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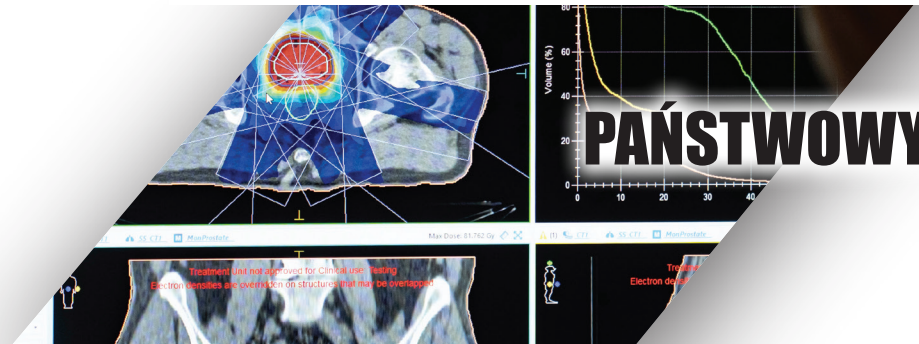

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   Books:
   Rudzki E. Alergia na leki: z uwzględnieniem odczynów anafilaktycznych i idiosynkrazji. Lublin, Wydawnictwo Czelej, 2002

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Letter from the Editor-in-Chief

Dear Readers,

I am pleased to present this year's third issue of *Military Physician*, which uniquely brings together peacetime and battlefield medicine – a particularly timely combination given the ongoing armed conflicts worldwide.

The issue opens with a review section featuring a noteworthy paper on battlefield neurosurgery. This segment also includes a study on high-altitude cerebral edema (HACE). The review section features articles on wound healing and modern treatment approaches for hypertrophic and keloid scars. In the original paper section, I recommend an analysis of the relationship between body mass index (BMI) and the risk of axillary fat infiltration in women with primary breast cancer initially classified as cN0.

A special place in this issue is occupied by the memorial section, in which we bid farewell to Professor Stanisław Ilnicki (1942–2025), an outstanding physician, scientist, and humanist whose achievements have become a lasting part of the history of Polish military psychiatry.

I would like to express my gratitude to all the authors for entrusting us with their work and the reviewers for their diligent efforts, which help maintain the journal's high standards.

I wish you an enjoyable and inspiring read, and continued success in your scientific and clinical work.

With best regards

Prof. Bolesław Kalicki, MD, PhD

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REVIEW ARTICLE

THE ROLE OF NEUROSURGERY IN ARMED CONFLICTS

Neurochirurgia w obliczu konfliktów zbrojnych

Miłosz Chwiałkowski

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Abstract

Neurosurgery, as a surgical subspeciality, frequently fulfils a crucial role during armed conflicts. The specific nature of craniocerebral injuries poses a challenge in diagnostic and therapeutic management. An analysis of military operations in recent years underscores the importance of developing and investing in neurosurgical resources within the military healthcare services.

Streszczenie

Neurochirurgia jako dziedzina zabiegowa odgrywa istotną rolę podczas konfliktów zbrojnych. Specyfika urazów czaszkowo-mózgowych jest wyzwaniem w odpowiednim procesie diagnostyczno-terapeutycznym. Analizując działania militarne ostatnich lat, warto mieć na względzie rozwój oraz inwestowanie w zaplecze neurochirurgiczne wojskowej służby zdrowia.

Keywords: neurosurgery; war; traumatic brain injury

Słowa kluczowe: neurochirurgia; wojna; pourazowe uszkodzenie mózgu

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Introduction

Armed conflicts pose significant challenges for both military and civilian healthcare systems. Evolving combat methods and novel technologies alter the nature of injuries sustained by those directly involved in military operations. As a specialty involved in trauma care, neurosurgery must adapt to meet these challenges. The head and spine are among the most frequently injured anatomical regions on the battlefield, underscoring the critical role of this medical subspeciality in preserving life and improving outcomes in patients with moderate to severe war-related trauma.

Discussion

Over the years, numerous treatment protocols have been developed for patients with traumatic brain injury (TBI), spinal cord injury, and peripheral nerve injury. However, in an era of continuous changes and advancements in clinical care, some of these protocols, such as the Guidelines for Field Management of Combat-Related Head Trauma, which was last revised in 2005 (Brain Trauma Foundation), require updating. Military conflicts over the past century have contributed to the development of neurosurgical practice. One example is the technique of surgical debridement of head wounds, which has shifted from a maximal to a minimal approach [1, 2].

Explosions are presently the most common cause of battlefield head injuries, accounting for more than half of all TBIs. In contrast, earlier conflicts, such as the Vietnam War, were characterized by a much higher proportion of gunshot wounds. Currently, gunshot wounds rank second. TBIs remain the leading cause of death on the battlefield [2]. It was already during World War I, when Harvey Cushing, one of the pioneers in global neurosurgery, recommended early treatment of patients with craniocerebral injuries as close to the battlefield as possible, an approach that reduced mortality by half.

In subsequent years, during military operations in Iraq, the concept of damage control neurosurgery emerged, encompassing the management of intracranial haemorrhage, evacuation of intracranial haematomas, and early wound debridement. Considering armed conflicts after 2000, decompressive craniectomy (DC) has been the most commonly employed treatment for patients with head trauma. It is worth noting, however, that this procedure is not indicated in every case. Knowledge of standard, non-invasive approaches for elevated intracranial pressure (including the use of hypertonic saline and mannitol) remains essential [3, 4]. The choice of treatment modality is largely guided by the widely used Glasgow Coma Scale (GCS), with aggressive therapy recommended for patients scoring 4–7. Decisions regarding invasive treatment require surgical personnel to be familiar with appropriate incision techniques, such as a trauma flap, Kempe incision, or Souttar incision, to preserve tissue integrity, minimize skin complications, and ensure adequate access to the cranial cavity [5]. This is particularly important in complex injuries involving the facial skeleton and skull base, where adequate bony opening, cranialization of the frontal sinuses, and water-tight dural closure are crucial [6]. Postoperative complications may include nervous system infections, epilepsy, and cerebrospinal fluid leakage [7]. It is important to note that nearly one-third of head injury patients may experience concomitant vascular complications. Traumatic intracranial aneurysms can lead to sudden death in the days following head injury; therefore, vascular imaging (e.g. angiography) should be considered in these patients. The devastating impact of war on children is a profound tragedy, as this population is at particularly high risk of death from TBI compared with adults. Clear guidelines for the management of paediatric battlefield-related head trauma are currently lacking. Furthermore, long-term sequelae, including depression, learning difficulties, impaired concentration, and aggression, may have profound developmental consequences [8]. It is worth noting that patients with severe TBI are at risk of coagulopathy requiring blood transfusion [1].

The management of spinal injuries is determined by the presence of neurological deficits. In facilities close to the front line, decompression and control of cerebrospinal fluid leakage are the primary priorities for these patients.

Peripheral nerve injuries, which affect 3–10% of patients with limb injuries depending on the source, represent another important neurosurgical challenge. Appropriate management of battlefield-related peripheral nerve injuries is crucial for ensuring a rapid return to military service and, consequently, maintaining optimal combat capability. The causes of these injuries range from gunshot wounds, backpack palsy, and the use of restraints on prisoners to explosions, which currently represent the most common cause. Peripheral nerve injuries can often be overlooked in patients with multiple organ injuries and concomitant brain damage who present with impaired consciousness. Typically, under wartime conditions, they do not require immediate surgical management, but rather delayed treatment after 2–3 months. Access to adequate diagnostic facilities, including electrophysiological and imaging techniques, is also important [9, 10].

The rapidly growing number of individuals requiring urgent medical attention poses a major challenge to healthcare services, which are often already strained even under peacetime conditions. The destruction of infrastructure and disruption of supply chains further exacerbate this situation. From a neurosurgical perspective, maintaining an adequate supply of equipment and materials, including surgical microscopes, craniotomy instruments, dural substitutes, and haemostatic materials, is essential [5]. Experience from the armed conflict in Ukraine has revealed some fundamental shortcomings, such as interruptions in electricity supply (e.g. preventing the use of surgical microscopes) and difficulties in sterilizing surgical instruments [11]. Doctors are often forced to perform procedures beyond the scope of their speciality [12]. Given that general surgeons account for the vast majority of physicians working under battlefield conditions, greater emphasis should be placed on training in basic neurosurgical procedures for craniocerebral injuries [2, 13]. Many civilian medical facilities may be repurposed into frontline hospitals during armed conflict, which underscores the importance of educating medical personnel and exchanging experience [14].

Another challenge is the growing number of patients requiring long-term therapy, including rehabilitation, necessitating a significant expansion of neurological rehabilitation facilities. From the perspective of comprehensive care for TBI patients, institutions providing access to a full range of services, enabling treatment of complex injuries (maxillofacial surgeon, neurosurgeon), as well as long-term complications related to post-traumatic vascular malformations (interventional radiology department), play a key role [15]. Imaging diagnosis is crucial for making prompt and appropriate therapeutic decisions. Accessibility is by all means the most important aspect. Portable computed tomography (CT) scanners can represent an excellent solution, as they help avoid the need for long-distance transport of the injured, as well as facilitate accurate diagnosis and further treatment in the frontline setting [16].

Conclusions

Given the high incidence of craniocerebral injuries and the critical importance of early intervention in reducing mortality and improving patients' long-term quality of life, the presence of a neurosurgeon within the medical personnel of the armed forces appears to be essential.

References

1. Maroufi SF, Sohrabi H, Dabbagh Ohadi MA, et al. Neurosurgery in 21st-century wars in the Middle East: narrative review of literature. World Neurosurg, 2022; 166: 184–190. doi: 10.1016/j.wneu.2022.07.134
2. Asfaw ZK, Greisman JD, Comuniello B, et al. Global neurosurgery advances from trenches to bedside: lessons from neurosurgical care in war, humanitarian assistance, and disaster response. Mil Med, 2024; 189(3–4): e532–e540. doi: 10.1093/milmed/usad170
3. Le TD, Gurney JM, Singh KP, et al. Trends in traumatic brain injury among U.S. Service Members deployed in Iraq and Afghanistan, 2002–2016. Am J Prev Med., 2023; 65(2): 230–238. doi: 10.1016/j.amepre.2023.01.043

4. Durrani S, Nathani KR, Mualem W, et al. The impact of major military war campaigns on neurosurgery: informetric data and time-trend analysis. World Neurosurg, 2022; 168: e240–e252. doi: 10.1016/j.wneu.2022.09.085
5. Splavski B. Personal reflections of a war neurosurgeon. World Neurosurg. 2024; 183: 76–78. doi: 10.1016/j.wneu.2023.12.031
6. Sirko A, Berlin C, Tsang S, et al. Wartime penetrating traumatic brain injury of the anterior skull base involving the paranasal sinuses: a single-center, first-year experience from Dnipro, Ukraine. J Neurosurg, 2024; 142(3): 829–838. doi: 10.3171/2024.6.JNS24852
7. Hanafi I, Munder E, Ahmad S, et al. War-related traumatic brain injuries during the Syrian armed conflict in Damascus 2014–2017: a cohort study and a literature review. BMC Emerg Med., 2023; 23(1): 35. doi: 10.1186/s12873-023-00799-6
8. Aguirre AS, Rojas K, Torres AR. Pediatric traumatic brain injuries in war zones: a systematic literature review. Front Neurol, 2023; 14: 1253515. doi: 10.3389/fneur.2023.1253515
9. Seddighi A, Nikouei A, Seddighi AS, et al. Peripheral nerve injury: a review article. International Clinical Neuroscience Journal, 2016; 3(1): 1–6. doi: 10.22037/icnj.v3i1.12016
10. Howard IM, Sedarsky K, Gallagher M, et al. Combat-related peripheral nerve injuries. Muscle Nerve, 2025; 71(5): 768–781. doi: 10.1002/mus.28168
11. Okon II, Rehman IU, Amir MA, et al. Addressing neurosurgical challenges in war conflict countries. Neurosurg Rev. 2024; 47(1): 390. doi: 10.1007/s10143-024-02655-y
12. Dubinski D, Kolesnyk V. War in Ukraine: a neurosurgical perspective. Acta Neurochir (Wien), 2022; 164(12): 3071–3074. doi: 10.1007/s00701-022-05388-3
13. Sirko A, Valadka AB, Yadav G, et al. Neurokirurgisk behandling av stridsrelaterade hjärnskador [Neurosurgical management of combat-related penetrating traumatic brain injury – lessons from 10 years of war in Ukraine]. Lakartidningen, 2025; 122: 24113. Swedish
14. Loskutov OA, Pylypenko MM. The courage of Ukrainian hospitals and Intensive Care Units in the first months of the Russia-Ukraine war. Intensive Care Med, 2022; 48(6): 790–792. doi: 10.1007/s00134-022-06694-1
15. Sirko A, Cherednychenko Y, Dowlati E, et al. Early multimodal neurointerventional and neurosurgical management of penetrating craniocerebral injuries: wartime experience from Ukraine. J Neurosurg, 2025; 143(2): 431–442. doi: 10.3171/2024.10.JNS241938
16. Illemann NM, Illemann TM. Mobile imaging trailers: A scoping review of CT and MRI modalities. Radiography (Lond), 2024; 30(2): 431–439. doi: 10.1016/j.radi.2023.12.008

REVIEW ARTICLE

POST-FINASTERIDE SYNDROME: AN OVERVIEW OF ITS MECHANISMS, SYMPTOMS, AND THERAPEUTIC OPTIONS

Zespół pofinasterydowy: przegląd mechanizmów, objawów i opcji terapeutycznych

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Abstract

Post-finasteride syndrome is a complex condition characterized by psychological, sexual, and somatic symptoms observed in patients currently or previously treated with 5α-reductase inhibitors. Although these agents are commonly used in the management of benign prostatic hyperplasia and androgenetic alopecia, an increasing number of cases report persistent adverse effects even after treatment discontinuation. The lack of clearly defined pathophysiological mechanisms and the limited availability of clinical research complicate the diagnosis and management of post-finasteride syndrome. This paper reviews the current understanding of post-finasteride syndrome, including its potential molecular pathways, clinical presentation, and therapeutic approaches. Strong evidence supports the existence of post-finasteride syndrome, and the European Medicines Agency has recognized suicidal ideation as an adverse effect of finasteride administered at doses used to treat androgenetic alopecia. Various therapies can be administered to alleviate the symptoms of post-finasteride syndrome, and effective communication with patients is essential to ensure that adverse events are recognized and addressed. An interdisciplinary framework should be used for the implementation of treatment with 5α-reductase inhibitors, with patients undergoing thorough physical and mental health assessments prior to treatment initiation.

