elevated to 30°.

MRI performed during hospital stay revealed three solid, homogeneous focal lesions in the left cerebral hemisphere, surrounded by Steinhoff grade II vasogenic oedema: two located adjacent to each other at the border of the peripheral parietal and occipital lobes, and one within the deep structures. The lesions showed hypointensity on T1-weighted images relative to white matter, intermediate signal on T2-weighted images, restricted diffusion on diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps, intense homogeneous contrast enhancement, and low relative cerebral blood volume (rCBV) on perfusion imaging. Susceptibility-weighted angiography (SWAN) revealed prior punctate microbleeds (Fig. 1).

Multifocal central nervous system (CNS) lymphoma was suspected, and glucocorticoids (GCs) were discontinued. The patient was scheduled for a core needle biopsy (CNB) of the left-sided parietal-occipital tumour; however, the procedure was postponed for 2 weeks due to the 6-day course of steroid therapy. As a result of the treatment used, the patient's condition improved in terms of

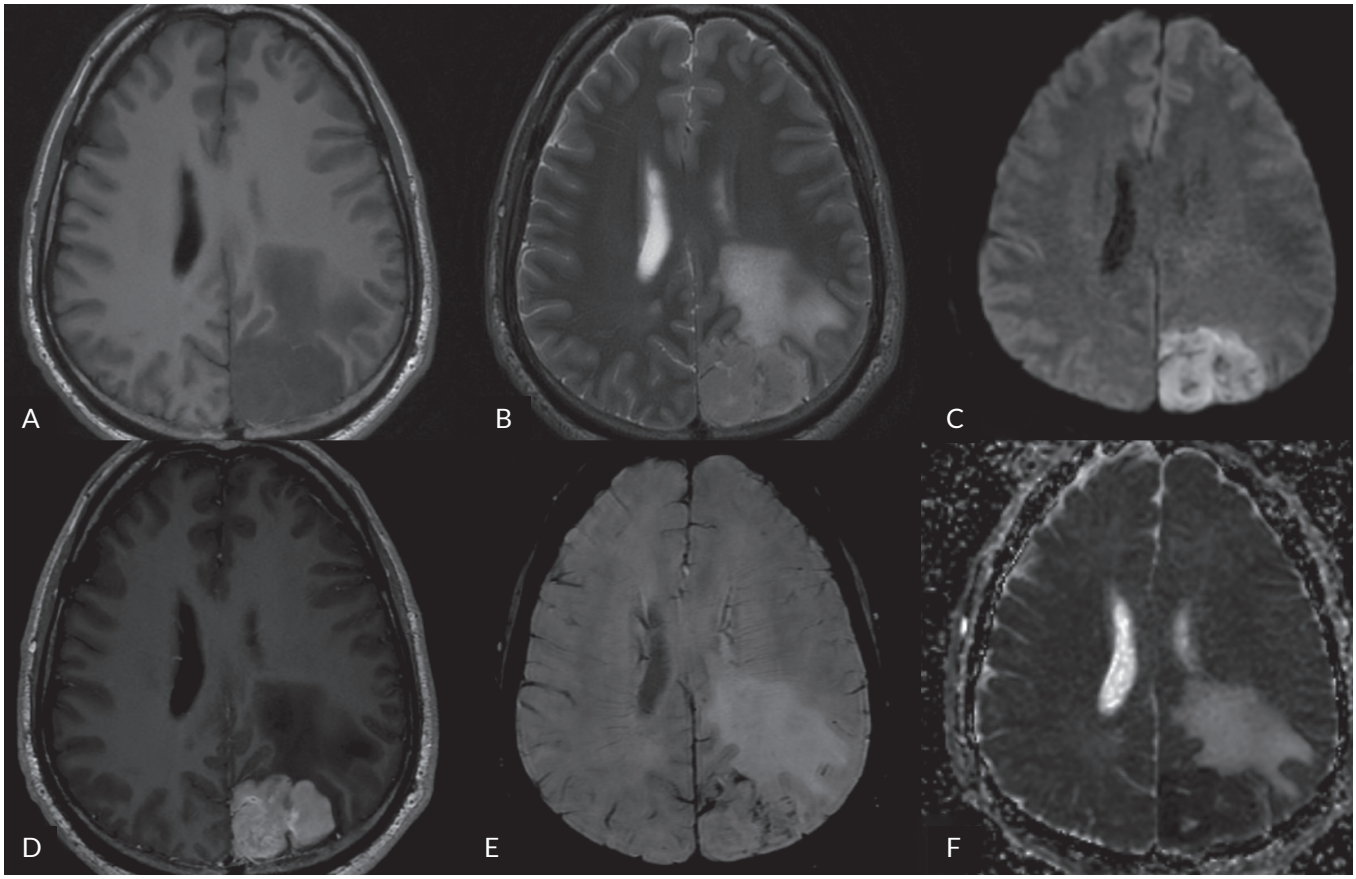

Figure 1. Selected MRI scans of the head, obtained during the patient's initial hospital stay, show two adjacent lymphomas in the left parieto-occipital region. **A.** Pre-contrast T1-weighted image. **B.** T2-weighted image. **C.** DWI image. **D.** Post-contrast T1-weighted image. E. SWAN image. F. ADC map

both subjective and focal symptoms. He was given recommendations and was discharged home in good general condition. Four days later, the patient returned to ED with morning vomiting, worsening headache, and general deterioration. A head CT demonstrated progression in the size of all focal lesions and the surrounding oedema. The patient was admitted to the Department of Neurosurgery, where a repeated head MRI confirmed disease progression (Fig. 2).

CNB was performed earlier than planned, 7 days after the last dose of dexamethasone. Histopathology revealed aggressive infiltration by primary diffuse large B-cell lymphoma of the CNS. The Ki-67 proliferation index exceeded 90%. The patient progressively deteriorated over the following days. He did not survive despite intensified anti-oedema therapy and ventricular drain implantation.

Case 2

A 71-year-old woman presented to the ophthalmology clinic with a sensation of pressure in her left eye socket and drooping of the left upper eyelid. She had a history of hypertension and rheumatoid arthritis (RA), for which she was on regular methotrexate (MTX) therapy. Ophthalmological examination revealed a hard, immobile, bulging mass over the left eyeball, accompanied by ptosis on the same side. Orbital MRI showed a solid, homogeneous, well-defined focal lesion measuring approximately 30 × 35 × 9 mm, located between the levator palpebrae superioris muscle and the left orbital roof. The mass showed marked diffusion restriction and intense contrast enhancement. Its T1-weighted signal intensity was similar to that of the extraocular muscles. There was no invasion of adjacent structures (Fig. 3 and Fig. 4). Based on these findings, orbital lymphoma was suspected. A biopsy of the lesion was performed. Histopathology revealed abundant lymphoid infiltrates, predominantly small B lymphocytes with amorphous nuclei. The Ki-67 proliferative index was 5–10%. These microscopic findings supported the diagnosis of extranodal marginal zone lymphoma (EMZL, mucosa-associated lymphoid tissue, MALT). A suspicion was raised that the lymphoma had developed as a result of the immunosuppressive effects of MTX. The patient was referred to a haematology clinic for further treatment, and showed gradual disease regression on subsequent follow-ups.

Case 3

A 33-year-old man with no significant medical history presented to ED with abdominal pain persisting for one month. Abdominal CT performed a few days earlier at another hospital had shown a small-bowel mesenteric haematoma measuring approximately 5 × 5 × 6 cm. The patient had initially refused hospitalization. Abdomi-

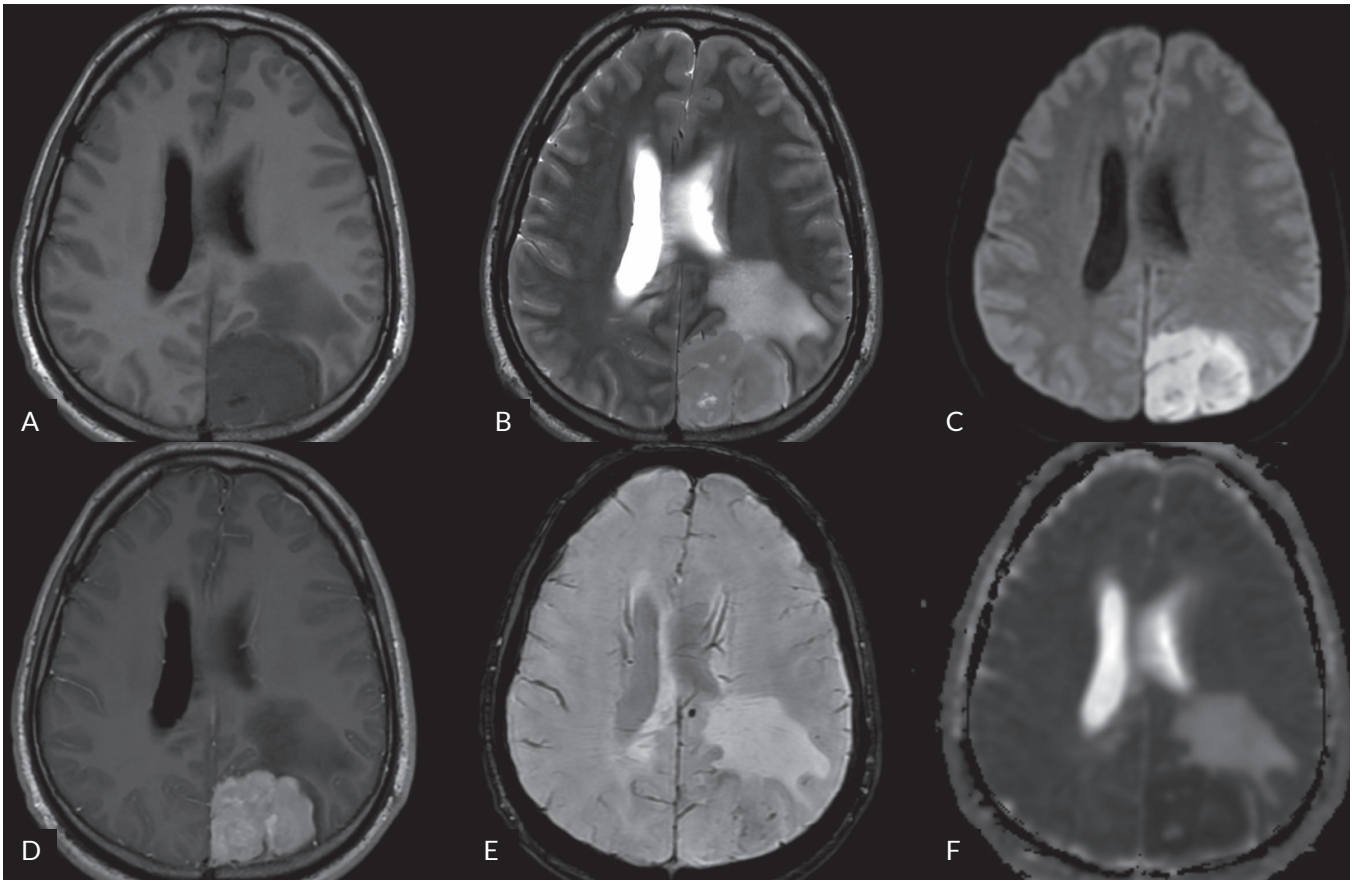

Figure 2. Selected MRI scans of the head, performed during the patient's second admission, show progression in the size of two lymphomas in the left parietal-occipital region, which had already merged into one. Peritumoral oedema is also visible, increased compared to the baseline scan. **A.** Pre-contrast T1-weighted image. **B.** T2-weighted image. **C.** DWI image. **D.** Post-contrast T1-weighted image. **E.** SWAN image. **F.** ADC map

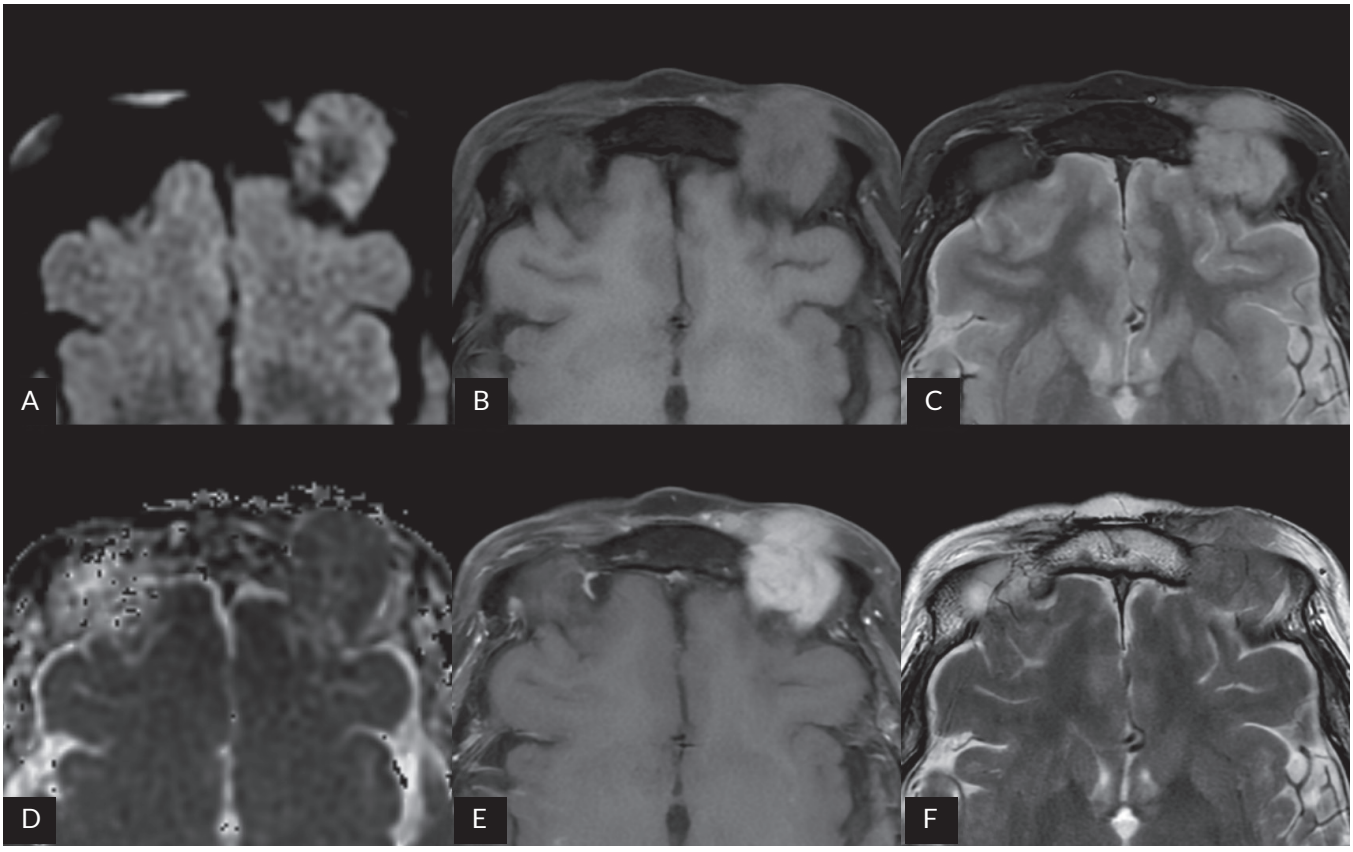

Figure 3. Selected transverse orbital MRI scans demonstrate a lymphoma at the left orbital roof. **A.** DWI image. **B.** Pre-contrast T1-weighted image with fat suppression. **C.** STIR image. **D.** ADC map. **E.** Post-contrast T1-weighted image with fat suppression. F. T2-weighted image