Streszczenie

Zespół pofinasterydowy jest złożonym stanem klinicznym obejmującym objawy psychiczne, seksualne i somatyczne, obserwowanym u pacjentów aktualnie lub uprzednio leczonych inhibitorami 5α-reduktazy. Choć leki te są powszechnie stosowane w terapii łagodnego rozrostu gruczołu krokowego oraz łysienia androgenowego, w coraz większej liczbie przypadków odnotowuje się utrzymywanie działań niepożądanych także po zakończeniu terapii. Brak jednoznacznie określonych mechanizmów patofizjologicznych oraz ograniczona liczba badań klinicznych utrudniają rozpoznawanie i leczenie tego zespołu. Niniejsza praca przedstawia aktualny stan wiedzy na temat zespołu pofinasterydowego, jego potencjalnych mechanizmów molekularnych, obrazu klinicznego oraz możliwych podejść terapeutycznych. Istnieją silne dowody potwierdzające istnienie tego zespołu, a Europejska Agencja Leków uznała myśli samobójcze za działanie niepożądane finasterydu stosowanego w dawkach terapeutycznych w leczeniu łysienia androgenowego. Różne metody terapeutyczne mogą być stosowane w celu łagodzenia objawów zespołu pofinasterydowego, a kluczową rolę odgrywa komunikacja z pacjentem, aby działania niepożądane mogły być wcześnie rozpoznane i odpowiednio leczone. Wdrożenie leczenia inhibitorami 5α-reduktazy powinno odbywać się w ramach podejścia interdyscyplinarnego, z uwzględnieniem szczegółowej oceny stanu somatycznego i psychicznego pacjenta przed rozpoczęciem terapii.

Keywords: 5α-reductase inhibitors; adverse effects; androgenetic alopecia; benign prostatic hyperplasia; post-finasteride syndrome

Słowa kluczowe: inhibitory 5α-reduktazy; działania niepożądane; łysienie androgenowe; łagodny rozrost gruczołu krokowego; zespół pofinasterydowy

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Introduction

Post-finasteride syndrome (PFS) is the term used to describe the occurrence of various adverse psychological, sexual, and somatic symptoms in patients who are currently using, or who used 5α-reductase inhibitors more than three months earlier, regardless of the therapeutic indication [1]. More than 50% of Caucasian men experience androgenetic alopecia, also known as male pattern hair loss. Over 60% of men older than 60 years are diagnosed with benign prostatic hyperplasia, of whom approximately 40% are symptomatic [2, 3]. Consequently, the number of patients eligible for treatment with 5α-reductase inhibitors is substantial, and drugs from this class are widely used in clinical practice.

Since 1992, the United States Food and Drug Administration has approved finasteride at a dose of 5 mg per day for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. Since 1997, the same active ingredient at a dose of 1 mg per day has been approved for treating androgenetic alopecia. Currently, dutasteride at a dose of 0.5 mg per day is another 5α-reductase inhibitor widely used for the treatment of symptomatic benign prostatic hyperplasia.

Finasteride acts as a weak inhibitor of the type I and a potent inhibitor of the type II isoform of the 5α-reductase enzyme. This enzyme, which is responsible for the conversion of testosterone to 5α-dihydrotestosterone, is expressed, among other tissues, in the prostate gland, seminal vesicles, epididymis, hair follicles, brain, and liver. Dutasteride has a strong inhibitory effect on the type II isoform and also exhibits significant affinity for the type I isoform, which is also present in the skin and muscles. The reduction in 5α-dihydrotestosterone concentrations achieved during therapy with 5α-reductase inhibitors results in decreased androgenic effects on prostate tissue and hair follicles.

Safety of therapy and controversies surrounding PFS

For many years, the use of finasteride and dutasteride for approved indications was considered safe and well tolerated. Recently, however, concerns have arisen regarding the safety of these drugs, partly due to the influence of patient organizations, particularly in the United States, that bring together individuals who have reported sexual, psychological, and somatic disorders during and after treatment with 5α-reductase inhibitors.

This has led to the initiation of research and systematic collection of data on potential adverse effects associated with the use of 5α-reductase inhibitors. To date, only a limited number of scientific studies dedicated to PFS have been published, most of which are based on subjective patient reports. Difficulties in analyzing PFS arise, among other reasons, from the lack of well-established molecular and genetic mechanisms underlying the syndrome, the absence of clear and widely accepted diagnostic criteria, and insufficient awareness among physicians prescribing 5α-reductase inhibitors. These physicians rarely report adverse effects.

In recent years, PFS has been listed as a potential consequence of 5α-reductase inhibitor use in the United States National Institutes of Health's rare disease registry (The Rare Diseases Clinical Research Network, funded by the NIH); however, PFS is still not recognized as a distinct clinical entity.

Use and mechanism of action of 5α-reductase inhibitors

The widespread use of 5α-reductase inhibitors in clinical practice results from the large target population and the proven beneficial effects of these drugs on lower urinary tract symptoms. These effects are due to the ability of the inhibitors to reduce prostate volume by inhibiting the conversion of testosterone to dihydrotestosterone, the key androgen that stimulates stromal and epithelial cell proliferation in the prostate [4, 5]. Lowering 5α-dihydrotestosterone levels leads to a reduction in prostate mass, decreased urethral pressure, and improved urinary flow.

Clinical trials, such as the Proscar Long-Term Efficacy and Safety Study, have demonstrated that treatment with finasteride reduces prostate volume by approximately 20% to 30% after 6 to 12 months of therapy, and significantly decreases the risk of acute urinary retention and the need for surgical intervention in patients with benign prostatic hyperplasia [6]. Moreover, dutasteride, which inhibits both type I and type II 5α-reductase isoforms, produces a greater reduction in 5α-dihydrotestosterone levels in serum and prostate tissue (over 90%) compared with finasteride (approximately 70%) [7].

The mechanism of action of 5α-reductase inhibitors also includes the reduction of inflammation and edema within the prostate, which further contributes to the alleviation of lower urinary tract symptoms. However, the therapeutic effect becomes apparent only after several months of use. This distinguishes 5α-reductase inhibitors from α-adrenolytic agents, which act more rapidly by relaxing the smooth muscles of the bladder neck and prostate.

The effect of 5α-reductase inhibitors on androgenetic alopecia results from their ability to reduce the local concentration of 5α-dihydrotestosterone in the scalp, specifically within the hair follicles, particularly in the frontoparietal region [8]. Excessive 5α-dihydrotestosterone activity leads to the miniaturization of hair follicles, shortening of the anagen phase, and prolongation of the telogen phase. Ultimately, this process causes hair thinning, reduced hair shaft diameter, and progressive hair loss.

Finasteride, a selective type II 5α-reductase inhibitor, reduces 5α-dihydrotestosterone levels in the scalp by approximately 60% and in plasma by approximately 70%. This helps halt follicular miniaturization, improve follicular blood supply and, consequently, nourishment, and prolong the anagen phase. Randomized clinical trials have shown that treatment with finasteride at a dose of 1 mg per day for 12 months increased hair density, halted hair loss in 83% of men, and led to significant aesthetic improvement in 66% of patients [9].

Dutasteride, by inhibiting both type I and II 5α-reductase isoforms, produces an even greater reduction in 5α-dihydrotestosterone levels (more than 90%), which may translate into greater clinical efficacy compared with finasteride. However, its use for androgenetic alopecia is approved in only some countries and remains off-label in the United States and Europe [9].

That 5α-reductase inhibitors are lipophilic and can cross the blood–brain barrier, thereby exerting effects on the central nervous system, is not widely recognized [10]. The enzyme 5α-reductase plays a crucial role in the metabolism of neuroactive steroids within the central nervous system. Three isoforms of this enzyme have been identified in the brain, where they participate in the conversion of testosterone and progesterone to their active metabolites of dihydrotestosterone and dihydroprogesterone, respectively.

These products are further metabolized into neuroactive derivatives such as allopregnanolone, isopregnanolone, 5α-androstan-3α,17β-diol, and 5α-androstan-3β, 17β-diol. These compounds modulate the activity of neurosteroid receptors, including the GABA-A receptor complex, thereby playing an important role in regulating emotional, cognitive, and behavioral processes [11].

As an inhibitor of type II 5α-reductase and, to a lesser extent, type I, finasteride disrupts this metabolic pathway. Such disruption may lead to significant alterations in the concentrations of neuroactive steroids in both plasma and cerebrospinal fluid.

Neurobiological and hormonal mechanisms of PFS

Studies in patients with PFS have demonstrated decreased concentrations of pregnenolone, progesterone, and dihydroprogesterone in the cerebrospinal fluid, accompanied by increased levels of dehydroepiandrosterone and testosterone. Concurrently, reductions in 5α-dihydrotestosterone and 17β-estradiol levels were observed, indicating extensive disturbances of the neurosteroid axis in this group of patients [12].

Experimental studies have also documented changes in the expression of androgen receptors, estrogen receptors, and GABA-A receptor subunits in the brain, which may contribute to the persistence of neuropsychiatric symptoms [12]. These mechanisms may be further modulated by epigenetic phenomena [13, 14]. The frequency of methylation of the *SRD5A2* gene promoter, which encodes type II 5α-reductase, has been shown to be higher in the cerebrospinal fluid of patients with PFS than in that of the control group [13, 14].

Studies using animal models have demonstrated that chronic inhibition of 5α-reductase activates inflammatory mechanisms within the central nervous system, including an increased number of astrocytes and elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin-1β, in the hippocampus. These changes are accompanied by reduced neurogenesis in the hippocampus: This may contribute to the depressive symptoms and cognitive deficits observed in patients.

Clinical presentation of PFS

At the clinical level, symptoms in patients with PFS can be classified into three main categories: sexual, psychological, and somatic.

The most frequently reported sexual dysfunctions include decreased or absent libido; erectile dysfunction, affecting both the initiation and maintenance of an erection; orgasmic disorders involving both the ability to achieve orgasm and the perception of orgasmic sensations; reduced ejaculate volume; and complete absence of ejaculation [15, 16]. Less common complications include testicular atrophy, prostatitis, subjective perception of penile shortening, and infertility. The literature also describes an unusual symptom – a subjective feeling of incoherence between central nervous system activity and the functioning of genital organs – described by patients as "penis disconnected from the body," and referred to in the English-language literature as *brain–penis disconnect*.

Among the psychological symptoms, affective disorders, including depressive episodes and dysthymia, are predominant. Anxiety disorders and cognitive impairment involving difficulties with comprehension, problem-solving, decision-making, and slowed thought processes – often referred to as *brain fog* – have been reported [17]. Emotional disturbances (such as blunted affect and anhedonia), memory deficits, sleep disorders, as well as suicidal thoughts and self-harming behaviors [18], have also been described.

Somatic manifestations include skin changes (rash), muscle atrophy and weakness, gynecomastia, chronic fatigue, and hearing disturbances (including hearing loss and tinnitus).

Criteria for the diagnosis and diagnostic evaluation of PFS

The diagnostic criteria for PFS were proposed in a consensus statement published in the *International Journal of*

Risk & Safety in Medicine by David Healy and colleagues under the auspices of the European Society for Sexual Medicine.

The primary criterion for the diagnosis of PFS is prior use of a 5α-reductase inhibitor, followed by the onset of sexual dysfunction during therapy with the inhibitor or after its discontinuation. These symptoms must persist continuously for at least 3 months (Fig. 1).

The key sexual symptoms recognized in the criteria and necessary for establishing the diagnosis include decreased libido, erectile dysfunction, reduced genital and orgasmic sensations, and decreased ejaculate volume. An important diagnostic element is the absence of pre-existing sexual dysfunction and the exclusion of other diseases, medications, or factors that could explain the current complaints.

In addition to sexual dysfunction, some patients present with the aforementioned cognitive and neuropsychiatric symptoms, which – although not essential for the diagnosis of PFS – frequently co-occur. These include brain fog, memory and concentration difficulties, slowed thinking, and emotional disturbances such as depression (including suicidal ideation), anxiety, panic attacks, irritability, anhedonia, and insomnia.

Notably, patients using 5α-reductase inhibitors may experience symptoms such as gynecomastia and changes in semen quality or volume; however, these symptoms are not pathognomonic for PFS and are not required for diagnosis.

Risk factors and predisposed groups

Importantly, most data on PFS are based on retrospective observations and patient reports, whereas available clinical studies have significant methodological limitations. The pathophysiological mechanisms underlying PFS remain a matter of debate and, in some cases, the contribution of the nocebo effect to the reported symptoms cannot be entirely ruled out.

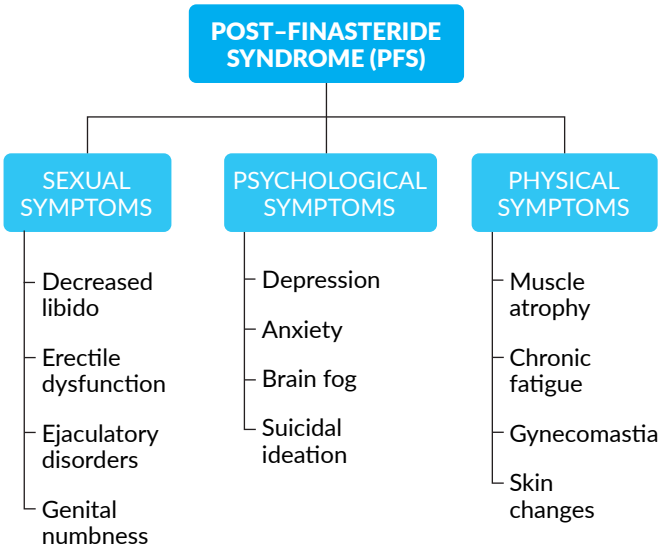

Figure 1. Post-finasteride syndrome – symptoms

Evidence suggests that PFS – although still controversial as a distinct nosological entity – may occur in predisposed individuals. An increasing number of reports indicate that even short-term exposure to 5α-reductase inhibitors can lead to the development of persistent neuropsychiatric disorders in susceptible individuals. Groups at particular risk of developing PFS include men with a history of depression, anxiety disorders, other psychiatric conditions, or sexual dysfunction, who – as shown in studies – are more likely to experience persistent neuropsychiatric and sexual adverse effects after discontinuing finasteride. Additional risk factors include a history of psychiatric disorders in first-degree relatives, a history of infertility or reduced fertility, and long-term use of finasteride. A treatment duration exceeding 7 months has been identified as an independent predictor of persistent symptoms.

Analysis of data from the United States Food and Drug Administration Adverse Event Reporting System indicates that reports of PFS are more frequent among younger men taking the 1 mg dose used for androgenetic alopecia than among older patients taking the 5 mg dose commonly prescribed for benign prostatic hyperplasia [19, 20]. Based on the available evidence, particular caution should also be exercised in patients older than 35 years with risk factors for metabolic syndrome; preliminary screening for insulin resistance is recommended in these patients. Attention should also be paid to potential molecular underpinnings, such as genetic variability (e.g., polymorphisms in the androgen receptor gene) and epigenetic mechanisms (including methylation of the *SRD5A2* gene promoter) [21], which may modulate the body's response to therapy and predispose certain individuals to developing PFS.

Therapeutic options and clinical approach

Given these observations, special caution is advised when considering treatment with 5α-reductase inhibitors in patients belonging to high-risk groups, and alternative therapeutic strategies should be explored. Topical preparations such as minoxidil can be used to treat androgenetic alopecia; this agent acts independently of the testosterone-to-dihydrotestosterone conversion pathway and has a different adverse effect profile. Furthermore, interest in low-level laser therapy devices is growing. This approach may stimulate hair growth through photobiomodulation.

Conclusions

For lower urinary tract symptoms in patients at risk of developing PFS, phosphodiesterase type 5 inhibitors, which can improve sexual function and urinary flow without directly affecting the androgen hormonal axis, may be a treatment option. Drugs from this class, along with α-adrenergic antagonists, may serve as pharmacologic alternatives for symptomatic benign prostatic hyperplasia. If pharmacotherapy is not effective in alleviating symptoms, patients can be offered a wide range of procedural interventions tailored to their individual needs and clinical condition.

Because the pathophysiological mechanisms underlying PFS remain unknown, causal treatment is currently

not possible, and interventions are symptomatic and supportive. Current recommendations emphasize the need for an integrated biopsychosocial approach that considers biological, psychological, and social aspects. Psychological and psychiatric support plays a key role and includes cognitive behavioral therapy, treatment of coexisting depressive or anxiety disorders, with a preference for antidepressants with a minimal impact on sexual function (e.g., bupropion, mirtazapine), and sex therapy incorporating sensate focus techniques and motivational interviewing.

PDE5 inhibitors or intracavernosal injections are used to treat erectile dysfunction, and supportive measures may include supplementation with, for example, vitamin D, vitamin E, L-arginine, or L-carnitine. These supplements may positively influence nitric oxide metabolism and vascular function.

Cilio et al. [22] describe PFS as a relatively rare syndrome, with symptoms that may persist for more than a year after finasteride discontinuation. The authors also discuss several potential factors that may contribute to PFS, including androgen receptor gene polymorphisms and changes in the gut microbiota. In another study, authored by Thaibah and published in 2025 [23], an extensive dataset involving more than 9,400 participants with PFS was analyzed. The results revealed that nearly 18% of participants reported suicidal ideation and 7% had attempted suicide. Based on these findings, the European Medicines Agency formally recognized suicidal ideation as an adverse effect of finasteride at a dose of 1 mg, the dose used to treat androgenetic alopecia.

Cilio et al. [22] discussed PFS and its core side effects, which require a complex diagnostic process. The authors emphasized that the absence of clearly established pathophysiological mechanisms cannot be grounds for denying the existence of the syndrome, especially given the increasing number of consistent clinical observations.

A promising, although still experimental, area of research is the development of therapies targeting neuroactive steroids and modulation of androgen receptor expression. However, none of the available therapeutic regimens guarantees complete remission of symptoms. The goal of treatment is the gradual alleviation of symptoms and improvement of patients' quality of life. Given the possible influence of the nocebo effect, effective communication with the patient is crucial, including ensuring that reported complaints are taken seriously and fostering a trust-based therapeutic relationship. Treatment should be implemented within an interdisciplinary framework involving physicians, psychologists, and sexologists. In every case, the decision to initiate therapy with a 5α-reductase inhibitor should be preceded by a thorough assessment of the patient's physical and mental health and by obtaining informed consent after discussion of the potential benefits and risks.

References

1. Traish AM, Hassani J, Guay AT, et al. Adverse side effects of 5α-reductase inhibitors therapy: persistent diminished libido and erectile dysfunction and depression in a subset of patients. J Sex Med, 2011; 8(3): 872–884. doi: 10.1111/j.1743-6109.2010.02157.x
2. Mysore V, Shashikumar BM. Guidelines on the use of finasteride in androgenic alopecia. Indian J Dermatol Venereol Leprol, 2016; 82(2): 128–134. doi: 10.4103/0378-6323.177432
3. Than J, Rodriguez K, Khera M. Post-finasteride syndrome: a review of current literature. Curr Sex Health Rep, 2018; 10: 152–157. doi: 10.1007/s11930-018-0163-4
4. Chapple C, Abrams P, eds. Male lower urinary tract symptoms (LUTS): an international consultation on male LUTS. Fukuoka, Japan, September 30 – October 4, 2012. Montréal, Société Internationale d'Urologie, 2013
5. Smith AB, Carson CC. Finasteride in the treatment of patients with benign prostatic hyperplasia: a review. Ther Clin Risk Manag, 2009; 5(3): 535–545. doi: 10.2147/tcrm.s6195
6. Bruskewitz R, Girman CJ, Fowler J, et al. Effect of finasteride on bother and other health-related quality of life aspects associated with benign prostatic hyperplasia. PLESS Study Group. Proscar Long-term Efficacy and Safety Study. Urology, 1999; 54(4): 670–678. doi: 10.1016/s0090-4295(99)00209-5
7. Clark RV, Hermann DJ, Cunningham GR, et al. Marked suppression of dihydrotestosterone in men with benign prostatic hyperplasia by dutasteride, a dual 5alpha-reductase inhibitor. J Clin Endocrinol Metab, 2004; 89(5): 2179–2184. doi: 10.1210/jc.2003-030330
8. Drake L, Hordinsky M, Fiedler V, et al. The effects of finasteride on scalp skin and serum androgen levels in men with androgenetic alopecia. J Am Acad Dermatol, 1999; 41(4): 550–554
9. Lee SW, Juhasz M, Mobasher P, et al. A systematic review of topical finasteride in the treatment of androgenetic alopecia in men and women. J Drugs Dermatol, 2018; 17(4): 457–463
10. Caruso D, Pesaresi M, Abbiati F, et al. Comparison of plasma and cerebrospinal fluid levels of neuroactive steroids with their brain, spinal cord and peripheral nerve levels in male and female rats. Psychoneuroendocrinology, 2013; 38(10): 2278–2290. doi: 10.1016/j.psyneuen.2013.04.016
11. Melcangi RC, Caruso D, Abbiati F, et al. Neuroactive steroid levels are modified in cerebrospinal fluid and plasma of post-finasteride patients showing persistent sexual side effects and anxious/depressive symptomatology. J Sex Med, 2013; 10(10): 2598–2603. doi: 10.1111/jsm.12269
12. Giatti S, Garcia-Segura LM, Barreto GE, Melcangi RC. Neuroactive steroids, neurosteroidogenesis and sex. Prog Neurobiol, 2019; 176: 1–17. doi: 10.1016/j.pneurobio.2018.06.007
13. Cauci S, Chiriacò G, Cecchin E, et al. Androgen receptor (AR) gene (CAG)n and (GGN)n length polymorphisms and symptoms in young males with long-lasting adverse effects after finasteride use against androgenic alopecia. Sex Med, 2017; 5(1): e61–e71. doi: 10.1016/j.esxm.2016.11.001

14. Traish AM. The post-finasteride syndrome: clinical manifestation of drug-induced epigenetics due to endocrine disruption. Curr Sex Health Rep, 2018; 10: 88–103. doi: 10.1007/s11930-018-0161-6
15. Irwig MS, Kolukula S. Persistent sexual side effects of finasteride for male pattern hair loss. J Sex Med, 2011; 8(6): 1747–1753. doi: 10.1111/j.1743-6109.2011.02255.x
16. Liu L, Zhao S, Li F, et al. Effect of 5α-reductase inhibitors on sexual function: a meta-analysis and systematic review of randomized controlled trials. J Sex Med, 2016; 13(9): 1297–1310. doi: 10.1016/j.jsxm.2016.07.006
17. Ganzer CA, Jacobs AR, Iqbal F. Persistent sexual, emotional, and cognitive impairment post-finasteride: a survey of men reporting symptoms. Am J Mens Health, 2015; 9(3): 222–228. doi: 10.1177/1557988314538445
18. Ali AK, Heran BS, Etminan M. Persistent sexual dysfunction and suicidal ideation in young men treated with low-dose finasteride: a pharmacovigilance study. Pharmacotherapy, 2015; 35(7): 687–695. doi: 10.1002/phar.1612
19. Baas WR, Butcher MJ, Lwin A, et al. A review of the FAERS data on 5-alpha reductase inhibitors: implications for post-finasteride syndrome. Urology, 2018; 120: 143–149. doi: 10.1016/j.urology.2018.06.022
20. Gupta AK, Carviel J, Gupta MA, Shear NH. Assessing dutasteride-associated sexual dysfunction using the U.S. Food and Drug Administration Adverse Event Reporting System. J Eur Acad Dermatol Venereol, 2018; 32(8): 1373–1376. doi: 10.1111/jdv.14728
21. Melcangi RC, Casarini L, Marino M, et al. Altered methylation pattern of the SRD5A2 gene in the cerebrospinal fluid of post-finasteride patients: a pilot study. Endocr Connect, 2019; 8(8): 1118–1125. doi: 10.1530/EC-19-0199
22. Cilio S, Tsampoukas G, Morgado A, et al. Post-finasteride syndrome – a true clinical entity? Int J Impot Res, 2025; 37(6): 426–435. doi: 10.1038/s41443-025-01025-6
23. Thaibah HA, Banji OJF, Banji D, et al. Suicidality risks associated with finasteride, a 5-alpha reductase inhibitor: an evaluation of real-world data from the FDA adverse event reports. Pharmaceuticals (Basel), 2025; 18(7): 957. doi: 10.3390/ph18070957

REVIEW ARTICLE

UROSEPSIS AS A CLINICAL CHALLENGE: DIAGNOSIS, TREATMENT, AND MEDICAL PERSPECTIVES

Urosepsa jako wyzwanie kliniczne: diagnostyka, leczenie i perspektywy medyczne

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Abstract

Urinary tract infections are among the most common bacterial diseases in adults and, in some cases, may lead to the development of urosepsis, defined as a septic syndrome originating from the urinary tract. In civilian healthcare settings, urosepsis is generally straightforward to recognise and manage; however, military medicine presents additional challenges, such as delayed evacuation, limited diagnostic capabilities, and restricted therapeutic resources. The aim of this study was to analyse the epidemiology, diagnostic criteria, and therapeutic strategies in urosepsis, based on a literature review of PubMed, Scopus, and Web of Science databases (2019–2025), as well as current international guidelines (Sepsis-3, Surviving Sepsis Campaign, European Association of Urology). Particular emphasis was placed on rapid diagnostic methods, simplified risk-assessment tools, and treatment procedures feasible, for example, in field hospitals. Urosepsis is the most common septic syndrome in urology, which accounts for approximately 25% of all sepsis episodes. Under field conditions, the use of simplified clinical criteria (fever, hypotension, altered mental status) and bedside tests (urinalysis, basic inflammatory markers) is of primary importance, as complex clinical scoring systems such as SOFA or qSOFA are often impractical. Management requires immediate initiation of empirical antibiotic therapy, fluid resuscitation, early administration of vasopressors, and rapid removal of the source of infection. Early recognition using simple criteria, prompt initiation of empirical treatment, and adaptation of therapeutic procedures to field conditions are critical for improving patient outcomes.

Streszczenie

Zakażenia układu moczowego należą do najczęstszych chorób bakteryjnych u dorosłych, a w części przypadków mogą prowadzić do rozwoju urosepsy, definiowanej jako zespół septyczny wywodzący się z układu moczowego. W warunkach cywilnych urosepsa jest stosunkowo łatwa do rozpoznania i leczenia, jednak w medycynie wojskowej pojawiają się dodatkowe wyzwania, takie jak opóźniona ewakuacja, utrudniony dostęp do diagnostyki oraz ograniczone zasoby terapeutyczne. Celem pracy była analiza epidemiologii, kryteriów rozpoznania oraz strategii terapeutycznych stosowanych w urosepsie, którą przeprowadzono na podstawie przeglądu piśmiennictwa z baz PubMed, Scopus i Web of Science (2019–2025) oraz aktualnych wytycznych międzynarodowych (Sepsis-3, Surviving Sepsis Campaign, European Association of Urology). Szczególną uwagę zwrócono na szybkie metody diagnostyczne, uproszczone narzędzia oceny ryzyka oraz procedury terapeutyczne możliwe do wdrożenia na przykład w szpitalach polowych. Urosepsa jest najczęstszą postacią sepsy w urologii, odpowiada za około 25% przypadków sepsy. W warunkach polowych kluczowe znaczenie ma stosowanie uproszczonych kryteriów klinicznych (gorączka, hipotensja, zaburzenia świadomości) oraz badań przyłóżkowych (analiza moczu, podstawowe markery zapalne), gdyż rozbudowane kliniczne skale SOFA i qSOFA są często niepraktyczne. Leczenie obejmuje natychmiastowe wdrożenie antybiotykoterapii empirycznej, resuscytację płynową, wczesne zastosowanie leków wazopresyjnych i szybkie usunięcie źródła zakażenia. Wczesne rozpoznanie, oparte na prostych kryteriach, natychmiastowe wdrożenie leczenia empirycznego oraz dostosowanie procedur terapeutycznych do warunków polowych mają kluczowe znaczenie dla poprawy rokowania.

Keywords: sepsis; urinary tract infections; urosepsis; SOFA; qSOFA

Słowa kluczowe: sepsa; zakażenia układu moczowego; urosepsa; SOFA; qSOFA

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Introduction

Urosepsis is defined as a severe form of urinary tract infection in which the infection disseminates into the bloodstream, leading to sepsis, septic shock, and ultimately multi-organ failure. Sepsis, as defined by the Sepsis-3 criteria, is a critical condition in which infection triggers an abnormal host response that results in organ failure and poses a threat to life [1]. Urosepsis is characterised by a primary infectious focus within the urinary tract, which distinguishes it from other sepsis aetiologies [2].

In everyday clinical practice, urinary tract infections rank among the most common infectious diseases, and one of their serious complications is urosepsis, which accounts for approximately 25% of all sepsis episodes [3]. Reported case fatality rates range from 20% to 40% and may be even higher once septic shock develops [3]. Notably, each hour of delay in initiating effective targeted antimicrobial therapy increases mortality risk by approximately 7–8%.

Urosepsis is primarily regarded as a complication of acute pyelonephritis. In line with Sepsis-3 guidance, current practice emphasises the objective assessment of organ dysfunction using the Sequential Organ Failure Assessment (SOFA) or quick SOFA (qSOFA) scores, which facilitates more accurate risk stratification and timely therapeutic decision-making [1]. Scoring systems such as SOFA and qSOFA are not intended as diagnostic criteria but rather as prognostic tools designed to assess disease severity and mortality risk.

Urosepsis occurs predominantly in older adults and in individuals with comorbidities such as diabetes, chronic kidney disease, or immunosuppression. Additional major risk factors include urinary outflow obstruction, nephrolithiasis, and benign prostatic hyperplasia [2, 4]. Field conditions, limited access to specialist care, and constraints on medical evacuation further increase the risk and complexity of urosepsis management in military populations [4].

From a military medicine perspective, episodes of urosepsis may necessitate medical evacuation from the operation theatre, directly affecting unit readiness. Prevention and early intervention depend on training medical personnel to recognise sepsis promptly and on implementing the “first-hour bundle”, which encompasses rapid initiation of appropriate antimicrobials and haemodynamic/supportive measures [5, 6].

In summary, urosepsis remains one of the most serious complications of urinary tract infections. Its high mortality rate, rapid clinical progression, and potential for multi-organ involvement pose substantial diagnostic and therapeutic challenges. The literature underscores the need for further research into biomarkers that support early recognition and effective adjunctive therapies [5, 6].