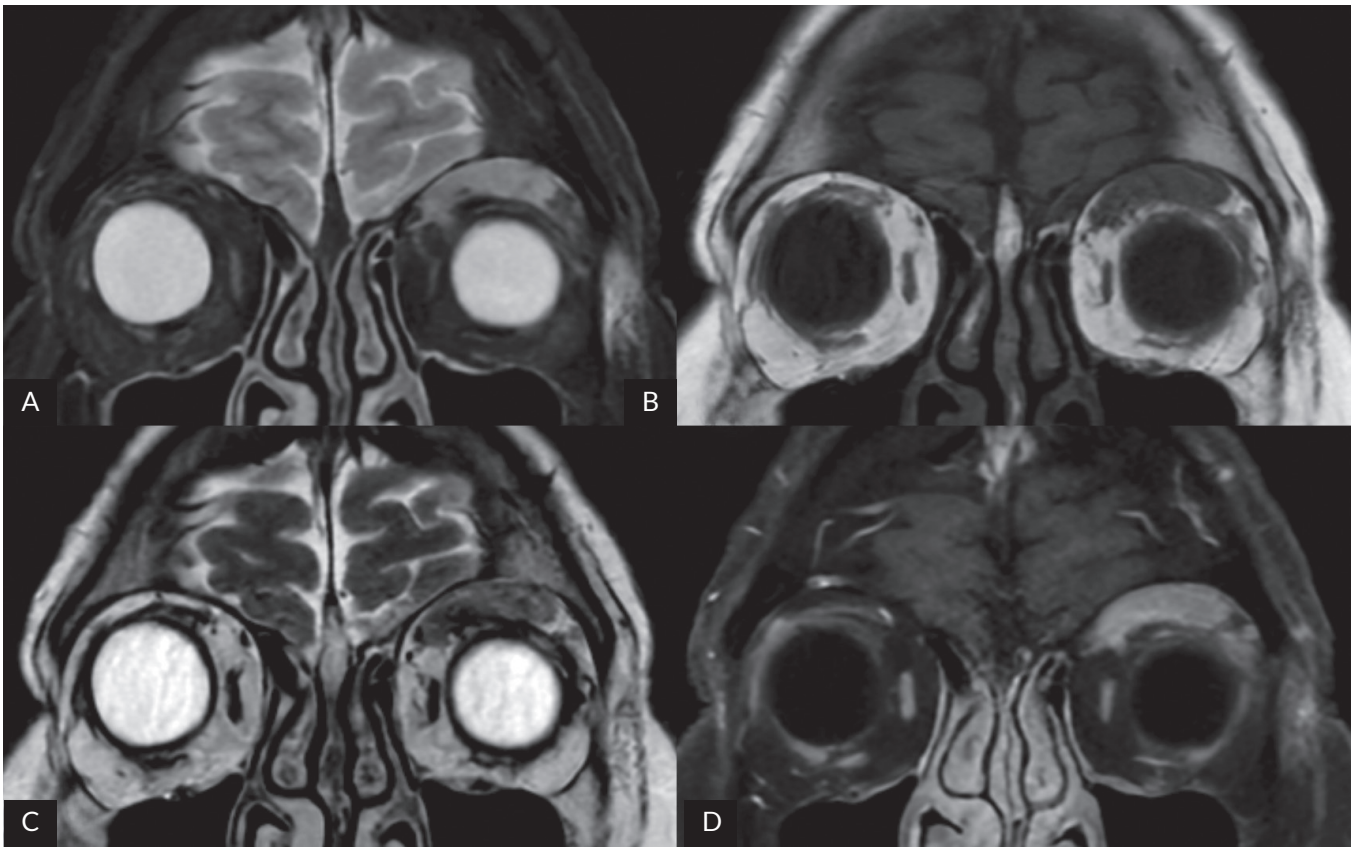

Figure 4. Selected coronal MRI scans of the orbits demonstrate a lymphoma at the roof of the left orbit. **A.** STIR image. **B.** Pre-contrast T1-weighted image without fat suppression. **C.** T2-weighted image. **D.** Post-contrast T1-weighted image with fat suppression

nal US on admission to ED identified a solid intraperitoneal tumour measuring approximately 8 × 10 cm in the left mid-abdomen. The man was admitted to the Department of General and Cancer Surgery for further diagnostic workup and treatment.

Abdominal MRI revealed several solid, relatively homogeneous tumours within the visceral adipose tissue. The largest, measuring approximately 8 × 10 cm, was located in the left small-bowel mesentery. The tumours showed restricted diffusion and marked contrast enhancement, with no cystic components visible (Fig. 5). These findings suggested disseminated lymphoma. Due to increasing pain and clinical manifestations of small-bowel obstruction, laparoscopy with biopsy was performed. Histopathology revealed monomorphic infiltrates of medium-sized lymphoid cells with scant cytoplasm, dispersed nuclear chromatin, several nucleoli, and numerous phagocytic macrophages, giving rise to the characteristic 'starry sky' pattern. The Ki-67 proliferative index was 100%, consistent with Burkitt's lymphoma.

The patient was referred to the Department of Haematology for further treatment. After two cycles of chemotherapy, imaging demonstrated a very good response: the largest lymphoma reduced by more than half, while the remaining lesions regressed completely.

Case 4

A 74-year-old woman presented to the surgical clinic with a slowly enlarging mass in her right axilla. Her sister (at 55 years) and mother (at 77 years) had both been diagnosed with lymphoma in the past. Ultrasound-guided fine-needle aspiration biopsy of the barely palpable right axillary mass was performed. Smears showed multiple small lymphocytes, but no atypical cells. A surgical biopsy of the lymph node group was subsequently performed. Histopathology, along with the overall clinical picture, confirmed the diagnosis of follicular lymphoma with a predominantly diffuse growth pattern (diffuse follicular lymphoma, dFL).

Whole-body positron emission tomography (PET) showed active lymphoproliferative involvement of the right axillary nodes and increased tracer uptake in the medullary cavity of the proximal left femoral shaft. MRI of the left thigh revealed a 15-cm focal lesion, which in some areas occupied the entire width of the femoral medullary cavity. The tumour demonstrated a homogeneous T1-weighted signal (similar to muscle) and an inhomogeneous T2-weighted and short tau inversion recovery (STIR) signal, ranging from intermediate to markedly increased, as well as intense contrast enhancement and restricted diffusion (Fig. 6).

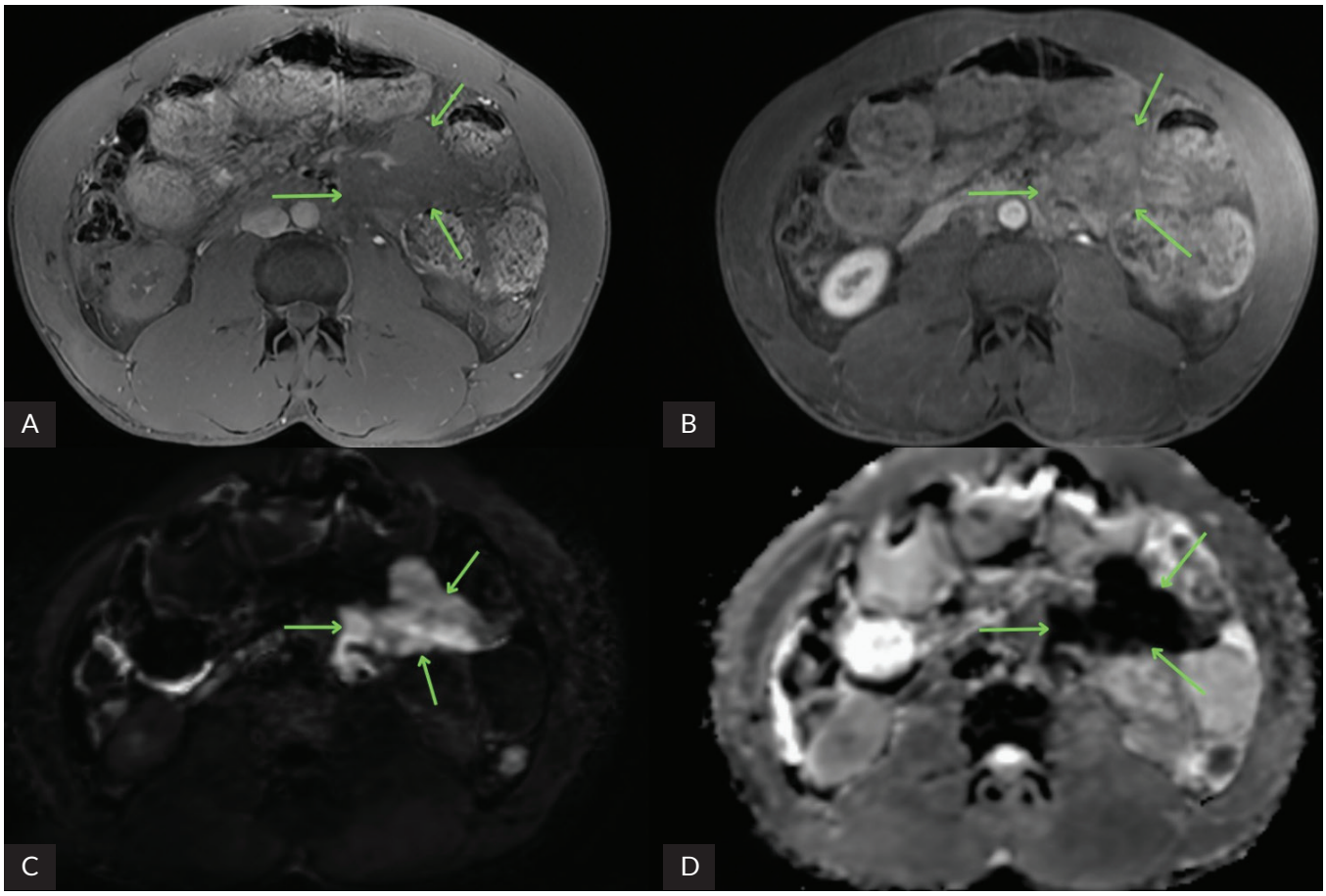

Figure 5. Selected transverse abdominal MRI scans show a lymphoma in the left mesentery of the small intestine (indicated by arrows). **A.** Pre-contrast T1-weighted image with fat suppression; **B.** Post-contrast T1-weighted image with fat suppression; **C.** DWI image; **D.** DC map

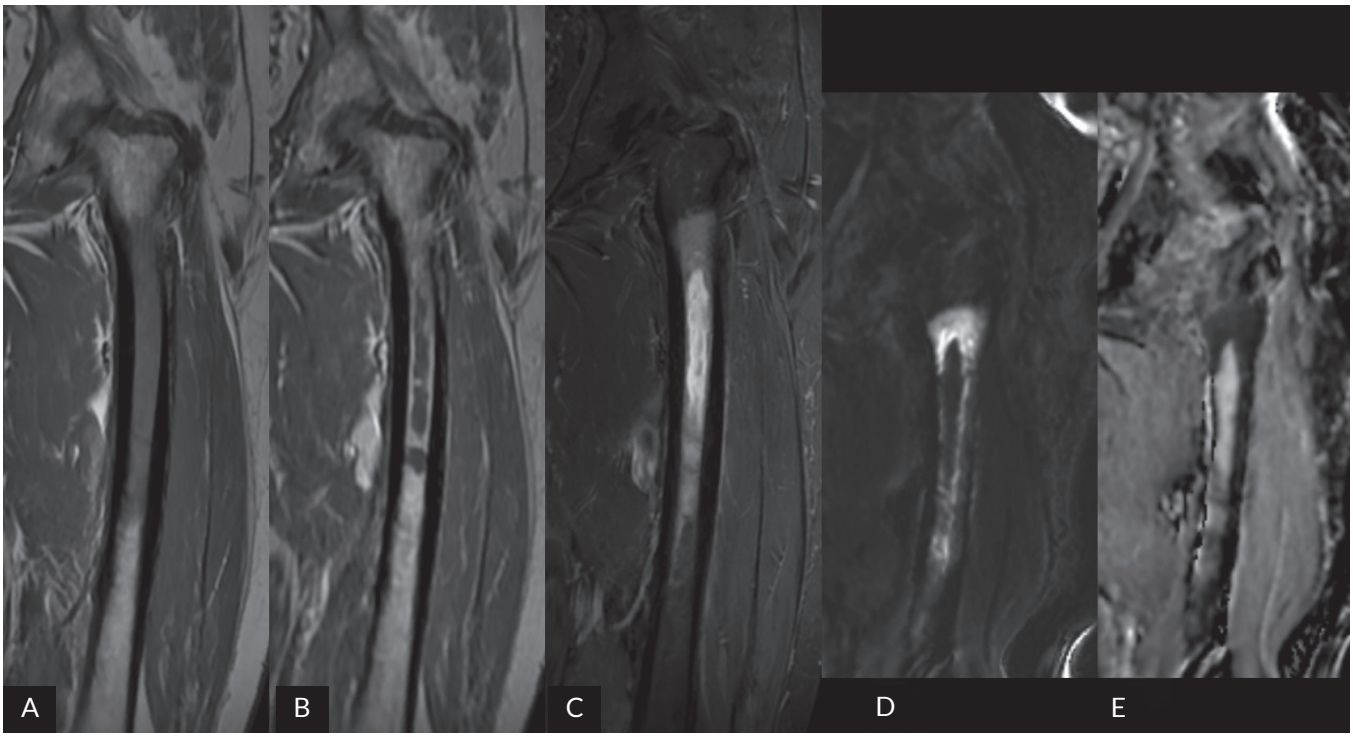

Figure 6. Selected coronal MRI scans of the left thigh show lymphoma involvement of the left femur. **A.** Pre-contrast T1-weighted image. **B.** Post-contrast T1-weighted image. **C.** STIR image. **D.** DWI image. **E.** ADC map

The overall clinical picture suggested a lymphoma involving the proximal left femur. This was confirmed by histopathological evaluation of fluid and curettings from the bone marrow cavity, which revealed cells with an immunophenotype consistent with follicular lymphoma. The patient is currently undergoing chemotherapy.

Discussion

CNS lymphomas are the second most common primary malignant brain tumours after gliomas [5]. Primary diffuse large B-cell lymphoma (DLBCL) is the predominant type, accounting for approximately 85% of cases. On MRI, these tumours typically show no cystic components, appear hypointense relative to surrounding cerebral parenchyma on T2-weighted images, demonstrate restricted diffusion, exhibit intense and relatively homogeneous contrast enhancement, and display low-to-intermediate rCBV values on perfusion imaging [6].

Historically, present or past haemorrhage on SWAN imaging strongly argued against a diagnosis of lymphoma. However, recent reports describe such findings in up to 50% of patients [7, 8].

Preoperative suspicion of lymphoma is crucial for appropriate management. Anti-oedema GC therapy should be withheld until a definitive diagnosis is reached. Immediate biopsy is recommended to promptly initiate chemotherapy rather than to proceed with tumour resection as in other suspected CNS malignancies [6, 7].

Lymphomas account for approximately 55% of all orbital malignancies [9], most commonly arising in the superolateral quadrant [10]. Extranodal marginal zone lymphoma (MALT lymphoma) represents 55–60% of orbital lymphomas [11].

On MRI, they appear as a well-defined, homogeneous, usually lobulated mass surrounding healthy intraorbital structures. They usually do not cause bone destruction. A homogeneous, intermediate T1- and T2-weighted signal is typical, with homogeneous, intense contrast enhancement. Compared to extraocular muscles, lymphomas are iso- or hypointense on T1-weighted images (due to high cell density) and hyperintense on T2-weighted images. High DWI signal and low ADC signal are valuable clues in differentiating lymphomas from inflammatory foci [12].

Burkitt lymphoma is one of the fastest-growing cancers, able to double its cell number within 24–48 hours [13]. In developed countries, its sporadic variant is the most common, accounting for less than 1% of all non-Hodgkin lymphomas in adults. The overall incidence is three cases per million people per year [4]. Patients typically present with massive abdominal masses [15]. Despite their rarity, they cannot be definitively distinguished from other lymphomas using MRI scans alone. These are solid, homogeneous masses, well demarcated from adjacent tissues. They exhibit homogeneous, fairly intense contrast enhancement [16], and restricted diffusion [14, 17].