Epidemiology and clinical significance

The epidemiology of urosepsis is a critical area of clinical and public health research, as it represents one of the most frequently encountered and aggressive forms of sepsis originating from urinary tract infections. Urosepsis accounts for approximately 25% of all sepsis cases, with reported mortality rates ranging from 20% to 40%, depending on the study population and the severity of disease at presentation [7, 8]. Differences in the epidemiological profile between community-acquired and hospital-acquired infections are illustrated in Figure 1.

In the general population, higher incidence rates are observed in older adults, particularly women, owing to their increased susceptibility to urinary tract infections. Additional risk factors include urolithiasis, urinary outflow obstruction, bladder catheterisation, immunosuppression, and chronic comorbidities, such as diabetes mellitus [7].

In hospital settings, antimicrobial resistance poses an escalating challenge, especially among *Enterobacterales* strains producing extended-spectrum beta-lactamases (ESBLs) and multidrug-resistant *Pseudomonas aeruginosa*. Rising prevalence of these pathogens complicates therapeutic management and is associated with poorer outcomes in patients with urosepsis [8].

The chart illustrates differences in incidence, mortality, pathogen spectrum, and antibiotic resistance. Hospital-acquired urosepsis is characterised by substantially higher incidence (approximately 70% vs. 30%), greater mortality (40% vs. 20%), more frequent involvement of multidrug-resistant organisms (80% vs. 40%), and a markedly higher rate of antibiotic resistance (90% vs. 30%) compared with community-acquired infections. These findings highlight the need for distinct diagnostic and therapeutic strategies depending on the site of infection onset, which is particularly relevant in field conditions where treatment options are limited.

An important epidemiological aspect is the distinction between community-acquired and hospital-acquired urosepsis. In the former, *Escherichia coli* remains the predominant pathogen, whereas in nosocomial infections, multidrug-resistant organisms such as *Klebsiella pneumoniae* and *Enterococcus faecium* are more frequently isolated. The latter group is also associated with higher

mortality rates, largely due to more severe clinical courses and limited therapeutic options [7].

In military settings, urosepsis carries particular significance, as field conditions such as dehydration, limited hygiene, and delayed access to specialised medical care during combat missions substantially increase the risk of severe urinary tract infections. Under these circumstances, rapid recognition and prompt intervention are crucial and can significantly reduce mortality.

Current projections indicate a global increase in the burden of urosepsis, driven by a longer life expectancy, more frequent use of urological procedures, and a growing number of immunocompromised patients. From this perspective, the epidemiology of urosepsis has emerged not only as a medical issue but also as a major challenge for healthcare systems worldwide [4, 9].

Pathophysiology of urosepsis

Among the most dangerous outcomes of urinary tract infections is urosepsis, a condition characterised by intricate mechanisms involving impaired immune regulation, alterations in microcirculation, and endothelial damage. Sepsis begins with the presence of pathogens in the urinary tract that trigger a systemic inflammatory response once translocated into the bloodstream. A critical factor is the imbalance between pro-inflammatory and anti-inflammatory mechanisms, ultimately leading to tissue injury and multi-organ dysfunction (MODS) [1].

In this process, key functions are carried out by macrophages, monocytes, and neutrophils, which release pro-inflammatory mediators including TNF-α, IL-1β, and IL-6. Excessive production of these mediators can result in a "cytokine storm", causing endothelial injury, increased vascular permeability, and arterial hypotension. Subsequent microcirculatory disturbances, including pericyte and endothelial cell dysfunction, lead to tissue hypoxia, lactic acidosis, and ultimately, MODS [10, 11].

Certain uropathogens, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterococcus faecalis*, can form biofilms that hinder host immune defences and reduce the efficacy of antimicrobial therapies. Moreover, urinary tract obstruction facilitates bacterial proliferation and increases the likelihood of progression to systemic infection [7, 12].

Clinically relevant biomarkers include serum lactate, a strong predictor of sepsis severity; procalcitonin (PCT); and C-reactive protein (CRP), which are widely used to assess infection activity and monitor treatment responses. Emerging markers such as presepsin and mid-regional pro-adrenomedullin show promise for future clinical application [13–15].

Overall, the pathophysiology of urosepsis is rooted in the complex interplay between pathogen virulence and the host immune response, leading to systemic organ dysfunction. A deeper understanding of these mechanisms is essential for improving early diagnosis and advancing the development of novel targeted therapies.

Importance of early diagnosis in urosepsis

The early diagnosis of urosepsis remains a critical determinant of effective treatment and mortality. Urosepsis is a severe clinical condition arising from urinary tract infection that leads to a systemic septic response, organ dysfunction, and a markedly increased mortality risk. The interval between symptom onset and the initiation of appropriate therapy is the primary prognostic factor, with each hour of delay in administering effective antibiotic treatment increasing mortality by approximately 7–8% [1, 6].

Standardised tools such as the SOFA score and the simplified qSOFA are employed to rapidly assess disease severity in urosepsis. Scoring systems such as SOFA and qSOFA do not serve as diagnostic tools in the strict sense; rather, they are intended solely for assessing the severity of organ dysfunction and forecasting the clinical

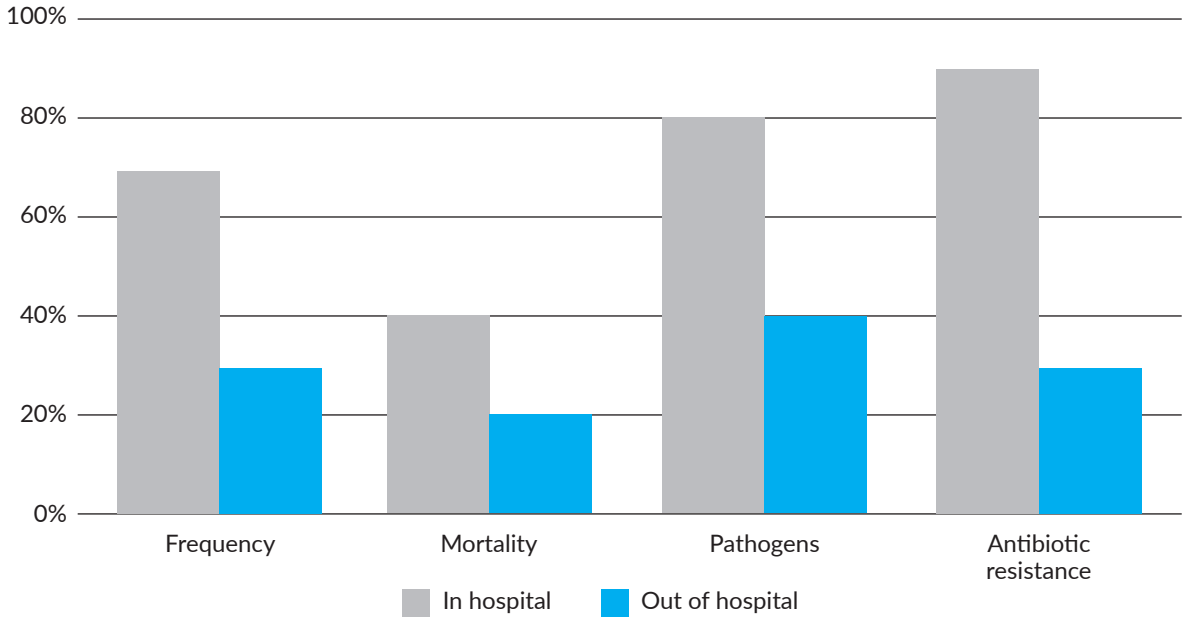

Figure 1. In-hospital and out-of-hospital differences in urosepsis [7, 8]

course. Their primary value lies in monitoring disease dynamics and identifying patients who require escalation of therapy, but they cannot substitute for sepsis diagnostic criteria. In military medicine, the diagnosis and management of urosepsis must be adapted to battlefield realities and limited access to specialised procedures. Simple assessment instruments, such as qSOFA, are of particular importance because they enable rapid identification of patients at risk of severe sepsis. When combined with physical examination and basic imaging such as point-of-care ultrasound (POCUS), these tools support early recognition and the initiation of life-saving interventions. In situations where full laboratory diagnostics are unavailable, therapeutic decisions must rely on the clinical picture and the immediate initiation of empirical antibiotics together with intensive supportive care. Implementing such a simplified protocol has the potential to improve prognosis and reduce mortality, even in field conditions. A practical battlefield approach involves a streamlined algorithm comprising: (1) rapid recognition of warning signs (fever, hypotension, altered mental status), (2) immediate initiation of empirical antibiotic therapy, (3) aggressive fluid resuscitation, and (4) evacuation to a referral centre if no improvement is observed [1, 4, 6].

These instruments facilitate the identification of patients at risk of severe sepsis who require urgent intervention. Owing to its simplicity and accessibility (evaluating respiratory rate, blood pressure, and mental status), qSOFA is particularly valuable in prehospital and military settings, where access to laboratory diagnostics may be limited [1].

In the evaluation of patients with suspected sepsis, the SOFA score demonstrates higher sensitivity (approximately 85%) compared with the qSOFA score (approximately 65%), making it more effective for detecting patients at risk of severe disease progression. Conversely, qSOFA exhibits greater specificity (80% vs. 70%), indicating that it is more reliable for ruling out false-positive cases. Importantly, both tools serve complementary roles: SOFA remains the standard for assessing sepsis severity in hospital and intensive care settings, while qSOFA, owing to its simplicity and higher specificity, is especially useful in prehospital environments and non-ICU wards [1].

The cornerstone of diagnosing and monitoring urosepsis is the rapid collection of biological samples (urine for analysis and culture; blood for microbiological testing) prior to the initiation of empirical antibiotic therapy [4]. Serum lactate concentration is considered a key prognostic biomarker, as elevated levels correlate with hypoperfusion and worse clinical outcomes [16, 17]. Additional biomarkers, including PCT and CRP, support the differentiation of bacterial infections and assist in monitoring treatment effectiveness [13, 16, 18].

Prompt detection of urinary tract obstruction is critical in urosepsis diagnostics. Ultrasonography of the urinary tract, particularly point-of-care ultrasound (POCUS), is a rapid and non-invasive method for identifying urinary retention and calculi, thereby preventing further clinical deterioration [19]. Computed tomography (CT) is recommended in cases with an ambiguous clinical presentation, especially when complications such as renal abscess or necrotising pyelonephritis are suspected, as CT enables superior visualisation of inflammatory changes and ischaemic areas within the renal parenchyma [19]. When urinary tract obstruction is identified as the underlying cause of sepsis, early urological intervention – such as percutaneous nephrostomy or placement of a JJ stent – may be required to decompress the collecting system and prevent further clinical decline [20, 21].

Within the framework of the "sepsis bundle," essential diagnostic and therapeutic measures should be performed within the first hour of recognition: microbiological sampling, assessment using SOFA/qSOFA, lactate measurement, initiation of empirical antibiotic therapy, and commencement of fluid resuscitation [6]. Early diagnosis is therefore an integral component of an effective therapeutic strategy.

In the military context, limited access to comprehensive diagnostics under field conditions poses a major challenge. Rapid and simple tools such as qSOFA and portable imaging modalities (POCUS), combined with adequate personnel training, are thus essential to minimise delays in recognition and intervention. A summary of key diagnostic and therapeutic approaches applicable in both civilian and field conditions is presented in Table 1.

The clinical management of urosepsis is critical for patient prognosis. Rapid identification and immediate treatment initiation significantly reduce mortality and limit the risk of multi-organ failure. Both the European Association of Urology guidelines [4] and the Surviving Sepsis Campaign unequivocally recommend a multidimensional approach including causal treatment (antibiotics and source control), life-supportive therapy, and continuous monitoring.

Therapeutic choices should depend on local resistance patterns, prior microbiological results, and the clinical condition of the patient. Carbapenems, third-generation cephalosporins, and fluoroquinolones are frequently used, while combination regimens are increasingly important in the context of increasing antimicrobial resistance [1, 4].

Supportive therapy must be initiated concurrently with causal treatment. The key element is aggressive crystalloid fluid resuscitation aimed at haemodynamic stabilisation, with close monitoring of cardiorespiratory parameters and hourly urine output. High-flow oxygen therapy or mechanical ventilation may be required in cases of severe respiratory failure [6].

Therefore, source control is essential. In urosepsis, this most often involves relief of urinary tract obstruction via JJ stent placement, percutaneous nephrostomy, or endoscopic urological intervention. The sooner the obstruction is removed, the greater the chance of eradicating the infection and reducing the risk of recurrence [4].

If hypotension persists after fluid therapy, vasopressor use (e.g. norepinephrine) is indicated. Metabolic monitoring of glucose, lactate, and electrolytes is also essential, with renal replacement therapy implemented if necessary. Therapy must be tailored to patient age,

Table 1. Diagnosis and management of urosepsis – comparison of civilian and military practice [1, 4, 6, 16, 22–24]

Stage of management	Civilian practice	Military / field practice
Diagnosis	Sepsis-3 criteria: infection + organ dysfunction (SOFA ≥2)	Clinical criteria: fever, tachycardia, tachypnoea, altered mental status; simplified qSOFA assessment
Laboratory diagnostics	Full laboratory panel: CBC, CRP, PCT, creatinine, blood and urine cultures	Urinalysis, CRP (where available), clinical evaluation; decisions often made without full diagnostics
Imaging	Ultrasound/Computed tomography to identify urinary tract obstruction	Point-of-care ultrasound or physical examination only
Antibiotic therapy	Broad-spectrum antibiotics according to local guidelines (European Association of Urology, Surviving Sepsis Campaign 2021)	Immediate empirical antibiotic treatment using agents available under field conditions (e.g. third-generation cephalosporins or carbapenems, where available)
Haemodynamic stabilisation	Early fluid resuscitation, blood pressure monitoring, vasopressor therapy (norepinephrine)	Intensive fluid therapy, basic monitoring; vasopressors where available (norepinephrine/alternatives in field hospitals)
Source control	Nephrostomy, JJ stent insertion, endoscopic or surgical procedures	Bladder catheterisation, nephrostomy (where feasible), evacuation to a higher-level facility
Follow-up care	Monitoring of biochemical parameters, fluid balance, organ function	Clinical observation, preparation for transfer to a referral centre
CBC – complete blood count; CRP – C-reactive protein; PCT – procalcitonin; SOFA – Sequential Organ Failure Assessment; qSOFA – quick Sequential Organ Failure Assessment		

comorbidities, and risk of antimicrobial resistance. Particular attention should be paid to elderly and immunosuppressed patients, in whom infections tend to progress rapidly and aggressively [6].

Effective management of urosepsis requires rapid diagnosis, immediate initiation of antibiotic therapy, haemodynamic support, timely source control, and individualised treatment strategies. Multidisciplinary collaboration (urology, intensive care, and microbiology) remains key to improving survival outcomes and reducing complications.

Although urosepsis is often described as one of the more common and clinically milder forms of sepsis, it remains a significant clinical challenge in both civilian and military medicine. Urinary tract infections, which are the usual source, rank among the most frequent infections in adults, and under combat conditions they may progress because of limited access to diagnostics and delays in therapeutic intervention. According to current epidemiologic data, early recognition and prompt initiation of treatment are critical determinants of patient outcomes.

Field diagnostics require simplification. Comprehensive scoring systems such as SOFA may be useful in facilities with full laboratory support; however, in military practice, greater emphasis is placed on the assessment of basic vital signs and readily available inflammatory markers. Simple tools such as urinalysis or CRP testing, combined with the assessment of clinical symptoms (fever, tachycardia, altered mental status), enable rapid decisions regarding the initiation of treatment and patient evacuation.

Therapeutic management should focus on the immediate administration of broad-spectrum antibiotics and haemodynamic stabilisation, in accordance with the Surviving Sepsis Campaign (2021) recommendations. Equally important is the prompt relief of urinary tract obstruction, which in many cases determines the success of therapy. In combat settings, the availability of simple urinary drainage procedures, such as catheterisation or nephrostomy, is critical, as is the ability to continue empirical therapy until evacuation can be undertaken.

From a military medical perspective, urosepsis may impair a soldier's ability to perform operational duties, even when its clinical course is relatively mild compared with other forms of sepsis. Its impact on physical performance and the potential for long-term complications (e.g. renal damage) justify considering it a significant health concern in military personnel.

The management of urosepsis requires different priorities depending on the operational setting. In civilian healthcare, comprehensive diagnostic assessment and guideline-based treatment (European Association of Urology) represent the standard of care. In military practice, however, the focus must be on rapid recognition based on clinical signs, immediate empirical treatment, and patient stabilisation prior to transport. An integrated approach that takes into account the unique aspects of military medicine may significantly reduce mortality and enhance operational readiness.

References

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 2016; 315(8): 801–810. doi: 10.1001/jama.2016.0287
2. Wagenlehner FM, Pilatz A, Weidner W. Urosepsis – from the view of the urologist. Int J Antimicrob Agents, 2011; 38 Suppl: 51–57. doi: 10.1016/j.ijantimicag.2011.09.007
3. Wagenlehner FM, Weidner W, Naber KG. Optimal management of urosepsis from the urological perspective. Int J Antimicrob Agents, 2007; 30(5): 390–397. doi: 10.1016/j.ijantimicag.2007.06.027
4. Bonkat G, Bartoletti R, Bruyère F, et al. EAU Guidelines on Urological Infections. European Association of Urology, 2023.
5. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Urological-infections-2023.pdf

6. Wagenlehner FME, Tandogdu Z, Bjerklund Johansen TE. An update on classification and management of urosepsis. Curr Opin Urol, 2017; 27(2): 133–137. doi: 10.1097/MOU.0000000000000364
7. Evans LE, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med, 2021; 47(11):1181–1247. doi: 10.1007/s00134-021-06506-y
8. Wagenlehner FME, Pilatz A, Weidner W, Naber KG. Urosepsis: Overview of the diagnostic and treatment challenges. Microbiol Spectr, 2015; 3(5). doi: 10.1128/microbiolspec.UTI-0003-2012
9. Talan DA, Takhar SS, Krishnadasan A, et al. Emergence of extended-spectrum β-lactamase urinary tract infections among hospitalized emergency department patients in the United States. Ann Emerg Med, 2021; 77: 32–43. doi: 10.1016/j.annemergmed.2020.08.022
10. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality. Lancet, 2020; 395(10219): 200–211. doi: 10.1016/S0140-6736(19)32989-7
11. Hotchkiss RS, Moldawer LL, Opal SM, et al. Sepsis and septic shock. Nat Rev Dis Primers, 2016; 2: 16045. doi: 10.1038/nrdp.2016.45
12. Ince C, Mayeux PR, Nguyen T, et al.; ADQI XIV Workgroup. The endothelium in sepsis. Shock, 2016; 45(3): 259–270. doi: 10.1097/SHK.0000000000000473
13. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection, and treatment options. Nat Rev Microbiol, 2015; 13(5): 269–284. doi: 10.1038/nrmicro3432
14. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. Crit Care, 2010; 14(1): R15. doi: 10.1186/cc8872
15. Vijayan AL, Vanimaya, Ravindran S, et al. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. J Intensive Care, 2017; 5: 51. doi: 10.1186/s40560-017-0246-8
16. Barichello T, Generoso JS, Singer M, Dal-Pizzol F. Biomarkers for sepsis: more than just fever and leukocytosis-a narrative review. Crit Care, 2022; 26(1): 14. doi: 10.1186/s13054-021-03862-5
17. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med, 2006; 34(6): 1589–1596. doi: 10.1097/01.CCM.0000217961.75225.E9
18. Hernandez G, Bellomo R, Bakker J. The ten pitfalls of lactate clearance in sepsis. Intensive Care Med, 2019; 45(1): 82–85. doi: 10.1007/s00134-018-5213-x
19. Schuetz P, Wirz Y, Sager R, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev, 2017; 10(10): CD007498. doi: 10.1002/14651858.CD007498.pub3
20. Sørensen SM, Schønheyder HC, Nielsen H. The role of imaging of the urinary tract in patients with urosepsis. Int J Infect Dis, 2013; 17(5): e299–E303. doi: 10.1016/j.ijid.2012.11.032
21. Goldsmith ZG, Oredein-McCoy O, Gerber L, et al. Emergent ureteric stent vs percutaneous nephrostomy for obstructive urolithiasis with sepsis: patterns of use and outcomes from a 15-year experience. BJU Int, 2013; 112(2): E122–E128. doi: 10.1111/bju.12161
22. Comza C, Georgescu D, Popescu R, et al. Double-J stent versus percutaneous nephrostomy for emergency upper urinary tract decompression. J Med Life, 2023; 16(5): 663–667. doi: 10.25122/jml-2022-0334
23. Raith EP, Udy AA, Bailey M, et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. JAMA, 2017; 317(3): 290–300. doi: 10.1001/jama.2016.20328
24. Freund Y, Lemachatti N, Krastinova E, et al. Prognostic Accuracy of sepsis-3 qSOFA criteria compared with SIRS for in-hospital mortality. JAMA, 2017; 317(3): 301–308. doi: 10.1001/jama.2016.20329
25. Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. Am J Respir Crit Care Med, 2017; 196(7): 856–863. doi: 10.1164/rccm.201609-1848OC

REVIEW ARTICLE

PSYCHIATRIC DISORDERS IN ONCOLOGY PATIENTS: CLINICAL IMPLICATIONS AND THERAPEUTIC CHALLENGES

Zaburzenia psychiczne u pacjentów onkologicznych: znaczenie kliniczne i wyzwania terapeutyczne

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Abstract

Mental disorders are among the most common and most burdensome complications in oncology. They include depression, anxiety, adjustment disorders, cancer-related fatigue, cognitive deficits, and symptoms of post-traumatic stress. Their presence reduces quality of life, impairs adherence to treatment, and worsens prognosis. Among soldiers and uniformed service personnel, these conditions pose an additional challenge, as they coincide with occupational demands and specific stressors. The aim of this study was to review current evidence on the epidemiology, diagnosis, and management of mental disorders in oncology patients, with particular emphasis on the military and uniformed services context in Poland. A review of the literature published between 2019 and 2025 (PubMed, Scopus, Web of Science) and of international guidelines (ESMO, NCCN, ASCO) was conducted. Diagnostic frameworks (ICD-11, DSM-5-TR) and validated psycho-oncological screening instruments were included in the analysis. Depression affects approximately 20–25% of patients with cancer, while anxiety disorders occur in 10–30%. Cancer-related fatigue is reported by up to 40% of patients. The highest risk is observed in individuals with lung, pancreatic, and head and neck cancers. Diagnosis requires combining structured clinical interviews with screening instruments (PHQ-9, HADS, GAD-7, DT). Exercise interventions have been shown to reduce symptoms of depression and anxiety, while early clinical trials of psilocybin suggest its potential efficacy in treatment-resistant depression. In military settings, systematic screening, strict confidentiality of medical data, and interdisciplinary care are of particular importance. Mental health disorders should be considered integral components of oncological care. In the military and uniformed services, priorities include routine psychological screening at key stages of therapy, adaptation of international guidelines to national conditions, and exploration of innovative interventions (physical activity, psychedelic-assisted therapies). Such measures may significantly improve outcomes and quality of life in oncology patients.

Streszczenie

Zaburzenia psychiczne należą do najczęstszych i najbardziej obciążających powikłań w onkologii. Obejmują one m.in. depresję, zaburzenia lękowe, zaburzenia adaptacyjne, zmęczenie nowotworowe, deficyty poznawcze i objawy stresu pourazowego. Ich obecność obniża jakość życia, utrudnia realizację terapii i pogarsza rokowanie. W populacji żołnierzy i funkcjonariuszy służb mundurowych znaczenie tych zaburzeń jest szczególne, ponieważ nakładają się one na wymagania zawodowe i specyficzne czynniki stresowe. Celem pracy była analiza aktualnych danych dotyczących epidemiologii, diagnostyki i leczenia zaburzeń psychicznych u pacjentów onkologicznych, ze szczególnym uwzględnieniem kontekstu wojskowego i służb mundurowych w Polsce. Przeprowadzono przegląd piśmiennictwa z lat 2019–2025 (PubMed, Scopus, Web of Science) oraz międzynarodowych wytycznych (ESMO, NCCN, ASCO). Uwzględniono systemy klasyfikacyjne ICD-11 i DSM-5-TR oraz specyficzne narzędzia przesiewowe stosowane w psychoonkologii. Depresja dotyczy około 20–25% pacjentów z chorobą nowotworową, a zaburzenia lękowe 10–30%. Zmęczenie nowotworowe zgłasza nawet 40% chorych. Najwyższe ryzyko dotyczy osób z rakiem płuca, trzustki oraz głowy i szyi. Diagnostyka wymaga połączenia wywiadu klinicznego z narzędziami przesiewowymi (PHQ-9, HADS, GAD-7, DT). Wykazano, że programy aktywności fizycznej zmniejszają nasilenie objawów depresji i lęku, natomiast badania nad psylocybiną sugerują jej potencjał w terapii depresji opornej na leczenie. W kontekście wojskowym kluczowe znaczenie mają systematyczne badania przesiewowe, poufność danych medycznych oraz interdyscyplinarna opieka. Zaburzenia psychiczne powinny być traktowane jako integralna część opieki onkologicznej. Priorytetem w wojsku i służbach mundurowych jest wdrożenie przesiewu psychologicznego na kluczowych etapach terapii, adaptacja mię-

dzynarodowych wytycznych do warunków krajowych oraz rozwój innowacyjnych interwencji (aktywność fizyczna, terapie psychodeliczne). Takie działania mogą istotnie poprawić rokowanie i jakość życia pacjentów onkologicznych.

Keywords: psycho-oncology; depression; anxiety disorders; soldiers; ICD-11

Słowa kluczowe: psychoonkologia; depresja; zaburzenia lękowe; żołnierze; ICD-11

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Introduction

Malignant neoplasms represent one of the greatest challenges in modern medicine, with consequences extending far beyond somatic health. In everyday clinical practice, increasing attention is now focused on the psychological and social implications of cancer diagnosis and treatment. According to the latest guidelines of the European Society for Medical Oncology (ESMO), symptoms of depression and anxiety are among the most prevalent psychological difficulties experienced by cancer patients, irrespective of tumour type or disease stage [1].

Studies indicate that mood disorders affect approximately one quarter of patients, while anxiety symptoms are observed in 20–30% of individuals undergoing anticancer therapy [1]. The clinical relevance of these conditions is twofold. First, depression and anxiety substantially reduce quality of life and impair daily functioning. Second, they negatively influence prognosis by decreasing treatment adherence, exacerbating somatic symptoms, and increasing suicide risk [1]. Evidence also suggests that certain patient groups – such as those with lung, pancreatic, or head and neck cancers – are at particularly high risk of developing mood disorders [2].

Another increasingly recognised issue is cancer-related distress, defined by the National Comprehensive Cancer Network (NCCN) as the "sixth vital sign in oncology." This concept encompasses a wide spectrum of emotional responses – from worry and irritability to depressive and adjustment disorders – that can significantly disrupt the treatment process [3]. Similarly, cancer-related fatigue, which often persists beyond the completion of therapy, is frequently reported and strongly associated with functional limitations [4].

Recent reports have highlighted the global dimension of this problem, indicating that it is not solely dependent on healthcare accessibility. For example, a cross-sectional study involving more than 270 patients in Palestine found that over half displayed depressive symptoms, with younger age, limited education, and financial hardship identified as major contributing factors [2]. A meta-analysis of 42 clinical trials demonstrated that psychological interventions – including cognitive-behavioural therapy, acceptance and commitment therapy, mindfulness-based interventions, and meaning-centred therapies – were associated with significant reductions in distress and depressive symptoms, alongside improvements in overall quality of life [3].

Despite a growing body of evidence, mental health problems in oncology remain underdiagnosed and undertreated. Many patients do not receive adequate pharmacological or psychotherapeutic support, as confirmed by both clinical observations and population-based studies [1, 4]. Consequently, the implementation of systematic screening, early diagnostic procedures, and interdisciplinary care – integrating oncologists, psycho-oncologists, psychiatrists, and clinical psychologists – is increasingly recognised as an essential component of comprehensive cancer treatment. This study aimed to review current data on the epidemiology, classification, diagnostic approaches, and therapeutic strategies for mental disorders in oncology, with particular emphasis on their impact on the treatment course and patients' quality of life.

Most common mental disorders in oncology patients

Contemporary psycho-oncology clearly demonstrates that mental health disorders are frequent and clinically significant components of cancer care. The latest ESMO guidelines emphasise that depressive and anxiety symptoms occur in many patients across all stages of the treatment trajectory. Their presence is associated with greater psychological distress, poorer quality of life, reduced treatment adherence, and increased suicide risk, particularly in the context of major depression [1]. The identification and differentiation of psychiatric disorders should follow the standards of the International Classification of Diseases, 11th Revision (ICD-11), and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), while recognising the distinct areas of focus within each system. For example, ICD-11 places greater emphasis on hopelessness in depression and autonomic hyperactivity in generalised anxiety disorder [1].

Depressive disorders: Depression is one of the most frequently identified psychiatric conditions in oncology patients, with prevalence estimates ranging from 20% to 25%, although rates vary depending on the assess-

ment tools used as well as cancer type and stage [1]. A key diagnostic challenge is the overlap between depressive symptoms (including fatigue, appetite loss, and hypersomnia) and the clinical presentation of cancer and treatment-related adverse effects. Cross-sectional studies illustrate these challenges; for example, in a Palestinian cohort of 271 patients assessed with the Beck Depression Inventory-II (BDI-II), depressive severity ranged from mild to severe, with younger age, lower educational attainment, and socioeconomic disadvantage identified as risk factors [2]. These findings underscore the importance of systematic screening and ongoing reassessment throughout the course of treatment.