A thorough evaluation of bone marrow is of paramount importance for staging, as bone marrow involvement (BMI), which is found in 5–15% of patients with Hodgkin's lymphoma (HL) and in 20–40% of patients with non-Hodgkin's lymphoma (NHL), by definition indicates stage

IV disease [1–4]. This fact has both therapeutic and prognostic implications [5, 6].

Lymphoma infiltrates the bone marrow, forming channels in the cancellous bone and penetrating between fibrous areas. MRI is the most sensitive tool for detecting these tumours. DWI images allow for assessing bone marrow infiltration at an earlier stage than other sequences. All MRI sequences show abnormal bone marrow signal. T1-weighted images typically exhibit uniformly low signal intensity, isointense relative to muscle. Greater signal variability is seen on STIR images, which demonstrate areas of high, intermediate, or low intensity [18]. Other notable MRI features suggestive of bone lymphoma include concomitant involvement of surrounding soft tissues with minimal destruction of the cortical bone, marked oedema, absence of necrosis or bleeding, and intense enhancement following intravenous contrast [19].

Normal, hypercellular lymphatic organs (e.g., spleen, lymph nodes, and tonsils) physiologically demonstrate increased DWI signal and decreased ADC signal compared to adjacent tissues [20, 21] (Fig. 7). Therefore, simply identifying an area or structure meeting these two criteria does not always constitute a basis for suspecting lymphoma. A thorough knowledge of anatomy and histology is crucial in this case to avoid misinterpretation of a normal image as a pathological one and, consequently,

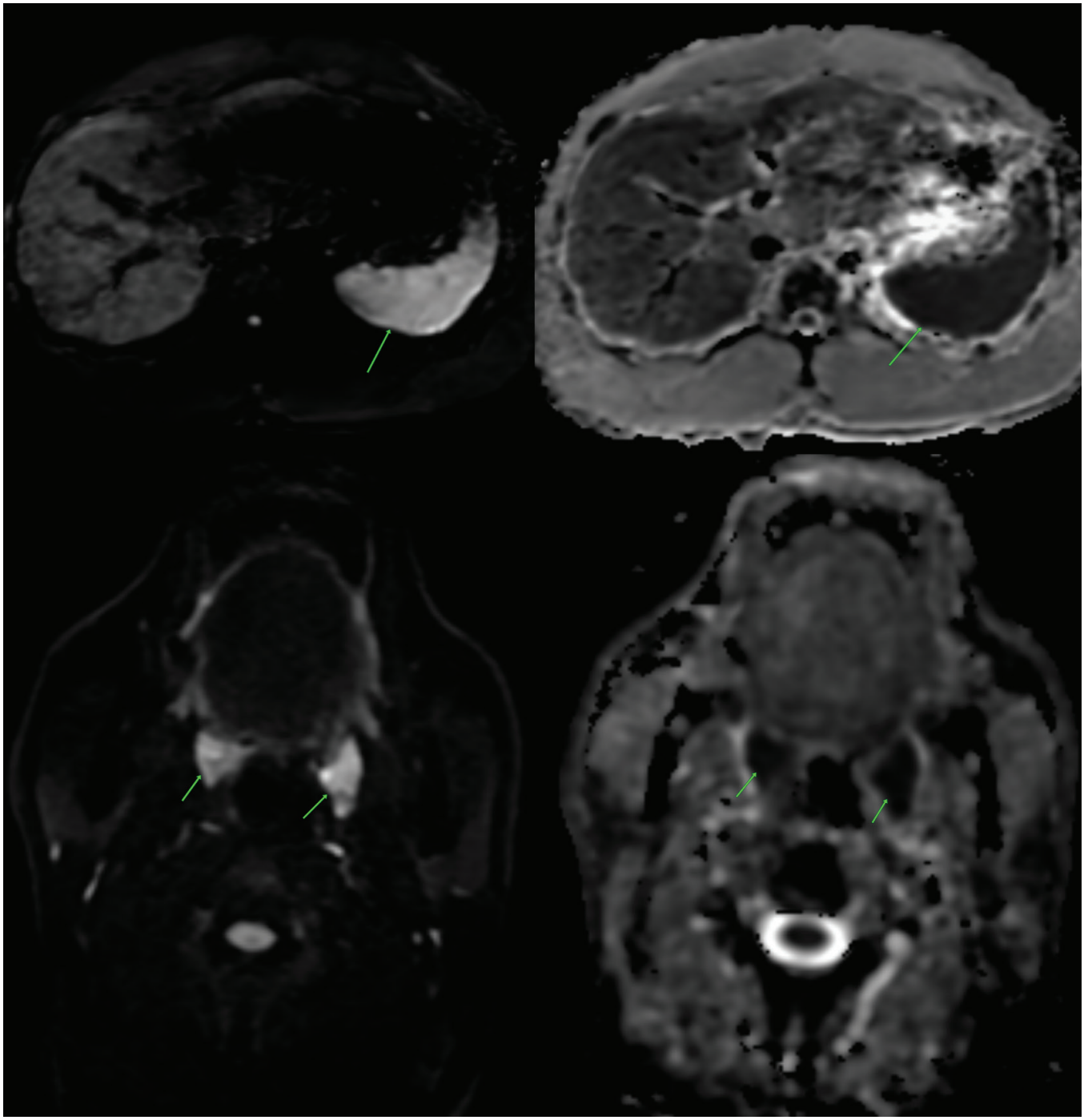

Figure 7. Images show physiological homogeneous diffusion restriction on DWI images and ADC map in normal spleen (marked with arrows at the top) and palatine tonsils (marked with arrows at the bottom)

exposing patients to unnecessary further diagnostic workup and anxiety.

Conclusions

Despite their diverse clinical presentation, lymphomas, regardless of their location, share several common MRI features, such as homogeneous T1-weighted signal, the absence of a fluid component within the tumour, limited diffusion, and intense, homogeneous contrast enhancement. However, it is important to remember that none of these features, or even their coexistence, is pathognomonic for lymphoma. Correct MRI interpretation and correlation with the clinical presentation can shorten the diagnostic path for patients with lymphoma and allow for earlier initiation of targeted therapy.

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PREVALENCE OF CARDIOVASCULAR DISEASE RISK FACTORS AMONG MILITARY SENIOR OFFICERS – AN EPIDEMIOLOGICAL ANALYSIS AND PREVENTIVE IMPLICATIONS

Występowanie czynników ryzyka chorób sercowo-naczyniowych wśród kierowniczej kadry wojska – analiza epidemiologiczna i implikacje profilaktyczne

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Abstract

Introduction and objective: Cardiovascular diseases remain the leading cause of death worldwide, including in Poland, where they account for 35% of total mortality. A high prevalence of risk factors such as hypertension, hypercholesterolemia, obesity, and chronic stress is particularly evident among military personnel. Due to the nature of their work, senior military officers may be especially vulnerable to these health threats. The aim of the study was to assess cardiovascular risk factors among senior military officers and identify potential preventive measures to reduce the risk of cardiovascular events. **Materials and methods:** A retrospective analysis of medical records of military personnel, including laboratory findings, blood pressure measurements, BMI, and a health questionnaire. The study group consisted of 34 officers (100% male) aged 40–58 years (mean 51 ± 4.2 years). **Results:** Hypertension was diagnosed in 54% of participants, with 23% having stage II or III hypertension. Overweight or obesity (BMI ≥25 kg/m^2) was present in 83% of participants. Hypercholesterolemia (LDL >115 mg/dL) was found in 65%, while elevated non-HDL cholesterol levels (>130 mg/dL) in 68% of participants. A high or very high 10-year cardiovascular event risk (based on SCORE2) was observed in 62% of officers. **Conclusions:** Senior military officers exhibit a high prevalence of cardiovascular risk factors, including hypertension, obesity, and lipid disorders. The findings highlight the need to implement preventive programs, including health education, stress reduction strategies, and lifestyle modification support, which may contribute to improved health and operational readiness of the armed forces.

Streszczenie

Wprowadzenie i cel: Choroby układu sercowo-naczyniowego pozostają główną przyczyną zgonów na świecie, także w Polsce, gdzie stanowią 35% całkowitej śmiertelności. Wysoka częstość występowania czynników ryzyka, takich jak nadciśnienie tętnicze, hipercholesterolemia, otyłość i przewlekły stres, jest szczególnie widoczna w populacji żołnierzy. Kadra kierownicza wojska, z uwagi na charakter pracy, może być szczególnie narażona na te zagrożenia. Celem badania była ocena czynników ryzyka sercowo-naczyniowego wśród kierowniczej kadry wojska oraz określenie potencjalnych działań profilaktycznych zmniejszających ryzyko incydentów sercowo-naczyniowych. **Materiał i metody:** Przeprowadzono retrospektywną analizę danych z dokumentacji medycznej żołnierzy, obejmującą wyniki badań laboratoryjnych, pomiary ciśnienia tętniczego, BMI oraz kwestionariusz zdrowotny. Badana grupa liczyła 34 oficerów (100% mężczyzn) w wieku 40–58 lat (średnia 51 ± 4,2 roku). **Wyniki:** Nadciśnienie tętnicze stwierdzono u 54% badanych, z czego 23% miało II lub III stopień tego schorzenia. Nadwagę lub otyłość (BMI ≥25 kg/m^2) stwierdzono u 83% uczestników. Hipercholesterolemię (>115 mg/dl LDL) rozpoznano u 65%, a 68% miało podwyższony poziom cholesterolu nie-HDL (>130 mg/dl). Wysokie lub bardzo wysokie 10-letnie r yzyko incydentu sercowo-naczyniowego (według SCORE2) występowało u 62% oficerów. **Wnioski:** Kadra kierownicza wojska charakteryzuje się wysokim rozpowszechnieniem czynników ryzyka sercowo-naczyniowego, w tym nadciśnienia tętniczego, otyłości i zaburzeń lipidowych. Wyniki wskazują na konieczność wdrożenia programów profilaktycznych, obejmujących edukację zdrowotną, strategie redukcji stresu oraz wsparcie w zakresie zmiany stylu życia, co może przyczynić się do poprawy zdrowia i zdolności operacyjnej sił zbrojnych.

Keywords: obesity; cardiovascular risk factors; military epidemiology; health prevention; hypercholesterolemia

Słowa kluczowe: otyłość; czynniki ryzyka sercowo-naczyniowego; epidemiologia wojskowa; profilaktyka zdrowotna; hipercholesterolemia

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Introduction

Cardiovascular diseases (CVDs) still remain the leading cause of death worldwide, with their prevalence in Poland being particularly high. According to data from the Central Statistical Office, CVDs accounted for 35% of all deaths in 2020–2021, surpassing cancer at 20% [1, 2]. The most significant scientifically proven CVD risk factors include hypercholesterolemia, chronic stress, smoking, hypertension (HT), and obesity, all of which are prevalent in the Polish population [3].

Similar trends are seen among Polish military personnel, where CVD risk factors are alarmingly prevalent. The MIL-SCORE study, which was conducted among 6,500 soldiers, revealed high rates of HT, hypercholesterolemia, and obesity [4]. The European Society of Cardiology (ESC) classifies Poland as a high-risk country for CVD, with a mortality rate nearly twice the European Union average [5, 6].

The leadership staff are a particularly vulnerable military group. Military commanders are exposed to high levels of chronic stress, which, combined with HT, lipid disorders, and obesity, creates a serious health risk. Studies have shown that more than 50% of officers have abnormal blood pressure, and 62% of them are at high or very high 10-year cardiovascular risk. The health of this group is essential for the functioning of the armed forces and maintaining operational readiness.

The aim of this study was to comprehensively assess CV risk factors among senior military officers, identify key threats, and develop recommendations for preventive programmes, the implementation of which may help reduce the prevalence of CV events and improve both long-term health and operational capacity of the armed forces.

Methods

The study was a retrospective analysis of medical records of Polish soldiers holding leadership positions. Due to the specific nature of their duties, this group is particularly exposed to chronic occupational stress.

Data were collected during a preventive campaign conducted among volunteers at the Military Institute of Medicine in 2023. The inclusion criteria were as follows: holding a leadership position in military structures and providing informed consent to participate.

Participants underwent a comprehensive health assessment, including:

- standard laboratory tests, including lipid profile (total cholesterol, LDL, HDL, triglycerides) and fasting glucose;
- structured questionnaire survey, including medical and family history, smoking status;
- anthropometric measurements, including height, weight, and BMI;
- haemodynamic measurements, including blood pressure (ESC guidelines).

The data were analysed statistically, comparing the results among participants with varying levels of CV risk.

Results

The study group included men aged 40–58 years (mean: 51 ± 4.2 years) (Tab. 1). Medical history showed a prior diagnosis of HT in 35.3% (*n* = 12), type 2 diabetes mellitus (T2DM) in 2.9% (*n* = 1), and hypercholesterolemia in 11.8% (*n* = 4) of subjects. Family history of CVD, which was reported by 26% of participants, represented an important component of the study. Documented cases included coronary heart disease, cerebrovascular incidents, and HT among first-degree relatives.

Analysis of blood pressure measurements taken during the study visit showed abnormal values in more than 50% of participants (Fig. 1, Fig. 2). When stratifying the observed haemodynamic disturbances, values consistent with grade III HT (≥180/110 mmHg) were found in 1 participant, while five participants presented with values classified as grade II HT (160–179/100–109 mmHg) as per ESC guidelines (Tab. 2) [7].

The analysis of anthropometric parameters showed normal body weight (BMI 18.5–24.9 kg/m²) in only 14.7% of participants (*n* = 5) (Tab. 3). The distribution of abnormal BMI values in the study population was as follows: overweight (BMI 25.0–29.9 kg/m²) in 50% of participants (*n* = 17), obesity class I (BMI 30.0–34.9 kg/m²) in 23% (*n* = 8), and obesity class II (BMI 35.0–39.9 kg/m²) in 10% (n = 3). The observed distribution of body weight disorders indicates a high prevalence of overweight and obesity (important risk factors for CVD) in the study group.

Table 1. Characteristic of the study group

Parameter	*n*	%
Gender (male/female)	34/0	100/0
Mean age (years)	51 (40–58)	-
History of hypertension	12	35
History of diabetes mellitus	1	3
History of hypercholesterolemia	4	12
Positive family history of cardiovascular disease	9	26

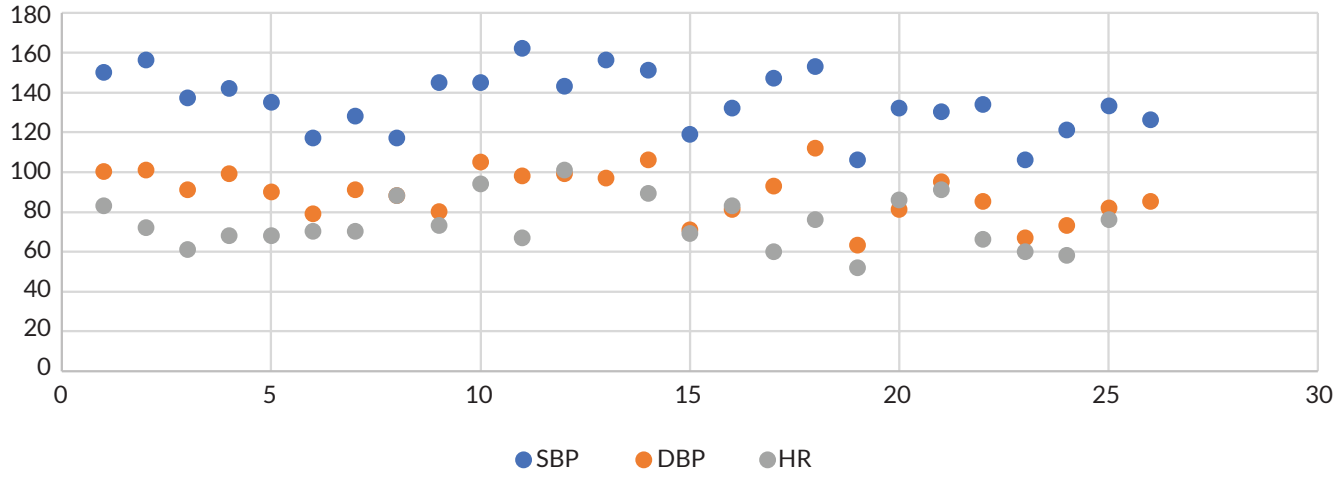

Figure. 1. Blood pressure and heart rate at the visit. SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate

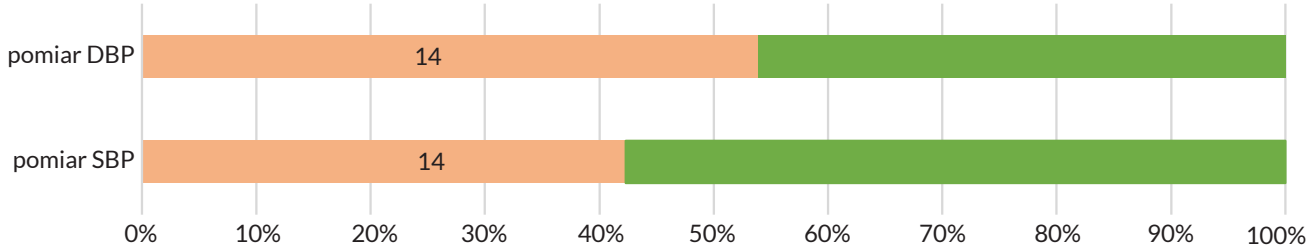

Figure. 2. Number of abnormal BP values at the visit . DBP – diastolic blood pressure; SBP – systolic blood pressure

The analysis of nicotine dependence in the study population showed a relatively low prevalence of this behavioural CVD risk factor (11.8%, *n* = 4).