- Anxiety disorders: Anxiety may present as subthreshold symptoms or meet full diagnostic criteria for conditions such as generalised anxiety disorder (GAD), panic disorder, or adjustment disorder with anxiety. Multicentre studies and meta-analyses cited by ESMO report clinically significant anxiety in 15–25% of oncology patients [1]. Fear of cancer recurrence (FCR) and fear of progression (FoP), although not formal diagnostic entities, are particularly important in survivorship care, as they significantly impair functioning, frequently co-occur with insomnia and depression, and require targeted clinical attention [1].
- Adjustment disorders: Emotional responses directly linked to cancer diagnosis and treatment are common. In the ICD-11 and DSM-5-TR, adjustment disorders are characterised by disproportionate distress and/or functional impairment arising within three months of a stressor [1]. In oncology, these disorders are diagnosed more frequently than major depressive disorder (MDD) and are associated with an elevated risk of subsequent psychiatric morbidity, underscoring the importance of early psychoeducation and short-term therapeutic interventions [1].
- Cancer-related fatigue (CRF): Chronic fatigue, disproportionate to exertion and unrelieved by rest, is among the most prevalent and burdensome symptoms in oncology, often persisting beyond the completion of treatment. CRF frequently co-occurs with depression and anxiety, contributing to severe limitations in daily and social functioning [4]. Differential diagnosis is crucial (such as anaemia and endocrine dysfunction), and management requires multimodal strategies, including physical activity, psychosocial interventions, and pharmacological support in selected cases [4].
- Cognitive impairment: Deficits in attention, working memory, and executive functioning – commonly referred to as chemobrain – may arise not only during or after systemic therapy but also as a direct consequence of cancer itself. Although heterogeneous in presentation, cognitive impairments are often clinically significant for occupational and daily functioning, yet remain underdiagnosed [4]. Recommended approaches include brief cognitive screening (such as the Montreal Cognitive Assessment) and referral for cognitive rehabilitation when symptoms are persistent and disabling.
- Post-traumatic stress symptoms and the coronavirus 2019 (COVID-19) context: Individuals experiencing post-traumatic stress disorder (PTSD) in connection with cancer may exhibit intrusive recollections, avoidance behaviours, heightened arousal, and alterations in mood. In DSM-5-TR, PTSD is classified as a trauma- or stressor-related disorder rather than an anxiety disorder [1]. The COVID-19 pandemic has increased rates of depression and anxiety globally, with oncology patients similarly affected [1]. Importantly, it has accelerated the implementation of remote psychological support and evidence-based interventions (including cognitive-behavioural therapy (CBT), acceptance and commitment therapy (ACT), and mindfulness-based programmes), which recent meta-analyses have shown to significantly reduce distress, anxiety, and depression while improving quality of life, even within telehealth models [3]. In clinical practice, routine use of screening tools (such as the Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire-9 (PHQ-9), GAD-7, and the Distress Thermometer (DT)) and fast-track access to psycho-oncological care remain essential.

The spectrum of psychiatric disorders in oncology encompasses both core diagnoses (depression, anxiety disorders, and PTSD) and clinically significant but less formally classified conditions (such as FCR, CRF, and cognitive deficits). Early identification – guided by ICD-11/DSM-5-TR criteria and ESMO recommendations – together with evidence-based interventions, constitutes a fundamental component of comprehensive oncological care [1, 3].

Classification and diagnosis of mental disorders

Within oncology, the identification of psychiatric disorders is primarily based on two diagnostic frameworks: the DSM-5-TR, developed by the American Psychiatric Association [5], and the ICD-11, published by the World Health Organization [6]. Although both systems define comparable nosological categories, they differ in emphasis. The DSM-5-TR focuses on numerical symptom thresholds and minimum duration criteria, thereby facilitating standardisation in clinical research, whereas the ICD-11 introduces greater diagnostic flexibility, allowing clinicians to consider the clinical and functional context of the patient more broadly [5, 6].

For example, in depressive disorders, DSM-5-TR requires the presence of at least five symptoms lasting a minimum of two weeks, with the mandatory inclusion of either depressed mood or anhedonia. In contrast, ICD-11 places greater emphasis on hopelessness and provides explicit stratification of severity into mild, moderate, and severe categories. Regarding anxiety disorders, ICD-11 incorporates autonomic hyperarousal features (such as palpitations and excessive sweating), which are particularly relevant for distinguishing psychiatric symptoms from somatic manifestations of oncological treatment [6].

Given the substantial overlap between psychological and physical manifestations (e.g., fatigue, appetite loss, and sleep problems), the evaluation of oncology patients should integrate standardised screening instruments with structured clinical interviews. The most commonly used questionnaires include HADS, PHQ-9, GAD-7, BDI-II, and DT, recommended by the NCCN as rapid screening instruments for distress [7]. The 2023 ESMO guidelines further recommend applying these instru-

ments at key points along the cancer care continuum: at diagnosis, during active treatment, during follow-up, and in the event of recurrence [1].

Increasing attention is also being directed towards psycho-oncology-specific phenomena that, although not formally recognised as diagnostic categories in either DSM or ICD, hold substantial clinical and prognostic significance. The most extensively studied examples are FCR and FoP. Evidence suggests that approximately 40–50% of cancer survivors in remission experience clinically significant FCR, which is associated with poorer quality of life, higher risk of depression and sleep disturbances, and lower adherence to therapeutic recommendations [8]. Although these phenomena are not formally classified within DSM-5-TR, they represent critical targets for psychological intervention and should be systematically monitored as part of comprehensive oncological care [8, 9].

Methodology of diagnosing and assessing mental disorders in oncology patients

The diagnostic process for mental disorders in oncology patients is complex and requires a multidimensional approach. This complexity arises from the convergence of psychiatric, somatic, and treatment-related symptoms, which may stem from the cancer itself, associated complications, or therapeutic interventions such as chemotherapy, hormone therapy, and radiotherapy. Symptoms including fatigue, loss of appetite, sleep disturbances, and weight loss may reflect manifestations of depression as well as treatment-related adverse effects, complicating clinical differentiation [4, 10].

Current guidelines therefore recommend triangulating diagnostic data through: (1) self-report instruments (including BDI-II, PHQ-9, HADS, GAD-7, and DT), which enable rapid symptom screening; (2) structured clinical interviews guided by DSM-5-TR and ICD-11 standards, allowing formal diagnosis consistent with recognised classification systems; and (3) evaluation of psychosocial functioning, including the impact of symptoms on daily life, interpersonal relationships, treatment adherence, and adjustment to illness [1, 2, 7].

The DSM-5-TR (2022) defines diagnostic categories through clearly specified symptom sets and threshold criteria, ensuring standardisation. In contrast, ICD-11 (2019) emphasises severity levels and functional impairment. In psycho-oncology practice, ICD-11 offers greater diagnostic flexibility, facilitating the differentiation of depressive and anxiety symptoms that frequently present with atypical features in somatically burdened patients [5, 6].

Structured or semi-structured interviews remain the "gold standard" for confirming diagnoses and should be implemented in patients with positive screening results [1]. Both ESMO and NCCN guidelines recommend repeated screening at critical points along the cancer trajectory – such as at diagnosis, treatment modification, and follow-up – to identify individuals at risk of depression, anxiety, or adjustment disorders and refer them for specialised care [3, 7].

Diagnostic criteria and assessment tools for mental disorders in oncology

Recognition of mental disorders in oncology patients requires strict adherence to standardised psychiatric classifications and careful consideration of the specific clinical context of this population. DSM-5-TR (American Psychiatric Association, 2022) and ICD-11 (World Health Organization, 2019) provide formal diagnostic criteria that form the basis of psychiatric assessment.

- MDD: requires the presence of ≥5 symptoms persisting for at least two weeks, including either depressed mood or anhedonia, accompanied by functional impairment in social or occupational domains [5].
- GAD: diagnosed in cases of chronic (≥6 months) tension and excessive worry, accompanied by somatic symptoms such as insomnia, irritability, or muscle tension [5, 6].
- Adjustment disorders: characterised by an emotional or behavioural response disproportionate to the stressor, emerging within three months of exposure [6].

In oncology, diagnostic assessment requires particular caution, as many symptoms typical of depression or anxiety (such as fatigue, anorexia, and insomnia) may result directly from the malignancy or treatment-related adverse effects, including chemotherapy, radiotherapy, and hormone therapy [1, 2].

Screening and assessment tools

Guidelines from ESMO and the American Society of Clinical Oncology recommend routine screening for psychological symptoms at key points along the cancer continuum, including at diagnosis, during treatment, post-treatment, and throughout survivorship follow-up [1]. The most frequently used and validated instruments include:

- BDI-II: evaluating the severity of depressive symptoms (range 0–63; categories: minimal, mild, moderate, and severe). Its reliability and validity have been confirmed in oncology populations [2].
- PHQ-9: a DSM-based instrument for depression; scores ≥10 are typically considered clinically significant [1].
- HADS: consists of two subscales, HADS-A (anxiety) and HADS-D (depression). Scores ≥8 indicate borderline cases, whereas ≥11 strongly suggest the need for further diagnostic evaluation [1].
- GAD-7: designed for screening GAD; a threshold of ≥10 suggests clinical relevance and warrants further assessment [1].
- DT: a rapid, single-item screening tool for distress; scores ≥4–5 indicate the need for additional psychological evaluation [3].

Supplementary questionnaires

In addition to general screening instruments, oncology-specific questionnaires are widely used:

- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) provides a multidimensional evaluation of quality of life, including emotional and cognitive functioning.

- The Functional Assessment of Cancer Therapy-General (FACT-G) evaluates how the illness and its management affect physical, emotional, and social quality of life.
- The Fear of Cancer Recurrence Inventory measures the intensity of fear of recurrence, a construct not formally classified in DSM or ICD but with substantial clinical and prognostic implications [1, 3].

Diagnostic procedure

An optimal diagnostic pathway includes four stages:

- Screening: application of brief instruments such as DT, HADS, or PHQ-9.
- In-depth assessment: for patients with positive screening results, more detailed scales are administered (such as BDI-II and GAD-7).
- Clinical interview: conducted by a mental health specialist, using DSM-5-TR and ICD-11 criteria, and interpreted in the context of the patient's medical background and physical condition [1, 2].
- Therapeutic decision-making: involves psychoeducation, psychotherapeutic interventions (including CBT, ACT, and Meaning-Centred Psychotherapy), and pharmacotherapy when indicated. Ongoing monitoring of treatment effectiveness is essential [3].

Methodological challenges

The greatest challenge lies in the overlap between somatic and psychiatric symptoms, necessitating clinical expertise and interdisciplinary collaboration among oncologists, psychiatrists, and clinical psychologists. Another substantial i ssue is the insufficient availability of screening. Studies indicate that a considerable proportion of patients with clinically relevant symptoms of depression and anxiety do not receive appropriate psychological support [2, 3]. Systematic use of standardised tools and the early identification of symptoms increase the likelihood of improved quality of life and better adherence to oncological treatment [1, 3].

Future research challenges and proposed clinical recommendations for patients with mental disorders

- Exercise interventions as a strategy to support mental health

  Physical activity is among the most thoroughly investigated supportive approaches for enhancing mental health in cancer populations. A recent meta-analysis of 27 randomised controlled trials, published in *JAMA Network Open* (2025), found that structured exercise interventions in older patients with cancer significantly reduced depressive symptoms (SMD = –0.53; 95% CI: –0.79–(–0.28)) and anxiety (SMD = –0.39; 95% CI: –0.66–(–0.12)), while improving quality of life (SMD = 0.63; 95% CI: 0.10–1.17) [11]. The greatest benefits were observed in mind–body interventions (including yoga and tai chi), which produced stronger therapeutic effects than standard exercise programmes – depression: SMD = –0.89 (95% CI: –1.51–(–0.27)); anxiety: SMD = –0.77 (95% CI: –1.54–(–0.01)) [11].

  These findings confirm that physical activity should be regarded not only as a means of promoting general well-being but also as a structured psycho-oncological intervention. Incorporating individualised, supervised exercise programmes into the care of older adults with cancer may enhance self-efficacy, reduce distress, and improve psychosocial functioning [11].

- Therapeutic potential of a single dose of psilocybin

  Growing interest has also turned towards the use of psychedelics in managing cancer-related depression. A phase II clinical study published in *Cancer* (2025) found that a single 25 mg administration of psilocybin, delivered with psychotherapeutic support in oncology care, was safe, well tolerated, and showed therapeutic efficacy. After two years of follow-up, 50% of participants achieved full remission of major depression, whereas 42.9% experienced sustained reductions in anxiety symptoms [12].

  These results suggest that psilocybin-assisted therapy may represent a breakthrough adjunct to conventional pharmacotherapy, particularly for treatment-resistant depression. Nevertheless, larger multi-centre randomised trials are required to verify its long-term safety and efficacy and to optimise treatment protocols [3].

Key research challenges

Although evidence is growing for the effectiveness of exercise and psychedelic therapies in alleviating psychological symptoms in cancer patients, significant methodological, clinical, and organisational barriers persist.

- Accessibility and scalability of interventions: implementing exercise programmes in routine clinical practice is hindered by logistical barriers, including limited infrastructure, insufficient availability of specialised therapists, and patient-related adherence challenges (such as cancer-related fatigue and transportation difficulties). Hybrid and remote programmes have shown promise in improving accessibility, particularly in rural populations and during public health crises [3, 11].
- Durability of therapeutic effects: most clinical studies assess outcomes over the short term (≤ 6 months), and data on the long-term persistence of benefits from exercise or psychedelic interventions remain limited. For example, Soong et al. (2025) reported sustained improvements in depression and anxiety for up to six months; however, no follow-up beyond one year was available [11]. By contrast, Agrawal et al. (2025) found that a single administration of psilocybin could yield benefits lasting up to two years, although the limited sample size restricts the broader applicability of these findings [12].
- Safety and risk profile: exercise interventions must be tailored to patient age, cancer stage, and comorbidities to prevent complications such as injury or overexertion [13]. Psychedelic therapies require rigorous clinical supervision owing to potential adverse effects, including anxiety, derealisation, or exacerbation of psychotic symptoms in predisposed

individuals [14]. Careful patient selection and strict control of the treatment environment are therefore essential.

- Ethical and legal considerations: psilocybin and other psychedelics remain controlled substances in many jurisdictions, creating barriers to clinical research and funding. In addition, societal stigma rooted in historical and cultural factors continues to hinder broader acceptance. Experts emphasise the urgent need for international ethical guidelines and regulatory reforms to facilitate clinical investigation [14, 15].
- Diversity of the patient population: existing studies have often focused on relatively homogenous groups (such as women with breast cancer). Broader inclusion of patients with diverse tumour types, advanced disease stages, and those receiving palliative care is necessary to develop more generalisable clinical recommendations [10].
- Treatment integration and personalisation: developing models that integrate pharmacotherapy, psychotherapy, exercise, and potentially psychedelic interventions remains a major challenge. There is a clear need for predictive instruments capable of identifying which patients are most likely to respond to specific interventions [1, 3].
- Funding and health policy: limited financial support for psycho-oncology research, together with insufficient integration of psychiatry and psychology into standard cancer care pathways, continues to constrain progress. Incorporating mental health assessments into oncology standards of care, as advocated by ESMO and NCCN, may expand access to interventions and improve patient outcomes [7, 10].