As part of the research protocol, all participants underwent a comprehensive assessment of lipid and carbohydrate metabolism parameters, including fasting glucose (Tab. 4). The analysis showed normal biochemical parameters in only 11.8% of participants (*n* = 4). Lipid profiles were evaluated using individualized reference values, considering each participant's cardiovascular risk stratification [5].

A detailed analysis of lipid parameters revealed significant abnormalities in the study population. LDL cholesterol >115 mg/dL (low CV risk threshold) was observed in 65% of participants (*n* = 22). Furthermore, 68% of participants (*n* = 23) had elevated non-HDL cholesterol

Table 2. Blood pressure at the visit

Parameter	Value
Mean systolic blood pressure	135,5 ± 14,97 mmHg
Mean diastolic blood pressure	88,9 ± 12,2 mmHg

Blood pressure classification	*n*	% (*n* = 26)
Systolic BP ≥140 mmHg	11	42
Diastolic BP ≥90 mmHg	14	54
Grade I hypertension	8	31
Grade II hypertension	5	19
Grade III hypertension	1	4

Table 3. BMI measurements in the study group of soldiers

BMI category	BMI range (kg/m²)	Number of people (n = 30)	%
Normal	18,5–24,99	5	17
Overweight	25–29,99	15	50
Grade I obesity	30–34,99	7	23
Grade II obesity	35–39,99	3	10
BMI – body mass index			

Table 4. Laboratory findings

Parameter	Value	*n*	%
Number of subjects with normal lipid profile and fasting glucose		4	12
LDL (mg/dL)	<55	2	6
	55–69	1	3
	70–99	3	9
	100–115	6	18
	>115	22	65
Mean LDL (mg/dL)	**131,2**		
Non-HDL (mg/dL)	<85	3	9
	85–99	3	9
	100–129	5	15
	≥130	23	68
Mean non-HDL (mg/dL)	**154,1**		
Triglycerides (TGs, mg/dL)	<150	23	67
	150–199	6	18
	200–499	4	12
	>500	1	3
Mean TGs (mg/dL)	**156,6**		
Fasting glucose (mg/dL)	<100	27	79
	100–125	6	18
	126–199	1	3
	≥200	0	0
Mean glucose (mg/dL)	94,2		

LDL – low density lipoprotein; HDL – high density lipoprotein, TG – triglycerides

(>130 mg/dL), exceeding the reference threshold for moderate CV risk.

Analysis of the overall 10-year risk of CV events (fatal and nonfatal), performed using the updated SCORE2 algorithms, revealed a concerning risk profile in the study population. Only 38% of participants (*n* = 13) were classified as low or moderate CV risk (Tab. 5). The remaining 62% of participants (*n* = 21) were identified as having a high or very high 10-year risk of CV events [5].

Discussion

The epidemiological analysis showed a significant prevalence of both modifiable and non-modifiable cardiovascular risk factors in the study group of military officers. Of particular note is that, due to the specific nature of their duties, this group is inherently exposed to chronic psychological stress, a recognized independent risk factor for CVD. The accumulation of chronic occupational stress, combined with additional risk factors identified in this study, may accelerate atherogenesis and increase susceptibility to CV events in this professional group. These observations highlight the need to implement dedicated preventive programmes that encompass interventions targeting both classic risk factors and occupational stress management strategies.

A detailed analysis of haemodynamic parameters revealed a significant discrepancy between the declared and actual prevalence of HT. While 35% of respondents reported a history of HT in the health questionnaire (Tab. 1), abnormal blood pressure (BP) was observed at the study visit in 54% of participants, with 23% exhibiting values consistent with grade II and III HT (Tab. 2). Comparison of the obtained results with the MIL-SCORE findings indicates a lower prevalence of HT in the study cohort compared to the corresponding age categories: 63.5% in the 41–50 age group and 68% in the >50 age group [4]. From a broader international perspective, the prevalence of HT in the Polish Armed Forces is notably higher than in allied armies. HT was found in 5% of soldiers in the US Armed Forces and 2% of soldiers in the French Army, despite the latter's slightly older average age than in the MIL-SCORE group [8, 9].

Table 5. 10-year risk of CVD (fatal and non-fatal) calculated in the study group according to Score2

Age group	Low-to-moderate risk of CVD (<2.5%; <5%)	High risk of CVD (2.5–7.5%; 5–10%)	Very high risk of CVD (≥7.5%, ≥10%)
<50 years	5 (42%)	2 (17%)	1 (8%)
50–69 years	5 (50%)	10 (45%)	2 (9%)
Total	10 (38%)	12 (46%)	4 (15%)

CVD – cardiovascular diseases, Score2 – tools for assessing 10-year risk of cardiovascular event

Analysis of anthropometric parameters demonstrated a disturbing body weight distribution in the study population (Tab. 3). Only 17% of participants had a healthy weight, while 50% were overweight and 33% were obese (mean BMI: 28.6 kg/m^2). The prevalence of obesity in this group is comparable to that in the general U.S. population (33.6%), but significantly exceeds the rates reported in the U.S. Armed Forces (18%), the MIL-SCORE cohort (14.1%), and the French Army (10%).

Assessment of metabolic parameters revealed normal lipid profile and fasting blood glucose in only 12% of participants, which indicates a high risk of atherosclerosis and cardiovascular complications (Tab. 4). Detailed analysis of the lipid profile revealed elevated LDL cholesterol (>115 mg/dL) in 65%, hypertriglyceridemia (>150 mg/dL) in 33%, and elevated non-HDL cholesterol levels (>130 mg/dL) in 68% of participants.

A positive aspect is the relatively low prevalence of nicotine dependence in the study population (approximately 10%), which is much lower compared to 46.2% reported in the MIL-SCORE study and rates observed in other military formations (USA: 19.9%, Germany: 25%). This percentage is only 10.5% among Polish pilots [10]. According to Centre for Public Opinion Research data from 2019, the percentage of smokers in the general population decreased from 31% to 26% (including from 40% to 31% among men) between 2012 and 2019 [11]. Furthermore, the prevalence of smoking is correlated with the level of education, with 33% of smokers declaring vocational education, and only 17% having higher education. Smoking was reported by 15% of specialists and management staff. These trends align with the nationwide decline in nicotine dependence, particularly evident among individuals with higher education and those in management positions.

Epidemiological analysis of NATO military health reports also shows significant differences in the prevalence of CV risk factors between pilots and other soldiers [10, 12–14]. The prevalence of overweight and obesity (40.8%) is lower in military pilots compared to the overall military population, where it exceeds 50%. Likewise, HT is less common among pilots (14.7%) compared to other soldiers (29.5%). A different pattern is seen with hypercholesterolemia, which affects 53.9% of pilots compared to only 24.4% of the rest of the military population. Smoking rates are similar in both groups, with a slight upward trend among pilots (31.7%).

Analysing these differences, several factors can be identified that explain this distribution and should be considered when developing recommendations for the conditions and organization of a cardiac prevention model in the military. Pilots undergo more rigorous health screening and regular, detailed examinations, which enable earlier diagnosis and treatment of metabolic disorders. However, their work is associated with high stress levels, which may contribute to unfavourable changes in lipid profiles and an increased risk of hypercholesterolemia. Age and experience are also important differentiators, with older pilots (over 45–50 years) being less likely to show accumulation of risk factors, which may reflect greater health awareness and more effective preventive strategies [13, 14].

Researchers at the Institute of Aerospace Medicine in Cologne (Germany) also assessed the overall CV risk among military pilots using the PROCAM score adapted to the German population. The results showed that the overall CV risk was lower in this group compared to the general German population, with high (≥5%) and very high (≥10%) risk observed in 0.8% and 0.1% of participants, respectively [11]. This risk was also significantly lower than that observed in the Polish military. Similar findings were reported in studies involving NATO air personnel, highlighting the effectiveness of dedicated educational programme and health monitoring in reducing CV risk.

SCORE2 risk tables, developed for high-risk populations, were used to assess the overall risk of CV events among the surveyed officers. About 28% of participants were classified as low or moderate risk (<5%), 46% as high risk (≥5%), and 15% as very high risk (≥10%) (Tab. 5). For comparison, 93.5%, 5.5%, and 1% of soldiers from the same age group, assessed with the PolSCORE 2015 tool as part of the MIL-SCORE study, were classified as low-to-moderate, high, and very high risk, respectively [4].

Study limitations

This was a retrospective analysis of medical records from preventive health screenings conducted among volunteers. Participants were officers holding leadership positions, with a mean age of 51 years. Therefore, the results are applicable only to this group and should not be generalized to the entire military population.

The incompleteness of data in the medical records and the lack of standardization for blood pressure measurements (e.g., missing information on devices used and measurement conditions), which could have affected result accuracy was a significant limitation of the study. Additionally, the relatively small study group limits the generalizability of the findings.

Body composition was assessed using the BMI, which, although widely used in medicine, not always accurately differentiates between excess fat and increased muscle mass. This limitation is particularly relevant for physically active individuals, as confirmed by previous analyses from the Military Institute of Aviation Medicine [10].

Conclusions

The study provided valuable public health data on the prevalence of cardiovascular risk factors in a selected group of Polish officers in leadership positions.

Our findings highlight the need to implement comprehensive preventive programmes in the Armed Forces. Regular screenings, increasing personnel awareness of healthy lifestyle principles, fostering habit development, and maintaining motivation to apply these habits during military service are essential. Tailoring dietary and training interventions to the specific professional requirements of officers is equally important. Preventive measures should include individually tailored nutritional strategies, appropriately planned physical activity, and, when justified, pharmacological management of metabolic disorders.

The data emphasize the need for further prospective studies to evaluate the effectiveness of implemented preventive interventions and their impact on long-term prognosis in this professional group. Analyses should include indicators such as changes in lipid profiles, blood pressure stabilisation, weight reduction, and improved physical performance. At the same time, given the benefits of technological advancements, the development and implementation of ICT tools for collecting, processing, and analysing behavioural, metabolic, and environmental health risk factors appear fully justified. Such solutions can support education, promote a healthy lifestyle, and monitor health status as well as adherence to health-oriented recommendations. Incorporating stress biomarkers and subjective assessments of quality of life could provide a more accurate evaluation of the efficacy of preventive measures.

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CONTRIBUTION TO THE HISTORY OF THE HEALTH CENTER OF THE STATE ARMAMENT FACTORY – WEAPONS FACTORY IN RADOM (1925–1942)

Przyczynek do dziejów Ośrodka Zdrowia Państwowej Wytwórni Uzbrojenia – Fabryki Broni w Radomiu (1925–1942)

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Abstract

A number of monographs and studies have been written so far about the Radom State Armament Factory – Weapons Factory, which was established in 1925, but none of these works has comprehensively addressed the subject of health support for the factory's employees. Also, no original source documentation has survived that would allow for the reconstruction of the staff composition, the location of the Center within the factory premises or the structure of injuries and illnesses. To address this gap, research was conducted in the Radom State Archives. The requested information, however, is not contained in the factory's files. Isolated details can only be found by reviewing thematically related folders on professional medical personnel, other medical institutions or in the order books of the Director of the Radom Social Insurance Company from the World War II period. The causal nature of the work is evident from the premises outlined above. This study, which takes a closer look at the history of the Armament Factory Health Center, which should be considered a local community, contributes to a deeper understanding of one of the aspects of military health care.

Streszczenie

Na temat powstałej w 1925 roku w Radomiu Państwowej Wytwórni Uzbrojenia – Fabryki Broni napisano dotychczas wiele monografii i opracowań, jednak żadna z tych prac nie podjęła tematu zabezpieczenia zdrowotnego pracowników zakładu w sposób kompleksowy. Nie zachowała się również żadna oryginalna dokumentacja źródłowa, która pozwoliłaby odtworzyć skład personelu, lokaliz ację Ośrodka na terenie fabryki czy strukturę urazów i zachorowań. Aby wypełnić tę lukę, przeprowadzono kwerendę w Archiwum Państwowym w Radomiu. Poszukiwanych informacji nie odnaleziono jednak w aktach dotyczących samej fabryki. Pojedyncze dane można znaleźć dopiero przeglądając teczki tematycznie zbieżne, dotyczące fachowego personelu medycznego, innych placówek medycznych czy też księgi Zarządzeń Dyrektora Ubezpieczalni Społecznej w Radomiu z okresu II wojny światowej. Z powyższych przesłanek wynika przyczynkarski charakter pracy. Opracowanie niniejsze, przybliżając dzieje lokalnej społeczności, jaką był Ośrodek Zdrowia Fabryki Broni, staje się przyczynkiem do lepszego poznania jednego z aspektów wojskowej służby zdrowia.

Keywords: World War II; Radom; health center; weapons factory

Słowa kluczowe: II wojna światowa; Radom; ośrodek zdrowia; fabryka broni

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Introduction

Little information has survived regarding the organization of premises and staffing of health care at the State Armament Factory – Arms Factory in Radom (PWU-FB) during the operation of its Health Center between 1925 and 1942. A brochure published in 1975 mentioned only briefly that a *small outpatient clinic was located in the administration building*, without specifying the number of rooms or staff. The brochure further states: *It was not until 1935 when funds from employee contributions (5%) to the Health Fund were used to adapt the building at 10 Słoneczna Street (now 1905 Street) for healthcare purposes, with Dr. Franciszek Waga appointed as its head. These funds were also used for the construction of a hospital on Narutowicza Street, opened in 1937 as the central facility for related institutions in Radom, Pionki, and Skarżysko. The hospital comprised three departments—internal medicine, surgery, and gynaecology—and four outpatient clinics: surgery, otolaryngology, ophthalmology, and gynaecology. At the time, it was the most modern and best-equipped hospital in Radom. The facility was taken over by the Polish Army in 1945, and it came under the authority of the municipal health service in 1950* [1]. However, the hospital on Narutowicza Street was not affiliated with the Armament Factory or related armaments plants. Its establishment, as the Garrison Hospital, was ordered on August 1, 1937, by directive of the General Command Department 3625 (Organizational, Secret) issued by the Minister of Military Affairs [2]. The hospital building, completed in 1937, was officially opened on Narutowicza Street on April 25, 1938 [3]. Similarly, limited data regarding the organization of health care at the facility are available in other sources [4].

Let us now return to the PWU-FB Health Center. According to the authors of the 1975 study, a separate building of the facility was opened in 1935. In the same year, the local press reported: *'Four major war industry plants, i.e. the gunpowder factory in Pionki, the weapons factory in Radom, and the weapon and rocket artillery factories in Skarżysko-Kamienna, will be excluded from the Social Insurance Fund as of April 1. These factories were to establish their own insurance system for illness and incapacity for work, and independently provide pension insurance for white- and blue-collar workers, accident insurance, and contributions to the Labor Fund. As a result, the Radom Social Insurance Institution lost one-third of its insured population and approximately 40% of its total revenue* [5].