Conclusions

This study demonstrated that mental disorders in oncology patients are both prevalent and insufficiently recognised, underscoring the need for systematic screening and comprehensive interdisciplinary care. In line with ESMO, NCCN, and ASCO guidelines, mental health assessment must be regarded as an integral component of the diagnostic–therapeutic pathway in oncology, rather than an optional adjunct to somatic treatment [1, 16, 17].

First, adapting established diagnostic frameworks (DSM-5-TR and ICD-11) to psycho-oncology is crucial, with close attention to the unique clinical features of this population. Distinguishing psychiatric manifestations from cancer-related somatic symptoms and adverse effects of treatment requires specialist expertise and the use of validated screening tools, including PHQ-9, HADS, GAD-7, and DT [2, 18, 19]. Their systematic use at key stages of care (diagnosis, active treatment, follow-up, and recurrence) should be implemented as routine practice in oncology centres in Poland.

Second, the provision of comprehensive care requires interdisciplinary collaboration among oncologists, psycho-oncologists, psychiatrists, and clinical psychologists. Evidence shows that integrated care approaches ("collaborative care") effectively alleviate depression and anxiety while enhancing quality of life in cancer patients [20, 21]. However, implementing such models in Poland necessitates systemic organisational and financial solutions, including linking the quality of screening to reimbursement mechanisms.

Third, adapting international guidelines to Polish conditions is indispensable – particularly within the military and uniformed services, where the burden of mental disorders among oncology patients is compounded by the specific demands of service. In this context, incorporating brief screening instruments (e.g., DT, HADS, PHQ-9) into clinical assessments and official health records may significantly improve access to early interventions while upholding rigorous confidentiality standards [21–23].

Fourth, future studies should focus on assessing the effectiveness of innovative interventions, both in the domain of physical activity and psychedelic-assisted psychotherapies (psilocybin). Recent evidence indicates that physical activity programmes in older adults can markedly reduce depressive and anxiety symptoms while enhancing quality of life [11], whereas clinical trials of a single psilocybin dose have shown sustained remission of depressive symptoms [12]. Although both approaches require further validation, their emerging clinical potential positions them as promising directions for psycho-oncology development.

In summary, the implementation of systematic screening and interdisciplinary care, together with the adaptation of international guidelines to the Polish healthcare system – with specific consideration for military and uniformed service settings – should be regarded as priority measures. Broadening the availability of novel interventions, grounded in robust clinical evidence, has the potential to significantly improve outcomes and quality of life for cancer patients in Poland.

References

1. Grassi L, Caruso R, Riba MB, et al.; ESMO Guidelines Committee. Anxiety and depression in adult cancer patients: ESMO Clinical Practice Guideline. ESMO Open, 2023; 8(2): 101155. doi: 10.1016/j.esmoop.2023.101155.
2. Battat M, Omair N, WildAli MA, et al. Assessment of depression symptoms among cancer patients: a cross-sectional study from a developing country. *Sci Rep*, 2024; 14: 11934. doi: 10.1038/s41598-024-62935-x
3. Paslaru AM, Plesea-Condratovici A, Moroianu L-A, et al. Mind over malignancy: a systematic review and meta-analysis of psychological distress, coping, and therapeutic interventions in oncology. *Medicina* (Kaunas), 2025; 61(6): 1086. doi: 10.3390/medicina61061086
4. Talarowska M. Zaburzenia psychiczne u pacjentów onkologicznych. *Psychiatria po Dyplomie*, 2020; 17: 50–57
5. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, 5th edition, text revision (DSM-5-TR).* Washington, DC: APA, 2022
6. World Health Organization. *International classification of diseases 11th revision (ICD-11): clinical descriptions and diagnostic guidelines.* Geneva, WHO, 2019
7. Riba MB, Donovan KA, Ahmed K, et al. NCCN Guidelines® Insights: Distress Management, Version 2.2023. J Natl Compr Canc Netw, 2023; 21(5): 450–457. doi: 10.6004/jnccn.2023.0026

8. Simard S, Thewes B, Humphris G, et al. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. *J Cancer Surviv*, 2013; 7(3): 300–322. doi: 10.1007/s11764-013-0272-z
9. Tauber NM, O'Toole MS, Dinkel A, et al. Effect of psychological intervention on fear of cancer recurrence: a systematic review and meta-analysis. *J Clin Oncol*, 2019; 37(31): 2899–2915. doi: 10.1200/JCO.19.00572
10. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *Lancet Oncol*, 2011; 12(2): 160–174. doi: 10.1016/S1470-2045(11)70002-X
11. Soong RY, Low CE, Ong V, et al. Exercise interventions for depression, anxiety, and quality of life in older adults with cancer: a systematic review and meta-analysis. JAMA Netw Open, 2025; 8(2): e2457859. doi: 10.1001/jamanetworkopen.2024.57859
12. Agrawal M, Roddy K, Jenkins B, Leeks C, Emanuel E. Long-term benefits of single-dose psilocybin in depressed patients with cancer. Cancer, 2025; 131(12): e35889. doi: 10.1002/cncr.35889
13. Schmitz KH, Campbell AM, Stuiver MM, et al. Exercise is medicine in oncology: engaging clinicians to help patients move through cancer. *CA Cancer J Clin*, 2019; 69(6): 468–484. doi: 10.3322/caac.21579
14. Reiff CM, Richman EE, Nemeroff CB, et al.; the Work Group on Biomarkers and Novel Treatments, a Division of the American Psychiatric Association Council of Research. Psychedelics and psychedelic-assisted psychotherapy. *Am J Psychiatry*, 2020; 177(5): 391–410. doi: 10.1176/appi.ajp.2019.19010035
15. Nutt D, Carhart-Harris R. The current status of psychedelics in psychiatry. *JAMA Psychiatry*, 2021; 78(2): 121–122. doi: 10.1001/jamapsychiatry.2020.2171
16. Deshields TL, Wells-Di Gregorio S, Flowers SR, et al. Addressing distress management challenges: Recommendations from the consensus panel of the American Psychosocial Oncology Society and the Association of Oncology Social Work. CA Cancer J Clin, 2021; 71(5): 407–436. doi: 10.3322/caac.21672
17. Andersen BL, Lacchetti C, Ashing K, et al. Management of anxiety and depression in adult survivors of cancer: ASCO guideline update. J Clin Oncol, 2023; 41(18): 3426–3453. doi: 10.1200/JCO.23.00293
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand, 1983; 67(6): 361–370. doi: 10.1111/j.1600-0447.1983.tb09716.x
19. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med, 2006; 166(10): 1092–1097. doi: 10.1001/archinte.166.10.1092. PMID: 16717171
20. Sharpe M, Walker J, Holm-Hansen C, et al.; SMaRT (Symptom Management Research Trials) Oncology-2 Team. Integrated collaborative care for comorbid major depression in patients with cancer (SMaRT Oncology-2): a multicenter randomized controlled effectiveness trial. Lancet, 2014; 384(9948): 1099–1108. doi: 10.1016/S0140-6736(14)61231-9
21. Decyzja Nr 155/MON Ministra Obrony Narodowej z dnia 26 października 2021 r. w sprawie organizacji i funkcjonowania opieki psychologicznej w resorcie obrony narodowej. Dz.Urz. MON 2021 poz. 235
22. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med, 2001; 16(9): 606–613. doi: 10.1046/j.1525-1497.2001.016009606.x
23. Weathers FW, Bovin MJ, Lee DJ, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): development and initial psychometric evaluation in military veterans. *Psychol Assess*, 2018; 30(3): 383–395. doi: 10.1037/pas0000486

DIETARY FACTORS IN KIDNEY STONE DISEASE: A SPECIAL FOCUS ON THE VEGETARIAN DIET

Czynniki dietetyczne w kamicy nerkowej: ze szczególnym uwzględnieniem diety wegetariańskiej

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Abstract

Kidney stones are a widespread medical issue that affects around 11% of the global population. They can be very painful and tend to recur. Their formation is complex and influenced by several factors, such as being overweight, not drinking enough fluids, eating poorly, and having long-term health conditions. This shows how important it is to implement effective prevention methods, with diet playing a key role. The purpose of this review is to look at the issue of kidney stones and to find out whether a vegetarian diet could be an effective way to prevent or treat them. Available evidence suggests that a vegetarian diet can be helpful in preventing and managing kidney stones. Potential benefits include 1) lower risk of calcium-oxalate stones: fruits and vegetables in a vegetarian diet contain high levels of citrates, which helps keep calcium in the urine and stop stones from forming. 2) prevention of uric-acid stones: a vegetarian diet is lower in purines, resulting in reduced urinary uric acid. 3) urine pH balance: the diet is rich in potassium and magnesium, helping to make the urine more alkaline, which supports the dissolution of uric-acid and cystine stones. 4) Oxalate balance: although some plant foods have high oxalate levels, a balanced vegetarian diet with adequate calcium can reduce intestinal oxalate absorption. A well-planned vegetarian diet can therefore be a useful tool for preventing and managing kidney stones. Its benefits stem from the ability to make urine more alkaline, lower uric acid levels, and increase citrate levels that protect against stones. However, it is important to ensure adequate calcium intake to counterbalance oxalate intake. More research is needed to fully understand the long-term benefits and possible risks of vegetarian dietary patterns for kidney health.

Streszczenie

Kamica nerkowa jest powszechnym problemem medycznym, który dotyka około 11% populacji na całym świecie. Może powodować silny ból i ma tendencję do nawrotów. Proces jej powstawania jest złożony i zależy od wielu czynników, takich jak nadwaga, niewystarczające nawodnienie, nieprawidłowa dieta oraz choroby przewlekłe. To podkreśla, jak ważna jest skuteczna profilaktyka, w której kluczową rolę odgrywa dieta. Celem niniejszego przeglądu jest omówienie czynników dietetycznych związanych z kamicą nerkową oraz ocena potencjalnej roli diety wegetariańskiej w jej profilaktyce i leczeniu. Dostępne dane sugerują, że dieta wegetariańska może wspierać profilaktykę i leczenie kamicy nerkowej. Do potencjalnych korzyści należą mniejsze ryzyko powstawania kamieni szczawianowo-wapniowych, związane z większą podażą cytrynianów pochodzących z owoców i warzyw, oraz mniejsze wydalanie kwasu moczowego z moczem w związku z niższym spożyciem puryn. Dieta bogata w potas i magnez może również sprzyjać alkalizacji moczu, co jest korzystne w profilaktyce kamicy moczanowej. Dobrze zaplanowana dieta wegetariańska może być skutecznym narzędziem w profilaktyce i leczeniu kamicy nerkowej. Jej korzystne działanie wynika z możliwości alkalizacji moczu, obniżenia poziomu kwasu moczowego oraz zwiększenia stężenia cytrynianów chroniących przed kamieniami. Należy jednak pamiętać o dostarczaniu odpowiedniej ilości wapnia, aby zrównoważyć spożycie szczawianów. Konieczne są dalsze badania, aby w pełni ocenić długoterminowe korzyści i potencjalne zagrożenia związane z dietą wegetariańską dla zdrowia nerek.

Keywords: urolithiasis; kidney stones; vegetarian diet; urinary tract stones; risk factors for kidney stones

Słowa kluczowe: kamica nerkowa; kamienie w drogach moczowych; dieta wegetariańska; urolitaza; czynniki ryzyka kamicy nerkowej

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Introduction

Kidney stones are a common condition affecting individuals around the world today [1]. People have been dealing with this issue for a long time, with early descriptions dating back to ancient Mesopotamia, between 3200 and 1200 BCE [2]. The way kidney stones form is complex and influenced by many factors [3]. One of these factors is diet and how it affects the urinary system [4]. This paper discusses how kidney stones form and how a vegetarian diet may influence this process.

Research objective

The aim of this review is to examine how a vegetarian diet influences the development of kidney stones, focusing on latest research and current scientific knowledge.

Research problems

Although kidney stones are very common and often recur, there is no single explanation for how all types of stones form. This highlights the need for better prevention strategies, and looking closely at how a vegetarian diet might help is important.

Research hypotheses

A vegetarian diet may help prevent kidney stones by altering the composition of urine and its pH, which can reduce the likelihood of stones forming and recurring.

Research materials and methods

The review is based on an analysis of research papers and articles found in databases such as Google Scholar and PubMed.

We used keywords such as “vegetarian diet,” “urinary tract stones,” “kidney stones,” “urolithiasis,” and “risk factors for kidney stones” to identify relevant studies. All team members were involved in searching for and analysing the literature, as well as interpreting the findings.

Artificial intelligence (AI)

Artificial intelligence was used only to improve the language quality of the paper. It helped make the writing clearer and more consistent with scientific standards by correcting grammar and style. It is important to note that AI was just a support tool under human supervision. It did not replace human judgment in analysing the data or drawing conclusions. All facts and final interpretations were made by the human authors.

Research results

Types of kidney stones

Kidney stones are made of both organic and crystalline materials [5]. The most common type is calcium oxalate. There are several different kinds of kidney stones. Up to 80% of all urinary stones are calcium-based, including calcium phosphate and calcium oxalate. Struvite and magnesium phosphate stones account for 10 to 15% of all cases. Uric acid stones make up about 3 to 10%, and cystine stones less than 2%. Some rare types of kidney stones can be caused by certain medications, such as guaifenesin, triamterene, atazanavir, and sulphonamide drugs [6].

Epidemiology of kidney stones

Kidney stones are a widespread problem affecting people worldwide. A study in the United States using data from the National Health and Nutrition Examination Survey (2015–2018) found that up to 11% of people had kidney stones [7]. The condition becomes more common with age. For example, among men aged 20 to 39, the rate was 5.1%, but it increased to 19.7% in men aged 80 and older. Among women, the rate was 5.8% for those aged 20 to 39 and 10.6% for those aged 80 and older [8]. In Asia, the incidence is estimated between 1 and 5%, in Europe between 5 and 9%, and in North America between 7 and 13% [9]. Because kidney stones often recur, they are a significant medical challenge. More than half of patients are expected to experience a recurrence within five years [10], and in some cases, the recurrence rate can be as high as 82.4% [11]. As the population ages, kidney stones are becoming more common, increasing the burden on healthcare systems worldwide. Therefore, effective prevention and treatment of this condition are very important.

Risk factors

The development of kidney stone disease is influenced by many factors, both modifiable and non-modifiable. Diet plays a direct role in the formation of kidney stones [12]. Other risk factors include smoking, alcohol use, diabetes, obesity, and family history [13, 14]. Following an unhealthy diet, such as drinking sugary drinks, consuming large amounts of oxalate, and not drinking enough water, increases the risk [15]. Preventing and managing modifiable factors like diet, smoking, alcohol use, and weight is essential for treating kidney stones and preventing them from recurring.

Process of kidney stone formation

Because kidney stones occur in several different types, the mechanisms behind their formation also vary. There-

fore, there is no single pathway by which all kidney stones develop. Research shows that at least three main mechanisms are involved.