The building at 10 Słoneczna Street has not survived, and no archival photographs of Radom have been found showing it in its entirety. The only known image, discovered in a German soldier's album and dated September 1939, shows merely a fragment of the structure [6].

This photograph, taken from the factory side along the arched internal road where cannons were displayed, shows four German soldiers. The wall of the Health Center outbuilding can be seen behind the second soldier from the right, appearing as if it had been added to the main Armament Factory building (marked as no. 54 on the attached plan). Above the head of the second soldier from the left, a fragment of a tall gable-roofed structure can be seen—this is the Health Center building at 10 Słoneczna Street (marked 53). Above the head of the first soldier on the left, a fragment of the building at 8 Słoneczna Street (marked 52) is visible (Fig. 1, Fig. 2). The Armament Factory plan is preserved in the collections of the State Archives in Radom (Fig. 3) [7]. Dr. Zygmunt Ehrlich (1885–1933) was the first head of the Center. He organized the outpatient clinic in the administration building and later earned the recognition of the facility's employees for his conscientiousness and dedication to patients, serving at the Health Center from 1927 to 1933. In 1927, his activities at the Armament Factory were criticized in a paper entitled "Mr. Dr. Ehrlich at 'Work'" published in *Życie Robotnicze* issued by the Radom Polish Socialist Party. The doctor's response was published in the daily *Słowo* (No. 231, October 7, 1928). In 1927, Dr. Ehrlich was also engaged in social activities; his name appears among those helping poor children as part of "Ochrona III" at 17 Skaryszewska Street, organized by the Charitable Society.

In February 1933, Dr. Ehrlich donated an X-ray room to the Railway Technical School. The local press reported: '*In these days, the State Railway Technical School received a generous gift from Dr. Zygmunt Ehrlich in the form of a complete X-ray room, worth several thousand PLN. The gift includes, among others, a mercury interrupter, induction coils, a marble switchboard, capacitors, a screen, and a number of vacuum tubes. The significance of this donation highlights the generosity of the donor* [8].

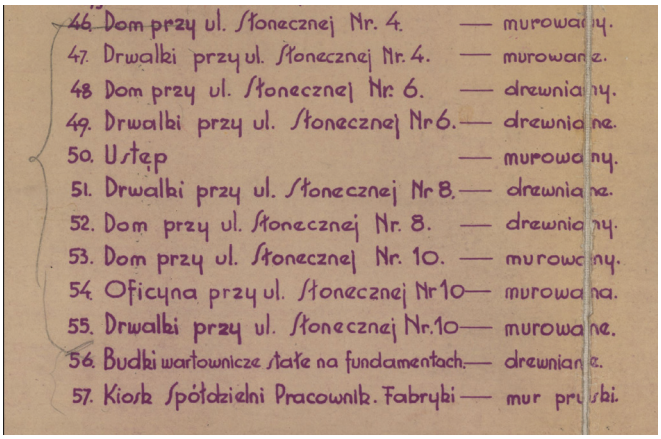
46. Dom przy ul. Słonecznej Nr. 4. — murowany.
47. Drwalki przy ul. Słonecznej Nr. 4. — murowane.
48 Dom przy ul. Słonecznej Nr. 6. — drewniany.
49. Drwalki przy ul. Słonecznej Nr 6. — drewniane.
50. Ustęp — murowany.
51. Drwalki przy ul. Słonecznej Nr 8. — drewniane.
52. Dom przy ul. Słonecznej Nr. 8. — drewniany.
53. Dom przy ul. Słonecznej Nr. 10. — murowany.
54. Oficyna przy ul. Słonecznej Nr 10 — murowana.
55. Drwalki przy ul. Słonecznej Nr. 10 — murowane.
56. Budki wartownicze stałe na fundamentach. — drewniane.
57. Kiosk Spółdzielni Pracownik. Fabryki — mur pruski.

Figure 1. Fragment of a legend from the 1938 Armament Factory plan

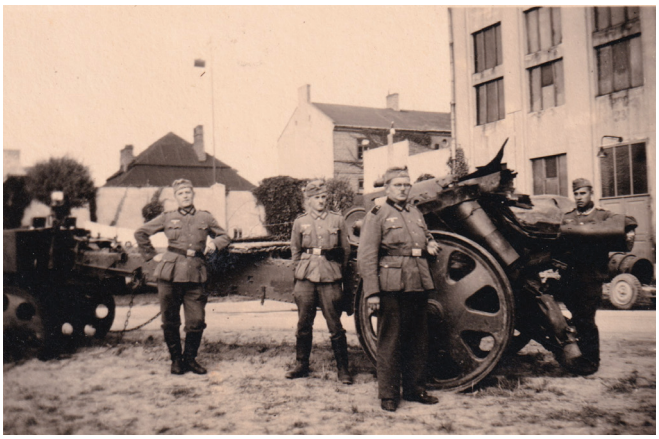

Figure 2. View of the buildings at 8 and 10 Słoneczna Street (in the background)

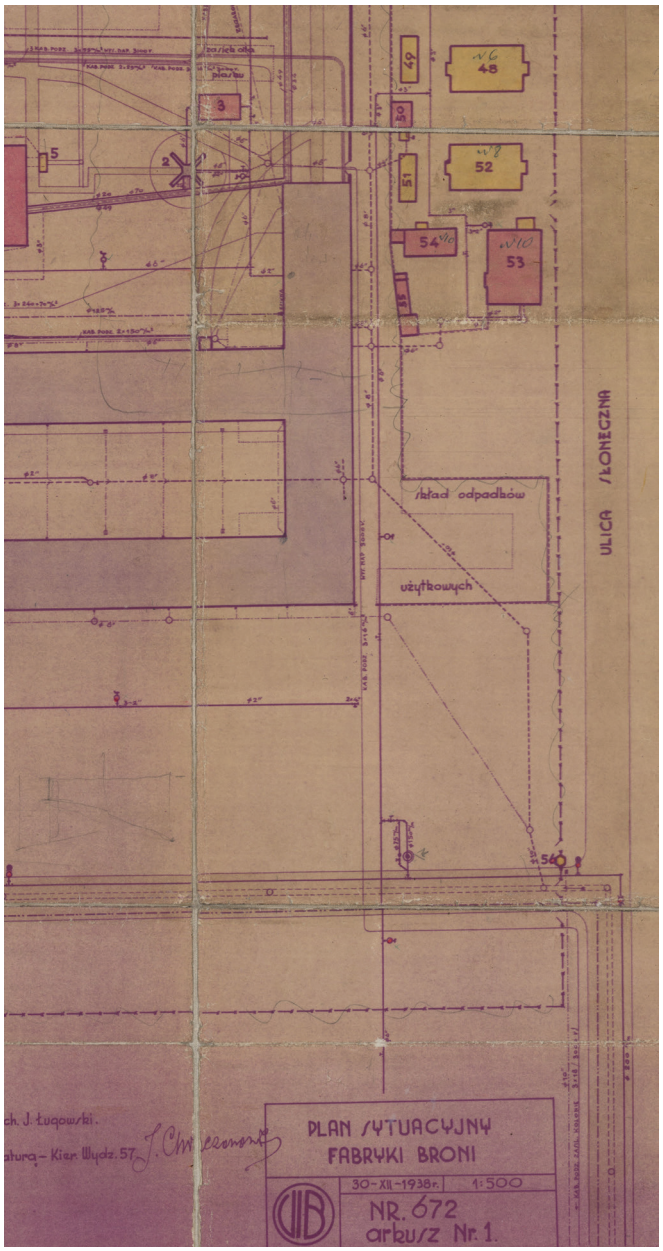

Figure 3. Location of the buildings at 6, 8, and 10 Słoneczna Street on the 1938 Armament Factory plan

Dr. Ehrlich died in 1933 in Krakow following a major surgery and was buried there. His posthumous memorial reads: *In every area of work, the Deceased was distinguished by his outstanding conscientiousness, which earned him the respect and affection of many employees of the State Armament Factory, where he served as doctor for many years. As a physician, he was an individual with a broad mind, profound knowledge, and work that continually advanced.*

He kept abreast of the latest achievements in medical science and practice, applying them energetically and skilfully—so much so that he was credited with 'preventing death' for many in our city through his adept care. This posthumous tribute also highlights another notable trait of Dr. Ehrlich: he was a steadfast advocate for truth. He consistently fought for truth in his actions and their adherence to ethical principles. This struggle was passionate and often uncomfortable for his opponents, yet always driven by ideological motives, impacting him both physically and morally. Dr. Ehrlich spared no effort, which contributed significantly to his premature death. He was generally regarded as a 'good man', a quality increasingly rare in the post-war era, and a compassionate physician, always ready to help the sick, never motivated by personal gain, and exceptionally willing to support his unwell colleagues and their families [9].

Following Dr. Ehrlich's death, Lieutenant Colonel Dr. Franciszek Waga (1887–1956), who relocated to the city from Warsaw, took over the Health Center. What is known about Dr. Waga? In 1926, as a major physician, he attended and graduated from the French School of Warfare (*École Supérieure de Guerre*) as one of 53 students [10]. From 1925, he collaborated with the editorial staff of the monthly *Military Physician*, published under the subtitle 'Organ Oficerów Korpusu Sanitarnego Wyznany i Rezerwy' (Office of Medical Corps Officers and Reserves) [11]. In 1932, as a lieutenant colonel, he wrote the foreword to the book *Psychotechnical Script (*According to Lectures at Officer Psychotechnical Courses*)*, published by the Ministry of Military Affairs [12]. As an activist of the Polish Red Cross (PCK), he participated in the re-establishment of the Radom branch board in September 1939, alongside other physicians: Stefan Wroński, Feliks Nowakowski, and Zofia Tochterman. The memoirs of Dr. Jerzy Borysowicz read: '*I worked most closely with Dr. Stefania Perzanowska, Tadeusz Orzeszko, Konrad Vieth, Franciszek Waga, Mamert Cywiński, and Wacław Raczyński. We exchanged information about impending arrests, avoided staying at home overnight, sent individuals requiring medical certificates or sick leaves, and informed each other about patients suspected of collaborating with the Germans, etc.*' [13]. In 1940, Dr. Waga transitioned from working with the Polish Red Cross to the Board of the Municipal Welfare Council in Radom. Social Insurance documents contain numerous entries regarding the payment of remuneration for his work as a surgeon at the outpatient clinic at 10 Słoneczna Street (where the Armament Factory Health Center was located before the war). After the war, he became the first Head of the Emergency Medical Service in Radom [14–17]. He also practiced as a dermatologist.

Over the years, the Health Center expanded its operations, offering services to an increasing number of insured persons, their families, and personnel. However, it is currently impossible to reconstruct the employment periods of individual doctors, paramedics, or nurses. Wartime censuses of the city's inhabitants contain information on only some physicians, along with notes regarding their work at the Armament Factory Health Center. Records mention Dr. Helena Popławska, born on September 13, 1899, who in 1940 lived at 18 Sienkiewicza Street and reported a monthly salary of 300 PLN; Dr. Wiktor Ogórkowski, who in 1940 resided at 21 Kelles-Krauza Street; and Dr. Józef Wiłkomirski, who in February 1942 lived at 14 Waryńskiego Street and received a salary of 300 PLN at the Health Center [18–20]. According to these records, a paramedic named Leon Stamirowski, born on April 7, 1888, also worked at the Health Center. In 1942, he earned 350 PLN per month and resided at 88 Bławatna Street [21].

On December 15, 1941, a conference was held regarding the takeover of the PWU-FB Health Center by the Social

Insurance Institution. Dr. Teofil Jórga (1893–1950) attended on its behalf. The Head of the institution in Radom ordered that *Dr. Jórga be reimbursed 20 PLN for travel expenses incurred while attending the conference at the Armament Factory Health Center concerning the takeover of the Health Center by the local Social Insurance Institution* [22, 23].

As of 1 January 1942, in accordance with Order No. II of 17 March 1941, which dissolved the health centres operating at Radom factories and workplaces, and following the arrangements adopted at the 15 December 1941 conference, the obligations toward employees arising from social insurance were assumed by the Social Insurance Institution in Radom. The formal date for the takeover of the buildings and personnel was 1 January 1942. In the case of the PWU-FB Health Center, the Social Insurance Institution assumed responsibility for the following personnel (monthly earnings in PLN are shown in brackets):

- **Doctors:** Dr. Władysław Cimiengo, physician (400 PLN); Dr. Helena Popławska, paediatrician (400 PLN); Dr. Eugeniusz Szylling, gynaecologist (550 PLN); Dr. Józef Wiłkomirski, otolaryngologist (300 PLN); Dr. Stefan Gajdziński, internist (550 PLN); Dr. Jerzy Borysowicz, neurologist (300 PLN); Dr. Mamert Cywiński, internist (300 PLN); Dr. Bronisław Masłowski, surgeon (330 PLN); Dr. Bronisława Skorko, paediatrician (350 PLN); Dr. Zofia Olszewska, dentist (560 PLN); Dr. Helena Jarczyńska, dentist (400 PLN); and Dr. Wiktor Ogórkowski, dentist (200 PLN).
- **Feldshers:** Walenty Staniewski (450 PLN) and Leon Sławomirski (350 PLN).
- **Nurses:** Jadwiga Żardecka (270 PLN); Janina Dydyńska (180) and Anna Orłowska (280) and Anna Brzozowska, hygienist (250) and Julianna Bilska, sanitary assistant (190)
- **Pharmacy employees:** Tadeusz Teski, MA, manager (600); Marian Sztencel (500); Halina Fijałkowska (300), Czesława Żebrowska, MA (420) and Leokadia Wach, bag maker (200).
- **Administrative staff**: Stanisław Piotrowski, bookkeeper (450); Stefan Zakrzewski, secretary (500); Tadeusz Piotrowski, clerk (200) and Stanisław Goździkowski, mechanic (300).
- **Support staff:** Stanisław Kurys, janitor (200); Władysław Siurek, janitor (170); Zofia Giza, cleaner (170); Władysława Krawczyk, cleaner (150) and Janina Pękala, cleaner (150).
- This marked the end of the period of operation of the PWU-FB Health Centre as an independent facility [24].

Conclusions

In addition to the history written in battlefields, military headquarters, and politicians' offices, local history remains of crucial importance, as it is with local history that communities most strongly identify. This history is shaped by the people and events in their immediate surroundings, influencing towns, workplaces, associations, health centres, and interpersonal relationships. Reconstructing this history is therefore of great importance, as it connects us closely to the past and helps prevent future mistakes. It is hoped that further archival materials related to this facility will be obtained, enabling continued research on the topic.

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MANAGEMENT OF PHARMACOTHERAPY IN A PATIENT WITH ANCA-ASSOCIATED VASCULITIS AND MULTIMORBIDITY, PREVENTION OF POLYPHARMACY – A CASE REPORT

Zarządzanie farmakoterapią u pacjenta z zapaleniem naczyń z przeciwciałami ANCA oraz wielochorobowością, zapobieganie polipragmazji – opis przypadku

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Abstract

Introduction: Multimorbidity is the co-occurrence of two or more chronic diseases. The prevalence of multimorbidity increases with age, although it is not limited to elderly individuals. Polypharmacy, understood as the simultaneous use of five or more medications, is closely linked to multimorbidity and increases the risk of adverse drug reactions. Antineutrophil cytoplasmic antibody-associated vasculitis predisposes patients to both multimorbidity and polypharmacy. Managing comorbid chronic conditions requires particular caution in patients with vasculitis. It is essential to account for drug interactions and balance the risk of adverse effects with the need to control disease activity. **Case report:** This case report describes a 63-year-old patient with vasculitis and multimorbidity admitted to the hospital following a traffic accident. The patient had multiple chronic conditions, including heart failure, coronary artery disease, rheumatoid arthritis, and osteoporosis. Despite treatment, the patient's condition deteriorated, necessitating a 4-month hospitalization during which the patient, due to the development of infectious complications, including sepsis, required multiple courses of antibiotic therapy and was qualified for chronic haemodialysis due to progressive renal failure. **Conclusion:** Managing multimorbidity and polypharmacy presents a significant challenge in everyday clinical practice, particularly among older patients, due to the increased risk of adverse drug reactions. An evidence-based therapeutic approach is crucial for treating complex medical conditions.

Streszczenie

Wstęp: Wielochorobowość definiuje się jako współwystępowanie co najmniej dwóch chorób przewlekłych. Częstość jej wzrasta z wiekiem, jednak jej występowanie nie ogranicza się wyłącznie do osób starszych. Polipragmazja, rozumiana jako jednoczesne stosowanie co najmniej pięciu leków, jest ściśle związana z wielochorobowością i zwiększa ryzyko wystąpienia działań niepożądanych farmaceutyków. Zapalenie naczyń związane z przeciwciałami przeciwko cytoplazmie neutrofilów predysponuje do wystąpienia zarówno wielochorobowości jak i polipragmazji. Leczenie współistniejących schorzeń przewlekłych u pacjentów z zapaleniem naczyń wymaga szczególnej ostrożności. Należy uwzględniać interakcje między lekami oraz równoważyć ryzyko działań niepożądanych z kontrolą aktywności choroby. **Opis przypadku:** W pracy przedstawiono przypadek 63-letniego pacjenta z zapaleniem naczyń i wielochorobowością, przyjętego do szpitala po wypadku komunikacyjnym. Chory był obciążony m.in. niewydolnością serca, chorobą wieńcową, reumatoidalnym zapaleniem stawów oraz osteoporozą. Pomimo leczenia jego stan pogarszał się i konieczna była 4-miesięczna hospitalizacja, podczas której z powodu rozwijających się powikłań infekcyjnych, w tym sepsy, wymagał kilkukrotnej antybiotykoterapii oraz względu na postępującą niewydolność nerek został zakwalifikowany do leczenia przewlekłymi hemodializami. **Wnioski:** Zarządzanie wielochorobowością i polipragmazją stanowi poważne wyzwanie w codziennej praktyce klinicznej, szczególnie u pacjentów starszych, ze względu na zwiększone ryzyko działań niepożądanych. Kluczowe w leczeniu złożonych schorzeń jest właściwe podejście terapeutyczne, oparte na najlepszych dostępnych dowodach naukowych.

Keywords: adverse drug reactions; multimorbidity; polypharmacy; ANCA antibody-positive vasculitis

Słowa kluczowe: działania niepożądane leków; wielochorobowość; polipragmazja; zapalenie naczyń z przeciwciałami ANCA

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Introduction

Multimorbidity is defined as the co-occurrence of at least two independent chronic conditions [1]. These may include metabolic, cardiovascular, and musculoskeletal diseases, as well as mental disorders, chronic pain, and substance abuse [2]. It should be distinguished from comorbidity, defined as the simultaneous presence of two or more disease entities that mutually influence prognosis [3]. Although the incidence of multimorbidity and comorbidity increases with age, younger populations may also be affected. As reported by Bandosz et al., the prevalence of multimorbidity was 69.3% among individuals aged 60–64 years, rising to 91% in those over 85 years, with a slight decrease after the age of 90 years [4]. Furthermore, more than 60% of patients over 80 years of age presented with at least four chronic conditions [4].

Inappropriate polypharmacy, defined as the concurrent use of five or more medications, is closely associated with multimorbidity. It increases the risk of non-compliance (non-adherence), pharmacotherapeutic errors, and adverse drug events (proportional to the number of medications used), as well as a higher incidence of hospital admissions, falls, and disability [5]. Appropriate polypharmacy, i.e., the use of multiple medications tailored to the patient's health condition, differs from inappropriate polypharmacy in that it aims to provide a broad therapeutic effect without increasing the risk of adverse effects [6]. Both appropriate and inappropriate types of polypharmacy are frequently observed among the elderly. Payne et al. [7] showed that 56% of individuals aged ≥85 years used five or more medications as compared to 9% in the 45–54 age group.

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) are a group of disorders involving severe, systemic, small-vessel vasculitis characterized by the presence of autoantibodies against proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA). AAV is classified into three types: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Although AAV can affect almost any organ, the upper and lower respiratory tract and the kidneys are most commonly and severely affected [8]. By causing vascular damage, the disease affects multiple systems and organs, contributing to dysfunction and the development of comorbidities [9].

Cao et al. [10] have shown that AAV patients experience significant polypharmacy, with over 80% taking five or more medications and more than 40% taking ten or more. Furthermore, older patients and those with additional chronic diseases were more likely to receive multidrug therapy. When multiple chronic conditions coexist, precise therapy selection is crucial. Drug interactions should be considered, and the risk of adverse reactions must be weighed against the need to control disease activity [11]. In this paper, we present a case of a patient with AAV and analyse the relationships between comorbidity, multimorbidity, and both appropriate and inappropriate polypharmacy.

The management of patients with multiple conditions should focus on optimizing pharmacotherapy and clearly defining therapeutic goals. In selected cases, de-escalating treatment may lead to more favourable clinical outcomes and a better quality of life compared with introducing modern, complex therapies.

Case report

A 63-year-old patient was transferred to a specialist hospital due to the failure of previous treatment at a lower-referral facility. Severe oedema and dyspnoea were the main reasons for admission. The man was in moderate clinical condition, with stable circulation. However, he presented with respiratory failure on admission to the Department of Internal Medicine and Nephrology. His vital signs were as follows: blood pressure 142/88 mmHg, heart rate 76 bpm, oxygen saturation 90% on room air, and 96% on passive oxygen therapy via a nasal cannula at 5 L/min. On auscultation, wheezing, isolated crackles, and decreased vesicular sounds were noted at the bases of both lungs. Massive oedema of the upper and lower extremities, sacrum, and genital area was observed. A stage 2 pressure ulcer was found over the sacrum.

The patient had been involved in a road traffic accident resulting in fractures of the third through eighth ribs on the right side a few days before admission. He had a history of multiple cardiovascular events, including two non-ST-elevation myocardial infarctions (NSTEMIs), both managed with angioplasty.

The patient had a history of multiple chronic conditions, including chronic obstructive pulmonary disease (COPD), mild aortic stenosis, hypertension (HT),

atherosclerosis, rheumatoid arthritis (RA), mixed hyperlipidaemia, reflux oesophagitis, benign prostatic hyperplasia, and mild erythematous gastropathy. He also had a history of osteoporotic Th5 and Th7 compression fractures. Additionally, alcohol dependence syndrome, nicotine dependence (40 pack-years), and colonization with multidrug-resistant microorganisms, including vancomycin-resistant *Enterococcus faecium* (VRE) and metallo-β-lactamase-producing *Klebsiella pneumoniae* were noted. He was diagnosed with pANCA-associated vasculitis coexisting with nephrotic syndrome in 2022. Renal biopsy revealed two coexisting types of glomerulopathy: necrotizing glomerulitis with crescents in some glomeruli, associated with ANCA, and membranous glomerulopathy (grade III/IV) without detectable anti-phospholipase A2 receptor (anti-PLA2R) antigen in the glomeruli.

The patient had been previously treated with 13 medications: prednisone, torasemide, acetylsalicylic acid, clopidogrel, pantoprazole, atorvastatin, bisoprolol, lercanidipine, ramipril, tamsulosin, ipratropium bromide, salmeterol, and pregabalin. He also received iron, calcium, vitamin D, and vitamin B supplements.

Laboratory tests revealed normocytic anaemia, hypoalbuminemia, elevated renal function parameters, and increased inflammatory markers; pANCA antibodies were negative on admission.

The patient was hospitalized for 4 months. After excluding acute coronary syndrome, intensive antibiotic therapy with piperacillin/tazobactam and metronidazole was initiated due to worsening dyspnoea, pain, deterioration of his general clinical condition, and elevated inflammatory markers. Blood and urine cultures were sterile.

During the subsequent days of hospital stay, the patient developed *Clostridioides difficile*-induced diarrhoea, which was treated with oral vancomycin. Transfusion of 11 units of packed red blood cells was performed due to progressive anaemia. Renal replacement therapy with haemodialysis was initiated due to worsening hypervolemia and nephrotic syndrome refractory to immunosuppressive therapy (no response to cyclosporine). Peripheral oedema decreased and respiratory function improved. However, two weeks later, the patient's condition deteriorated rapidly, with septic shock requiring catecholamine infusion. The patient was started on empirical antibiotic therapy with meropenem and vancomycin. Blood and urine cultures were sterile, but the central-line tip was positive for vancomycin-sensitive *Staphylococcus haemolyticus* (MRS, MLS_BK). Once pharmacotherapy was modified, inflammatory markers decreased, but respiratory failure persisted. Chest X-ray revealed significant right-sided pleural effusion. Purulent fluid drained from the pleura gave a positive culture for *Serratia marcescens*. Based on these findings, vancomycin was discontinued, and sulfamethoxazole/trimethoprim was added. Following a thoracic surgery consultation, continuous pleural drainage was maintained. An attempt to discontinue haemodialysis due to gradual improvement in diuresis was unsuccessful, and the patient was therefore started on chronic haemodialysis.

As a result of treatment, the patient's condition improved, with reduced oedema and dyspnoea. Persistent respiratory failure required continued supplemental oxygen therapy. The patient was discharged with a referral to a hospice.

Considering the patient's overall clinical picture and health status, the following therapeutic regimen was prescribed : home oxygen therapy, trimethoprim/sulfamethoxazole, prednisone, bisoprolol, furosemide, acetylsalicylic acid, atorvastatin, omeprazole, ipratropium bromide, salmeterol, pregabalin, acetylcysteine, and epoetin. Additionally, iron, calcium, and vitamin D supplements were prescribed. Diagnoses and treatments are summarised in Table 1.

Discussion

The presented patient faced multiple chronic conditions. During hospital stay, antibiotic therapy, blood product transfusions and pleural drainage were performed , and dialysis was started. Managing therapy in a patient with ANCA-positive vasculitis, coexisting

Table 1. Pharmacotherapy at discharge and indications

Pharmacotherapy at discharge	Indications
Prednisone	p-ANCA-associated vasculitis, membranous glomerulopathy, rheumatoid arthritis
Dialysis therapy	End-stage renal disease
Furosemide, bisoprolol , ASA	Hypertension, history of NSTEMI , heart failure
Atorvastatin	Generalized atherosclerosis, mixed hyperlipidemia
Acetylcysteine, ipratropium bromide, salmeterol	COPD
Home oxygen therapy	Chronic respiratory failure
Trimethoprim/sulfamethoxazole	Pleural empyema
Omeprazole	Erythematous gastropathy, reflux esophagitis
Epoetin, iron preparations	Anaemia
Ca2+, vitamin D supplementation	Osteoporosis
Pregabalin	Anxiety disorders, chronic pain
ANCA – anti-neutrophil cytoplasmic antibody; ASA – acetylsalicylic acid; NSTEMI – non-ST-elevation myocardial infarction; COPD – chronic obstructive pulmonary disease	

chronic conditions, and polypharmacy is a major clinical challenge due to the elevated risk of complications in this population [9]. Despite a prolonged hospital stay and numerous therapeutic challenges, optimal causal and symptomatic treatment was tailored to the patient's individual needs, resulting in clinical stabilization.

Multimorbidity and polypharmacy present significant challenges in everyday medical practice, particularly in older patients. Adding further medications in patients who are already receiving multiple drugs may not yield proportional therapeutic benefits, while the risk of adverse reactions increases with the number of treatments used. The rates of adverse effects are 4% for five, 10% for 6–10, 28% for 11–15, and up to 54% for more than 15 drugs [12]. It should be emphasized, however, that not all cases of polypharmacy are inappropriate. Implementing optimal therapy based on the best available scientific evidence is the appropriate approach for complex conditions. Neither advanced age nor the number of medications should be a barrier to effective treatment [13]. Key aspects of managing elderly patients with multimorbidity and polypharmacy include early identification of those with multiple conditions, assessment of their vulnerability to additional health problems, and shared, individualized therapeutic decisions focused on the patient's needs [14, 15]. In the described case, despite the use of twelve medications, guideline-based therapy accounting for multiple comorbidities and potential drug interactions (Tab. 1) led to an improvement in the patient's overall condition.

The patient was admitted to the hospital one year after his AAV diagnosis. Studies have shown that, compared to the general population, patients with microscopic polyangiitis face increased risks for other conditions, especially within the first two years after diagnosis. These individuals develop chronic inflammation, which contributes to vascular damage and, consequently, kidney failure, a significant risk factor. Multidrug therapy, which is associated with an increased risk of adverse effects, is an additional burden. For instance, glucocorticoids increase the risk of osteoporosis and metabolic disorders, while their concurrent use with acetylsalicylic acid promotes the development of gastric and duodenal ulcers.

A study found that 23% of patients developed multimorbidity within one year of AAV diagnosis, a rate that increased to 37% after 10 years. Patients with AAV and multimorbidity incur significantly higher healthcare costs, particularly those with three or more comorbidities [9].

Since AAV treatments may interact with other medications, the risk of interactions should be carefully assessed before introducing further treatments. For this purpose, clinicians may consider using available online tools for identifying potential risks associated with planned pharmacotherapy. When discharging a patient to hospice, it is important to prioritize maintaining the best possible quality of life. Therapy should be symptomatic, focusing on the relief of dyspnoea, pain, oedema, and anxiety.

Conclusions

Patients with AAV face an increased risk of inappropriate polypharmacy and multimorbidity due to the underlying disease and the use of multiple medications. Key elements of care for this population include accurate identification of comorbidities and optimization of therapy, taking into account the patient's individual therapeutic goals.

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CARDIAC TAMPONADE SECONDARY TO PERICARDITIS IN A DIALYSIS PATIENT – A CASE REPORT

Tamponada serca na podłożu zapalenia osierdzia u pacjenta dializowanego – opis przypadku

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Abstract

Introduction: Pericarditis is a known cause of chest pain, particularly in young men. It may be complicated by cardiac tamponade, which requires urgent intervention. The aetiology of acute pericarditis may pose a diagnostic challenge. Possible causes include viral and bacterial infections, rheumatic diseases, aortic dissection, and others. Uremic pericarditis is also a potential cause, primarily occurring in dialysis patients, and less common in those with chronic kidney disease prior to initiating dialysis. **Case report:** A 65-year-old male patient was admitted to the hospital due to deterioration of general condition and dyspnoea. Based on the clinical presentation, cardiac tamponade secondary to pericarditis was suspected, which was confirmed by imaging studies. Emergency pericardiocentesis was performed. The differential diagnosis included uremic and viral aetiologies. Daily haemodialysis and corticosteroid therapy were initiated, resulting in clinical improvement. **Discussion:** Uremic pericarditis predominantly occurs in patients with chronic kidney disease and may develop both prior to and during dialysis, irrespective of serum urea levels. Intensified dialysis, as in the case described, frequently leads to clinical improvement. Pharmacological treatment for viral acute pericarditis has limited efficacy in patients with chronic kidney disease, making corticosteroid therapy the primary therapeutic option. **Conclusion:** In dialysis patients presenting with acute pericarditis, uremic aetiology, along with other potential causes, should always be considered. Early diagnosis and prompt pericardiocentesis are crucial in cases of cardiac tamponade.

Streszczenie

Wstęp: Zapalenie osierdzia jest jedną z przyczyn bólu w klatce piersiowej, szczególnie u młodych mężczyzn. Jego powikłaniem może być tamponada serca, wymagająca pilnej interwencji. Etiologia ostrego zapalenia osierdzia bywa trudna do ustalenia. Możliwe przyczyny obejmują infekcje wirusowe i bakteryjne, choroby reumatologiczne, rozwarstwienie aorty i inne. Jedną z nich jest również mocznicowe zapalenie osierdzia, występujące głównie u pacjentów dializowanych, rzadziej w przewlekłej chorobie nerek przed rozpoczęciem dializ. **Opis przypadku:** 65-letni pacjent został przyjęty do szpitala z powodu pogorszenia stanu ogólnego i duszności. Na podstawie obrazu klinicznego podejrzewano tamponadę serca w przebiegu zapalenia osierdzia, co potwierdzono w badaniach obrazowych. W trybie ostrego dyżuru przeprowadzono perikardiocentezę. Diagnostyka różnicowa obejmowała etiologię mocznicową i wirusową. Włączono codzienne zabiegi hemodializ oraz terapię glikokortykosteroidami uzyskując poprawę stanu pacjenta. **Omówienie:** Mocznicowe zapalenie osierdzia występuje głównie u pacjentów z przewlekłą chorobą nerek i może rozwijać się zarówno przed dializoterapią, jak i podczas niej, niezależnie od stężenia mocznika. Intensyfikacja dializ, jak w opisanym przypadku, często przynosi poprawę. Leki stosowane w ostrym zapaleniu osierdzia o etiologii wirusowej mają ograniczone zastosowanie u pacjentów z przewlekłą chorobą nerek, co sprawia, że steroidoterapia często pozostaje jedyną opcją terapeutyczną. **Wnioski:** U dializowanych pacjentów z ostrym zapaleniem osierdzia należy zawsze uwzględniać zarówno etiologię mocznicową, jak i inne potencjalne przyczyny. W przypadku pojawienia się tamponady serca kluczowe jest wczesne rozpoznanie i przeprowadzenie perikardiocentezy.

Keywords: pericarditis; cardiac tamponade; uremic pericarditis

Słowa kluczowe: zapalenie osierdzia; tamponada serca; mocznicowe zapalenie osierdzia

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Introduction

Pericarditis is diagnosed in about 5% of patients presenting to emergency departments with chest pain that is not related to acute coronary syndrome [1], most commonly affecting men aged 20–50 years [2]. It may give rise to a serious complication known as cardiac tamponade, one of the causes of sudden cardiac arrest in the 4H/4T classification, which requires immediate pericardial decompression. Hypotension, muffled heart sounds, and distension of the jugular veins, collectively referred to as Beck's triad, are typical clinical manifestations. Rapid diagnosis of cardiac tamponade is vital for effective treatment.

Over 95% of patients with acute pericarditis present with pleuritic retrosternal pain of varying severity [3], which may radiate to the neck, jaw, or arm, resembling myocardial infarction. It typically worsens when lying down or coughing and improves when sitting or leaning forward, when compression on the pericardium is smaller [1].

The aetiology of acute pericarditis can pose a diagnostic challenge. Possible causes include viral and bacterial infections, rheumatic diseases (such as sarcoidosis or lupus), neoplastic processes, trauma, aortic dissection, and iatrogenic factors [2]. Uremic pericarditis, which was previously considered a complication of advanced untreated chronic kidney disease (CKD), has also been distinguished. Currently, it is observed mainly in dialysis patients. In 2017, Bentata et al. found uremic pericarditis in only 1.7% of cases, with its incidence markedly reduced by the use of highly efficient dialysis membranes [4, 5]. The introduction of medium cut-off (MCO) membranes has allowed for eliminating medium- and high-molecular-weight uremic toxins without the need for large convection volumes or significant albumin loss [6].

The pathophysiology of uremic pericarditis is complex and involves the accumulation of toxic metabolites (such as methylguanidine and guanidinoacetate), nitrogen-containing metabolic products, as well as electrolyte and acid–base imbalance [7]. Hyperparathyroidism, hyperuricemia, and hypocalcaemia may also contribute to the development of this disorder [8]. In patients with CKD, elevated urinary albumin excretion and volume overload increase endothelial permeability and promote fluid accumulation in the pericardial sac, which also contributes to pericarditis [9].

Case report

A 65-year-old patient presented to the Department of Internal Medicine, Nephrology, and Dialysis with general deterioration, weakness, and exertional dyspnoea. He had developed an upper respiratory tract infection followed by reduced exercise tolerance one week before admission.

On admission, the patient was in serious condition with significant respiratory distress, blood pressure of 95/80 mmHg, oxygen saturation of 95%, and faint heart sounds on auscultation. The patient had a history of abdominal aortic aneurysm repair, followed by renal artery occlusion complicated by acute kidney injury two months later. Creatinine was approximately 10 mg/dL, with preserved diuresis and no oedema or other signs of fluid overload. This was likely related to anatomical variation in the patient's renal vasculature, which included accessory arteries. An unsuccessful revascularization attempt was made, after which the patient was started on chronic haemodialysis. The man additionally presented with poorly controlled hypertension, renal cysts, lower limb atherosclerosis, and a history of hepatitis B.

Chest X-ray on admission showed a markedly enlarged cardiac silhouette compared with the image taken two months earlier (Fig. 1). Based on Beck's triad (hypotension and muffled heart sounds) and imaging findings, a suspicion of cardiac tamponade was raised. Electrocardiography (ECG) showed low QRS voltage, which is typical of this condition.

Point-of-care echocardiography (ECHO) found a large pericardial effusion, prompting emergency pericardiocentesis, during which 840 mL of bloody fluid was evacuated. The drain was removed three days later, having yielded an additional 50 mL. Only trace fluid was detected on follow-up ECHO.

Laboratory workup showed elevated inflammatory markers, while blood and pericardial fluid cultures were negative. Troponin levels were measured to rule out acute coronary syndrome and were stable. Computed tomography angiography (CTA) performed to rule out aortic dissection detected fluid in both pleural cavities, the rectovesical recess, the perihepatic space, and the perisplenic region. Because of signs of hypervolemia, the patient was put on daily haemodialysis, and glucocorticoids were added to the treatment regimen. His clinical condition improved, and dyspnoea resolved.

Discussion

The differential diagnosis in the discussed case primarily included uremic and infectious pericarditis, as aortic dissection was ruled out by CT angiography. A recent mild

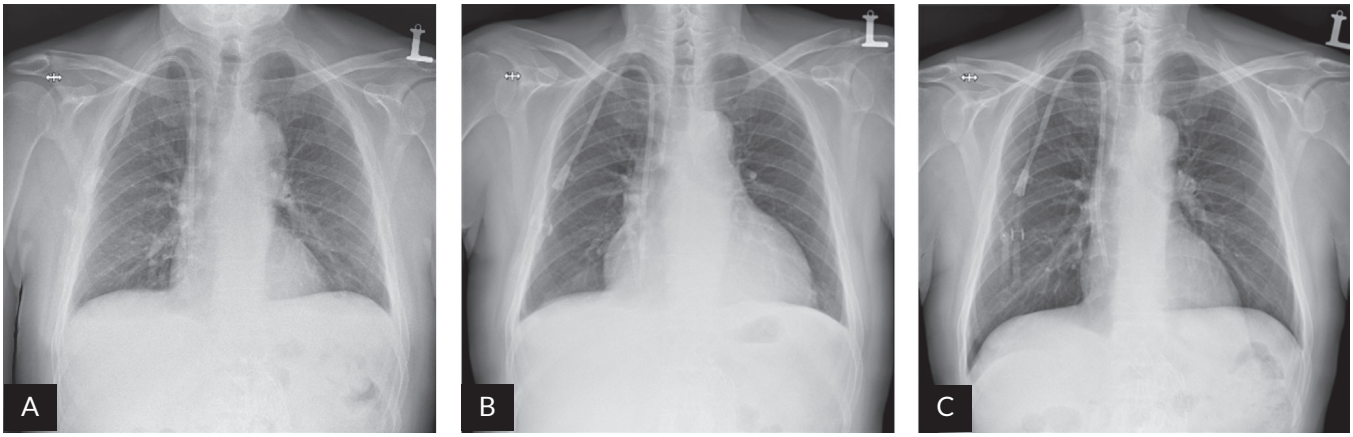

Fig. 1. Chest X-ray: **A.** Before admission (March 2024); **B.** On admission, suspected tamponade (May 2024); **C.** Post-treatment follow-up X-ray (June 2024)

respiratory infection may suggest viral aetiology, with coxsackieviruses and adenoviruses being the most common causes, though SARS or HIV can also be responsible [10]. However, no polymerase chain reaction (PCR) testing was performed to unequivocally confirm viral aetiology. Elevated C-reactive protein (CRP) and leukocytosis indicated an ongoing infection, although the patient did not present any symptoms of infection on admission and maintained an oxygen saturation of 95%. The rapid onset of symptoms after an infection may have indicated viral aetiology of pericarditis and tamponade.

A history of renal failure and chronic dialysis therapy may suggest uremic aetiology. Uremic pericarditis can occur both pre- and post-dialysis. It is known as dialysis-associated pericarditis, which occurs primarily in haemodialysis patients, less frequently in those on peritoneal dialysis. The possible causes include inadequate dialysis therapy, individual patient predispositions, and poor adherence to medical recommendations [11]. From a clinical perspective, uremic pericarditis differs from acute pericarditis. It typically has a slow onset, and aside from a pericardial rub, other symptoms may be absent. Leukocytosis and fever are uncommon, and there are often no significant ECG abnormalities [12]. Rutsky and Rostand reported pericarditis in 13% of patients on chronic dialysis during a 13.7-year follow-up period. Cardiac tamponade and impending tamponade developed in 20% and 22% of patients with pericarditis [11].

Pericarditis in advanced CKD is managed by either initiating or intensifying dialysis [4]. Patients with uremic pericarditis typically respond rapidly to renal replacement therapy [13]. The regimen for intensified dialysis is 4 hours of dialysis daily for 7–14 days. Patients should be closely monitored, with ECHO performed every 3 days to assess pericardial effusion [13, 14]. Systemic anticoagulation should be avoided due to the increased risk of bleeding and potential pre- or post-tamponade complications [15].

For viral pericarditis, patients should receive colchicine for 3 months along with nonsteroidal anti-inflammatory drugs (NSAIDs) to relieve symptoms and reduce the risk of recurrence. In recurrent cases, colchicine should be continued for at least 6 months. Corticosteroids are often used if pericarditis does not improve with NSAIDs and colchicine. Interleukin-1 (IL-1) blockers have demonstrated efficacy in some patients with repeated long-lasting (several years) recurrences, and may be preferred over corticosteroids [16]. The use of NSAIDs, colchicine, and IL-1 blockers is limited in patients with renal failure [17]. GCs are preferred in G5 CKD, as in the described case.

Given the ambiguous aetiology of the pericarditis, treatment targeting both uremic and infectious causes was initiated, leading to rapid clinical improvement. Uremic pericarditis shows a greater improvement with intensified dialysis in patients on renal replacement therapy for less than two months. Consequently, patients on long-term renal replacement therapy require intensified treatment [17].

Uremic pericarditis can also occur in well-dialyzed patients with mildly elevated serum urea due to other toxic metabolites and high levels of free radicals [8]. Even mild uraemia has been observed to create a pro-oxidant state [18]. Pupima et al. [19] showed that dialysis reduces toxic metabolite levels, but is ineffective in correcting oxidative stress or lowering inflammatory biomarkers. This may account for the development and progression of pericarditis in patients on long-term renal replacement therapy despite normal blood urea. Although uremic aetiology is usually suspected in dialysis patients with pericarditis, other causes should always be considered. Regardless of aetiology, rapid diagnosis and treatment are crucial in emergency cases, such as cardiac tamponade secondary to pericarditis.

Conclusions

Determining the aetiology of tamponade poses a diagnostic challenge in dialysis patients, as uremic pericarditis, seen only in renal failure, often comes to the fore. However, other causes should also be considered in the diagnosis and treatment planning. Early identification of tamponade and prompt pericardiocentesis are vital.

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SQUAMOUS CELL CARCINOMA IN A BURN SCAR – A CASE REPORT

Rak płaskonabłonkowy skóry w bliźnie pooparzeniowej – opis przypadku

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Abstract

Squamous cell carcinoma (SCC) arising in a burn scar, known as a Marjolin ulcer, is a rare aggressive skin cancer. We describe a case of a 63-year-old patient with squamous cell carcinoma arising from a 24-year-old thermal burn scar on the dorsal aspect of the left metacarpus. The lesion exhibited gradual ulceration. Local treatment was ineffective. Following histopathological verification and additional diagnostic workup, surgical intervention was undertaken. This consisted of complete resection of the lesion, with simultaneous coverage of the defect using an autologous intermediate-thickness skin graft harvested from the patient's thigh. The described case emphasises the importance of early diagnosis, regular follow-up of burn scars, and prompt intervention, all of which contribute to improving patient prognosis.

Streszczenie

Rak płaskonabłonkowy rozwijający się w bliźnie pooparzeniowej, znany jako owrzodzenie Marjolina, jest rzadkim, ale agresywnym nowotworem skóry. W artykule opisano przypadek 63-letniego pacjenta, u którego rak płaskonabłonkowy rozwinął się na grzbietowej powierzchni śródręcza ręki lewej w miejscu blizny po oparzeniu termicznym sprzed 24 lat. Zmiana stopniowo ulegała owrzodzeniu. Nie poddawała się leczeniu miejscowemu. Po jej histopatologicznej weryfikacji oraz dodatkowych badań diagnostycznych przeprowadzono leczenie chirurgiczne polegające na całkowitej resekcji zmiany z jednoczasowym pokryciem ubytku przeszczepem skóry autologicznej pośredniej grubości pobranej z uda pacjenta. Opis przypadku podkreśla znaczenie wczesnej diagnostyki, regularnej kontroli blizn pooparzeniowych oraz szybkiej reakcji na niepokojące objawy, co przyczynia się do poprawy rokowania pacjentów.

Keywords: surgical treatment; squamous cell cancer; burn scar; oncological diagnosis; Marjolin ulcer

Słowa kluczowe: leczenie chirurgiczne; rak płaskonabłonkowy; blizna pooparzeniowa; diagnostyka onkologiczna; owrzodzenie Marjolina

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Introduction

The skin is the largest organ of the human body, serving as a barrier against external factors and contributing to temperature regulation, water and electrolyte balance, as well as immune responses [1]. It maintains overall homeostasis, protecting the body from harmful external influences [2]. Burned skin loses its integrity and ceases to function as a mechanical and biological barrier against external factors [3].

According to available literature, 1–2% of burn scars can transform into malignancies [4].

The term 'Marjolin ulcer' refers to a malignant tumour arising in areas of chronic inflammation, such as non-healing wounds, burn scars, or other scarred tissues [5]. Patients typically experience tissue damage with scarring or chronic ulceration several decades before diagnosis. Marjolin ulcer is generally considered a highly aggressive tumour with a high mortality rate [6]. A sudden change in the characteristics of a chronic ulcer or a scar should prompt diagnostic testing [7]. Up to 2% of chronic burn scar lesions can transform into malignancies. Most of these are squamous cell carcinomas (SCCs) and, though less frequently, basal cell carcinomas (BCCs) [8]. The incidence of malignant melanoma (MM) arising in such lesions is exceptionally low [9].

Early diagnosis and surgical treatment improve patient prognosis [10].

This paper presents a case of SCC involving the left upper limb following a thermal burn.

Case report

A 63-year-old patient was electively admitted to the Clinical Department of Plastic, Reconstructive, and Burn Surgery at the Military Institute of Medicine in Warsaw for surgical treatment of a skin cancer on the dorsal surface of the left metacarpus.

The patient presented to the Outpatient Clinic of the Military Institute of Medicine in Warsaw in November 2024. He reported a history of a second-degree thermal burn of the left hand and the head sustained from flame contact approximately 24 years earlier. The burn healed, leaving scars. Since then, the patient had experienced periodic skin tears and micro-injuries within the scar. In June 2024, a chronic ulcer developed within the dorsal metacarpal scar of the left hand and gradually enlarged. Local treatment was ineffective. The lesion failed to heal and progressed into a chronic wound. In September 2024, a sample was taken from the dorsal metacarpal surface of the left hand for histopathological examination. SCC was confirmed and the patient was referred for further diagnosis in December 2024. Laboratory workup showed no significant abnormalities. Ultrasound of the peripheral lymph nodes revealed no enlargement in the cervical, supraclavicular, infraclavicular, axillary, or inguinal regions. CT of the chest, abdomen, and pelvis (both with and without contrast) found no neoplastic processes or metastases. Contrast-enhanced magnetic resonance imaging (MRI) of the upper limb was performed to assess disease extent and rule out metastases, and found a heterogeneous lesion on the dorsal skin and subcutaneous tissue of the left hand, measuring 13 mm (AP) × 46 mm (transverse) × 79 mm (craniocaudal), showing irregular contrast enhancement, infiltrating the subcutaneous tissue, and causing oedema of the surrounding soft tissue. At the level of the third metacarpal head, it involved fatty tissue and adhered to vessels without extending to the finger extensor tendons.

The patient was admitted to the Clinical Department of Plastic, Reconstructive, and Burn Surgery at the Military Institute of Medicine in Warsaw in January 2025.

Physical examination revealed an ulcerated tumour measuring approximately 10 × 5 cm and appearing cauliflower-like in the centre, located on the dorsal surface of the left metacarpus (Fig. 1).

The patient had a history of arterial hypertension and classical cholecystectomy. He reported no allergies or drug sensitivities and was regularly taking valsartan with hydrochlorothiazide and amlodipine. He worked as a confectioner. The patient was qualified for surgical treatment. Under general anaesthesia, total resection of the tumour with adequate margins was performed in the operating room (Fig. 2). The specimen was sent for histopathology, with the lesion's poles were carefully marked to assess resectability (Fig. 3).

The tissue defect was immediately covered with a split-thickness skin graft (STSG) harvested from the patient's

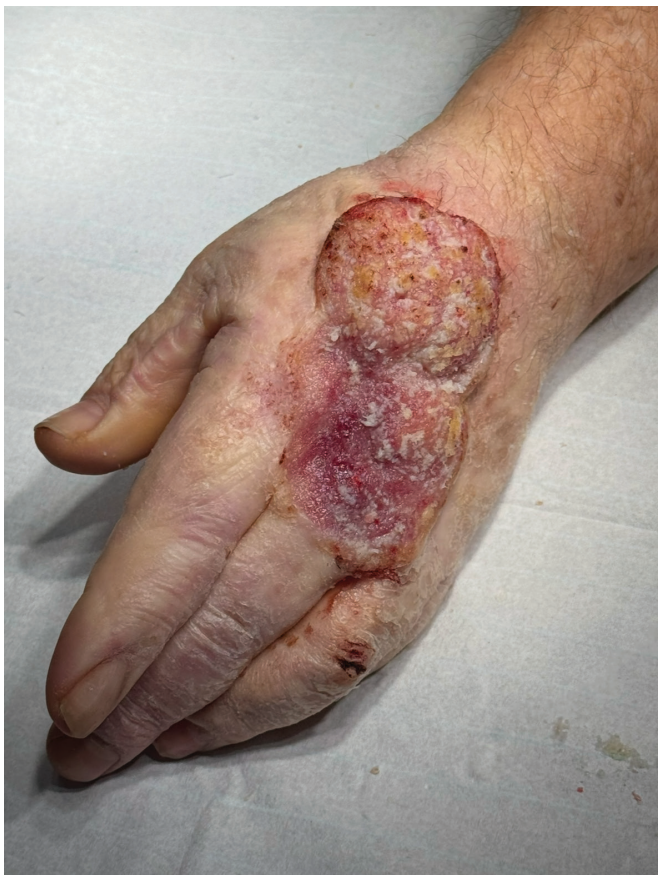

Figure 1. Skin lesion on the patient's left hand

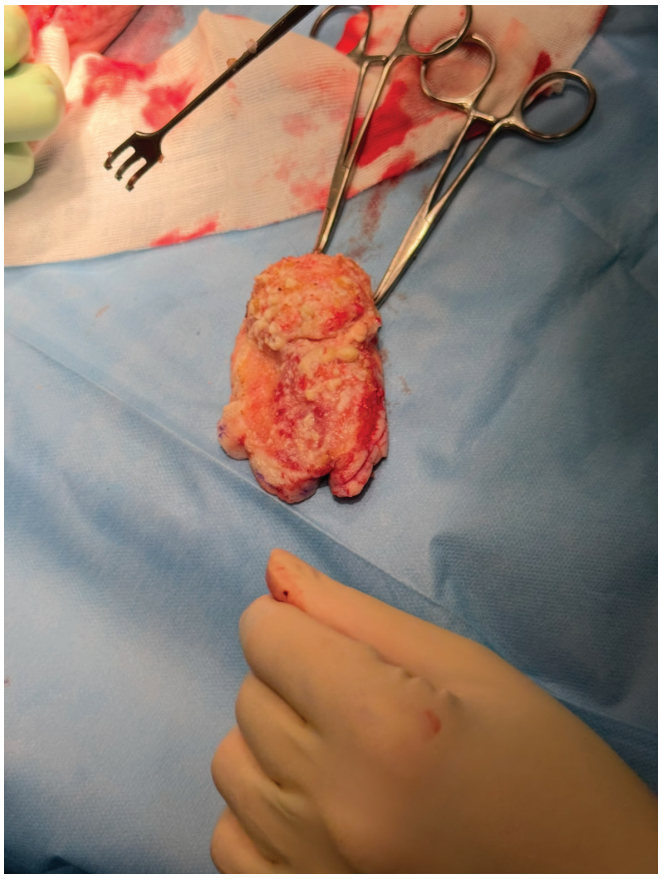

Figure 2. Resected malignancy within the scar on the left hand– intraoperative image

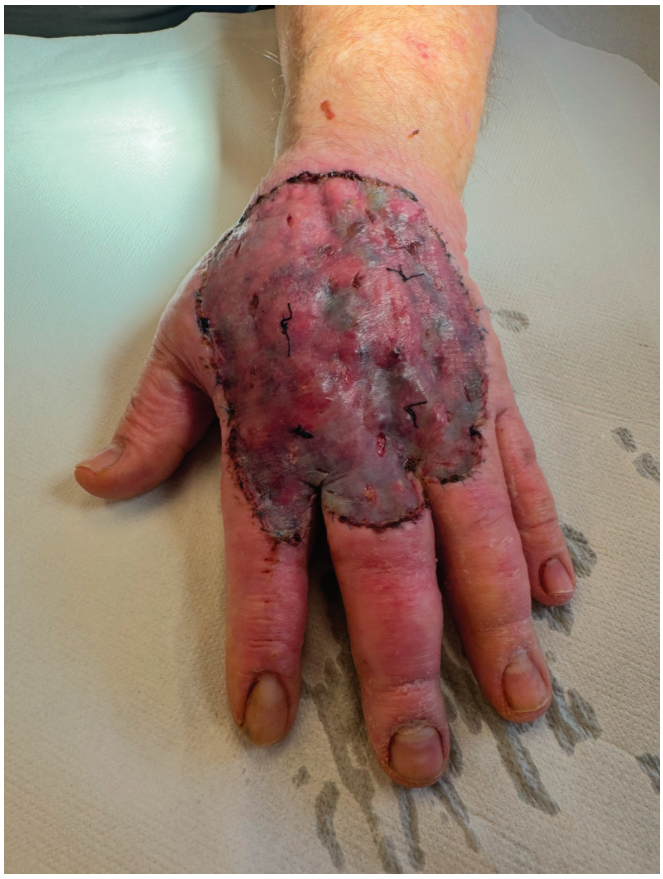

Figure 3. An image taken after resection of the lesion combined with a split-thickness skin graft (STSG) – postoperative outcome

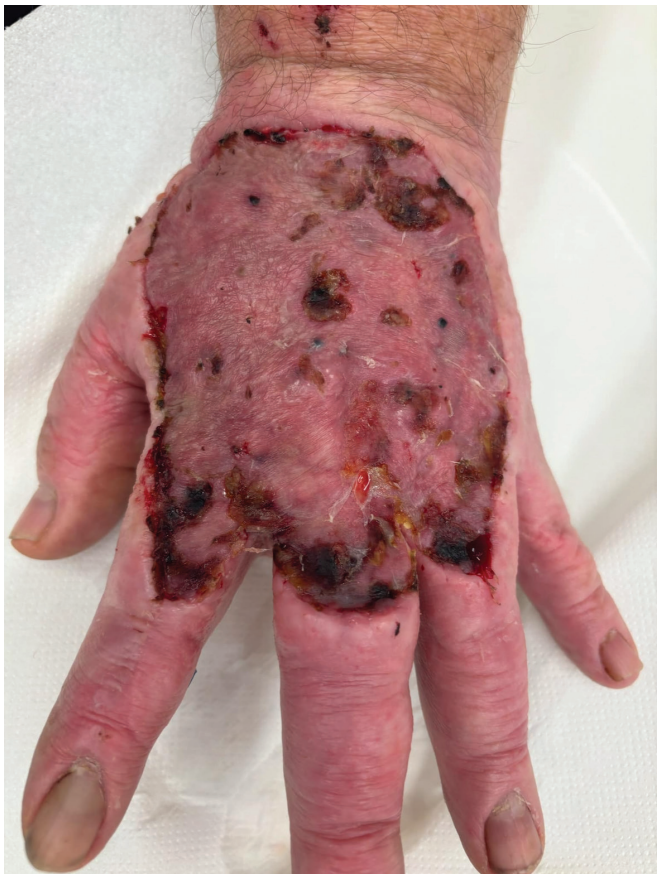

Figure 4. At 1 week postoperatively

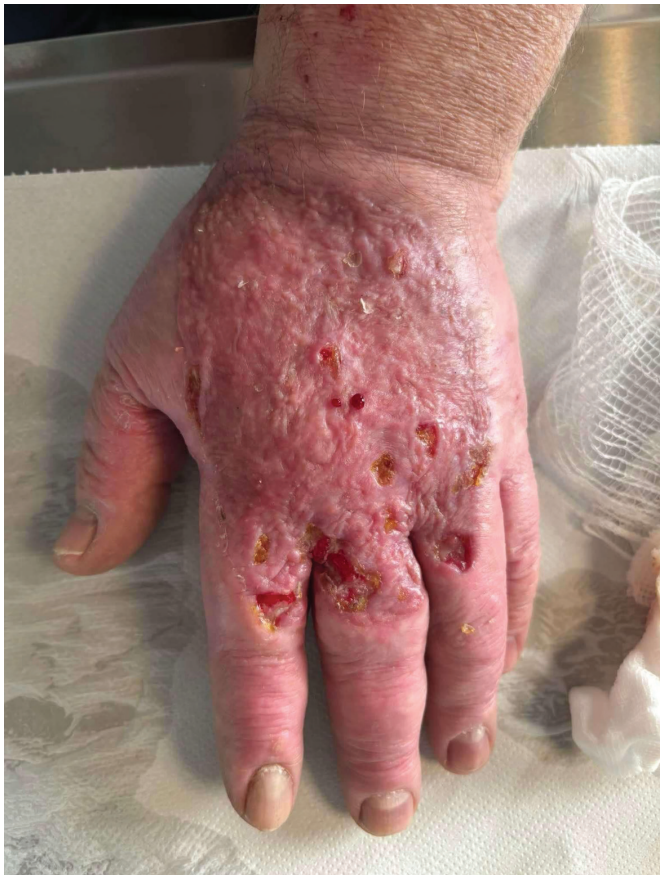

Figure 5. At approximately 3 weeks postoperatively

left thigh. The perioperative and early postoperative periods were uneventful, with regular dressing changes and satisfactory wound healing observed during hospital stay. On the second postoperative day, a wound swab was taken to identify potential microorganisms and guide targeted antibiotic therapy if needed. The patient was discharged home on postoperative day 2 in good general and local condition, with further recommendations.

The first outpatient follow-up, one week after surgical intervention (Fig. 4), showed normal wound healing with no signs of infection or purulent drainage. A subsequent follow-up on February 20, 2025, approximately three weeks postoperatively, showed continued normal healing (Fig. 5). Histopathology, performed about three weeks postoperatively, confirmed invasive, well-differentiated (G1) SCC of the skin, with a maximum diameter of 83 mm and invasion depth of 12 mm. Lymphatic invasion was present, but no neuroinvasion was observed. Surgical margins were free of tumour.

The patient will remain under outpatient oncological follow-up for the next two years.

Discussion

Marjolin ulcer is a malignant tumour arising in previously damaged skin, often in scars or chronic non-healing wounds. Although its pathophysiology has been a subject of debate for many years, it is considered that areas of scar tissue lacking immune cells contribute to its development [11]. These lesions are aggressive, have a poor prognosis, and tend to recur [5]. Squamous cell carcinoma, typically arising in long-standing, chronic scars is the most common histological type [12].

While Marjolin ulcer appears to be more common in some ethnic groups, it is very rare in European populations [13]. It is most often diagnosed in patients in their fifth decade, with men being three times more likely to become affected than women. Lower extremities are most commonly involved (over 50%), followed by the upper limbs, the trunk, and the head [14].

Cancer vigilance is crucial in patients with burn scars, with special attention given to chronic non-healing wounds. Early diagnosis and treatment allow for complete removal of the lesion [13]. Metastases are the most important prognostic factor, with regional and distant metastases observed in 20–66% and 14% of cases, respectively [15].

Radical excision of the lesion and surrounding lymph nodes is the primary treatment. If adequate margins of healthy tissue cannot be achieved, amputation of the affected neurovascular structures is recommended. Neoadjuvant and adjuvant therapies are advised for patients with distant metastases or poor prognostic factors. Local radiation therapy may be considered as an alternative for patients who decline surgery or in cases where tumour location precludes radical excision. However, it should be remembered that radiation may impair wound healing [15].

Particular attention should be paid to the early management of burn patients, and especially interventions to protect the affected area immediately after the burn. Such interventions are crucial for long-term clinical outcomes and may help prevent proliferative changes within the damaged tissues. Although malignant tumours typically develop 25–40 years after a burn, they may occur as early as three months. The risk of recurrence after radical surgery is 14.7% [16]. There is a proven causal link between burns and the subsequent risk of SCC. Given the poor prognosis of advanced scar cancers, early skin grafting is the preferred strategy to prevent recurrent scar ulceration. The incidence of cancer in burn scars has declined in recent years, possibly due to the wider use of this approach [12].

However, the diagnosis of a pathological lesion within a burn scar should not reduce the physician's vigilance. Different types of pathological cells have been found within a single scar in the same patient. There is a known case of a patient in whom SCC in situ, melanoma in situ, and a multinucleated giant cell reaction were identified in an extensive burn scar [12]. Identification of a pathology in one scar area should not lead to underestimating the remaining areas. Cancers arising within different scar regions can occur multifocally; therefore, monitoring and early treatment of the entire burn-healed area are vital.

Also, a case has been reported of a patient with multiple melanomas within a scar on the right side of the body and the upper limb. The tumours were excised, and the resulting defect was covered with STSG. No metastases were detected during diagnostic workup, highlighting the importance of early diagnosis [17].

Marjolin ulcers are also encountered in our population, often developing in burn scars that have healed spontaneously. Vigilant surveillance is essential for managing chronic non-healing ulcers, and all suspicious lesions should be biopsied [18]. Early diagnosis, aggressive treatment, and close follow-up are crucial for patient outcomes [12].

Conclusions

Squamous cell carcinoma arising in burn scars, known as Marjolin ulcer, is a rare yet highly aggressive skin malignancy. The described case of our 63-year-old patient demonstrates that chronic scar tissue can undergo malignant transformation even many years after the injury. Careful monitoring, appropriate scar management, and prompt evaluation of symptoms, such as bleeding, changes in appearance, itching, or increased susceptibility to trauma, are essential for prevention. Early histopathological diagnosis of chronic, non-healing wounds within burn scars is crucial for guiding treatment and improving patient prognosis, highlighting the importance of close patient-physician collaboration to promptly detect any abnormalities. Surgical excision with adequate margins combined with a split-thickness autologous skin graft proves an effective treatment approach. Regular oncological monitoring and close postoperative follow-up are vital for preventing recurrence and improving outcomes. The described case underscores the importance of prompt cancer diagnosis and appropriate management of burn scar lesions.

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