The first mechanism involves stones growing on interstitial apatite plaque [16] located in the papillary region of the kidney. This plaque is known as Randall's plaque, and it was discovered as early as 1937 [17]. The pathway involving Randall's plaque is linked to the formation of calcium oxalate stones. These stones form when crystals build up and persist in the urine even as it flows. This happens when crystals become large enough to adhere to the lining of the urinary tract or become trapped in the renal tubules before being passed out. It is believed that this retention and stone formation occur at the site of Randall's plaque. The plaque originates in the basement membrane of the loop of Henle and spreads into the interstitial medulla. As the plaque grows, it weakens the transitional epithelium, making it more vulnerable to the effects of urine and its chemical components such as osteopontin and Tamm-Horsfall protein. These urine substances interact with the plaque to form new layers of matrix and crystals. Eventually, a true calcium oxalate stone forms as crystals move into the urine space. This is the most common pathway by which calcium oxalate stones develop on Randall's plaque. Factors such as urine volume, pH, and calcium content are all connected to the presence of Randall's plaque [18].

The second mechanism involves crystal deposits in the renal tubules. Much about this process is still unknown. Urine pH and composition – especially calcium and phosphate concentrations – play a major role in how this process unfolds.

The third mechanism is called free solution crystallisation. This is best seen in the formation of cystine stones. It occurs when there is too much cystine in the urine, which can happen in a condition called cystinuria. When the concentration of cystine exceeds a certain point, it starts to form crystals that aggregate into kidney stones. Interestingly, these stones float freely and are not attached to the walls of the renal pelvis [16].

It is also important to consider how different urine components can either promote or inhibit stone formation. Uric acid and very acidic urine pH help crystals form, including uric acid crystals and calcium oxalate crystals. These crystals can act as templates, helping other types of crystals form. In contrast, substances such as citrate, pyrophosphate, and magnesium contribute to inhibiting the formation of stones [19]. Although the full details of how kidney stones form are not yet fully understood, it is likely that the balance and interactions between all these factors determine how stones develop in the urinary system.

Vegetarian diet and kidney stones

There are many different types of vegetarian diets described in the literature, but four are the most common: strict vegetarian, which avoids all animal products; pescatarian, which excludes meat but includes fish and seafood; ovo-lacto-vegetarian, which excludes meat but allows eggs and dairy; and flexitarian, which limits or rarely includes red meat [20]. The main idea of vegetarianism is avoiding meat. The International Vegetarian Union defines it as a plant-based diet that may also include dairy, eggs, or honey [21]. Recent studies show that a vegetarian diet has many benefits, not just for the kidneys. It can reduce the risk of death from diabetes, chronic kidney disease, heart disease, and stroke [22]. A vegetarian diet also helps lower cholesterol, body weight, and blood pressure, and may help prevent certain chronic diseases, including cancer [23]. It has also been suggested as a supportive approach for kidney stone prevention because of its multiple benefits. A diet that increases citrate while reducing animal protein, oxalates, and sodium has been helpful for patients with calcium oxalate stones. Because obesity and metabolic syndrome can make urine more acidic, increasing the likelihood of uric acid stone formation, vegetarian diets help reduce weight and make the urine more alkaline, which prevents stones from forming. Eating less animal protein also helps lower uric acid content by reducing purine intake. In the case of cystine stones, lower animal protein intake is linked to reduced cystine and its precursor, methionine. Vegetables contain high amount of organic anions, such as citrate and malate, which raise urine pH and lower the risk of cystine stones because cystine is more soluble in alkaline urine [4]. A study on cystinuria showed that ten men who followed an ovo-lacto-vegetarian diet had lower levels of cystine and cysteine in their urine compared with those on other diets. Since fruits and vegetables make urine more alkaline, this diet appears effective against cystine stones [24]. However, a vegetarian diet has not been shown to be very effective against struvite stones, as these are usually caused by bacterial infections. For individuals with oxalate stones, a vegetarian diet may lead to higher oxalate intake, which could be problematic. Research by Thomas et al. found that people on a vegetarian diet had higher oxalate absorption and excretion than those on a mixed diet, although these concentrations were similar when oxalate intake was increased [25]. Adding more calcium to the diet helps prevent oxalate absorption and reduces the amount entering the urine, where stones can form. This is because calcium binds to oxalates in the intestines, making them insoluble and preventing them from passing into urine [26]. Individuals who are overweight are at higher risk of kidney stones. A vegetarian diet can help with weight loss by reducing high-calorie foods like meat, so a balanced vegetarian diet rich in fruits and vegetables and low in animal fats and proteins may lower the risk of kidney stones [27]. A study in India found that 81.8% of people with kidney stones did not follow a vegetarian diet [28]. A 2021 meta-analysis showed that higher intake of non-dairy animal protein and meat was linked to a higher risk of kidney stones, while higher dairy protein intake was associated with lower risk [29]. Another study found that factors such as consuming too much red meat, high BMI, and low water intake were common causes of kidney stones [30]. A Chinese study found that healthy vegetarians had better kidney function than meat-eaters, and the higher fibre content of vegetarian diets was also protective for kidney health [31]. Therefore, avoiding animal products may help reduce the risk of kidney stones. In the EPIC study, which included 51,336 participants, the risk of developing kidney stones was compared across dietary groups. Those who

ate moderate, low, or no meat had lower risks compared to those who consumed large amounts of meat. Vegetarians had the lowest risk [32]. Another study from the EPIC-Oxford group, which included 65,000 people in the United Kingdom, found that vegetarians were less likely to develop kidney stones, diabetes, cataracts, and heart disease compared with others. A vegetarian diet tends to be lower in fat, which is why it is often linked to weight loss. However, people who follow plant-based diets may have a higher risk of stroke and bone fractures compared with those who eat meat. This is because it can be harder to obtain enough of certain nutrients such as calcium, vitamin B12, and vitamin D from plant foods alone. To avoid these issues, it is important to add supplements to the diet [33]. Vegetarian diets also contain high amounts of magnesium, citrate, and potassium, which help prevent the formation of kidney stones. These nutrients reduce the levels of calcium oxalate and calcium phosphate in the urine. However, because of the risk of kidney stones, it is important to maintain a good balance between calcium, oxalates, and phytates in the diet. If there is not enough calcium in the gut to bind with oxalates from fruits and vegetables, problems may occur. Phytates can also bind calcium, preventing it from reacting with oxalates, which may lower the calcium content [34].

Discussion

Based on the findings of this review, a vegetarian diet can help prevent and manage kidney stones to some extent. The data suggest that reducing animal protein consumption and increasing plant-based meals rich in minerals such as citrate, potassium, and magnesium can improve urine composition, which in turn lowers the risk of stone formation. However, even though a vegetarian diet has several benefits, there are challenges that should be considered. One concern is the potential for higher oxalate intake from large amounts of vegetables, which may contribute to the formation of calcium oxalate stones if dietary calcium is insufficient. Therefore, vegetarian diets should be carefully balanced, especially with regard to calcium and oxalate content.

Also, the protective effects of vegetarian diets may not be the same for all types of stones. While there are clear benefits for calcium oxalate, uric acid, and cystine stones, struvite stones, which are caused by bacterial infections, may not respond well to dietary changes alone. Additionally, factors such as body weight, metabolic health, and hydration continue to play a significant role, regardless of eating patterns. Most current studies are observational or retrospective, and often include mixed factors that make it difficult to prove a direct cause-and-effect relationship.

In the future, more detailed studies, such as randomised trials, would be helpful to better understand how vegetarian diets affect the risk of kidney stones. When giving dietary advice, it is also important to consider individual differences in metabolism, nutrient absorption, and genetic factors.

Overall, the available evidence suggests that a well-planned vegetarian diet, along with good hydration and attention to mineral balance, can be a helpful strategy for reducing the occurrence and recurrence of kidney stones. However, more high-quality research and personalised dietary recommendations are needed to improve prevention efforts for different groups of people.

Conclusion

A vegetarian diet appears to be a useful approach for preventing and managing kidney stones. However, it should be tailored to each patient to ensure effectiveness and avoid negative effects. It is important to maintain adequate calcium intake to counteract harmful oxalates. Above all, drinking plenty of fluids remains the most important factor in preventing stone formation. More research is still needed to better understand this condition.

References

1. Stamatelou K, Goldfarb DS (2023). Epidemiology of kidney stones. Healthcare (Basel), 2023; 11(3): 424. doi: 10.3390/healthcare11030424
2. Shah J, Whitfield HN. Urolithiasis through the ages. BJU Int, 2002; 89(8): 801–810. doi: 10.1046/j.1464-410x.2002.02769.x
3. Dardamanis M. Pathomechanisms of nephrolithiasis. Hippokratia, 2013; 17(2): 100–107
4. Heilberg IP, Goldfarb DS. Optimum nutrition for kidney stone disease. Adv Chronic Kidney Dis, 2013; 20(2): 165–174. doi: 10.1053/j.ackd.2012.12.001
5. Khan SR, Pearle MS, Robertson WG, et al. Kidney stones. Nat Rev Dis Primers, 2016; 2: 16008. doi: 10.1038/nrdp.2016.8
6. Alelign T, Petros B. Kidney stone disease: an update on current concepts. Adv Urol, 2018; 2018: 3068365. doi: 10.1155/2018/3068365
7. Hill AJ, Basourakos SP, Lewicki P, et al. Incidence of kidney stones in the United States: the continuous National Health and Nutrition Examination Survey. J Urol, 2022; 207(4): 851–856. doi: 10.1097/JU.0000000000002331
8. Chewcharat A, Curhan G. Trends in the prevalence of kidney stones in the United States from 2007 to 2016. Urolithiasis, 2021; 49(1): 27–39. doi: 10.1007/s00240-020-01210-w
9. Sorokin I, Mamoulakis C, Miyazawa K, et al. Epidemiology of stone disease across the world. World J Urol, 2017; 35(9): 1301–1320. doi: 10.1007/s00345-017-2008-6
10. Scales CD Jr, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol, 2012; 62(1): 160–165. doi: 10.1016/j.eururo.2012.03.052
11. Daudon M, Jungers P, Bazin D, Williams JC Jr. Recurrence rates of urinary calculi according to stone composition and morphology. Urolithiasis, 2018; 46(5): 459–470. doi: 10.1007/s00240-018-1043-0
12. Sofia NH, Manickavasakam K, Walter TM. Prevalence and risk factors of kidney stone. Glob J Res Anal, 2016; 5(3): 183–187
13. Howles SA, Thakker RV. Genetics of kidney stone disease. Nat Rev Urol, 2020; 17(7): 407–421. doi: 10.1038/s41585-020-0332-x
14. Khalili P, Jamali Z, Sadeghi T, et al. Risk factors of kidney stone disease: a cross-sectional study in the southeast of Iran. BMC Urol, 2021; 21(1): 141. doi: 10.1186/s12894-021-00905-5
15. Siener R. Nutrition and kidney stone disease. Nutrients, 2021; 13(6): 1917. doi: 10.3390/nu13061917

16. Coe FL, Evan AP, Worcester EM, Lingeman JE. Three pathways for human kidney stone formation. Urol Res, 2010; 38(3): 147–160. doi: 10.1007/s00240-010-0271-8
17. Randall A. The origin and growth of renal calculi. Annals of Surgery, 1937; 105(6): 1009–1026
18. Chung HJ. The role of Randall plaques on kidney stone formation. Transl Androl Urol, 2014; 3(3): 251–254. doi: 10.3978/j.issn.2223-4683.2014.07.03
19. Ratkalkar VN, Kleinman JG. Mechanisms of Stone Formation. Clin Rev Bone Miner Metab, 2011; 9(3–4): 187–197. doi: 10.1007/s12018-011-9104-8
20. Hargreaves SM, Raposo A, Saraiva A, Zandonadi RP. Vegetarian diet: an overview through the perspective of quality of life domains. Int J Environ Res Public Health, 2021; 18(8): 4067. doi: 10.3390/ijerph18084067
21. Hargreaves SM, Rosenfeld DL, Moreira AVB, Zandonadi RP. Plant-based and vegetarian diets: an overview and definition of these dietary patterns. Eur J Nutr, 2023; 62(3): 1109–1121. doi: 10.1007/s00394-023-03086-z
22. Rocha JP, Laster J, Parag B, Shah NU. Multiple health benefits and minimal risks associated with vegetarian diets. Curr Nutr Rep, 2019; 8(4): 374–381. doi: 10.1007/s13668-019-00298-w
23. Mehta V. Vegetarian diet: A boon or bane for health? Journal of Medical Research and Innovation, 2018; 2(1): e000084. doi: 10.15419/jmri.84
24. Siener R, Bitterlich N, Birwé H, Hesse A. The impact of diet on urinary risk factors for cystine stone formation. Nutrients, 2021; 13(2): 528. doi: 10.3390/nu13020528
25. Thomas E, von Unruh GE, Hesse A. Influence of a low- and a high-oxalate vegetarian diet on intestinal oxalate absorption and urinary excretion. Eur J Clin Nutr, 2008; 62(9): 1090–1097. doi: 10.1038/sj.ejcn.1602832
26. von Unruh GE, Voss S, Sauerbruch T, Hesse A. Dependence of oxalate absorption on the daily calcium intake. J Am Soc Nephrol, 2004; 15(6): 1567–1573. doi: 10.1097/01.asn.0000127864.26968.7f
27. Barghouthy Y, Corrales M, Somani B. The relationship between modern fad diets and kidney stone disease: a systematic review of literature. Nutrients, 2021; 13(12): 4270. doi: 10.3390/nu13124270
28. Sandilya A, Sandilya P. A demographic study of urolithiasis in patients attending tertiary urological hospital in Dibrugarh, Assam, India. Int J Res Med Sci, 2019; 7(2): 417. doi: 10.18203/2320-6012.ijrms20190345
29. Asoudeh F, Talebi S, Jayedi A, et al. Associations of total protein or animal protein intake and animal protein sources with risk of kidney stones: a systematic review and dose-response meta-analysis. Adv Nutr, 2022; 13(3): 821–832. doi: 10.1093/advances/nmac013
30. Sangolli A, Nerli R, Ghagane S. Dietary risk factors and trends of kidney stones in north Karnataka patients attending a urology clinic at tertiary care center hospital – based study. Medical Science, 2024; 28: e108ms3414. doi: 10.54905/disssi.v28i150.e108ms3414
31. Xu K, Cui X, Wang B, et al. Healthy adult vegetarians have better renal function than matched omnivores: a cross-sectional study in China. BMC Nephrol, 2020; 21(1): 268. doi: 10.1186/s12882-020-01918-2
32. Turney BW, Appleby PN, Reynard JM, et al. Diet and risk of kidney stones in the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC). Eur J Epidemiol, 2014; 29(5): 363–369. doi: 10.1007/s10654-014-9904-5
33. Key TJ, Papier K, Tong TYN. Plant-based diets and long-term health: findings from the EPIC-Oxford study. Proc Nutr Soc, 2022; 81(2): 190–198. doi: 10.1017/S0029665121003748
34. Nouvenne A, Ticinesi A, Morelli I, et al. Fad diets and their effect on urinary stone formation. Translational Andrology and Urology, 2014; 3(3): 303–312. doi: 10.3978/j.issn.2223-4683.2014.06.01

REVIEW ARTICLE

THE IMPACT OF PHYSICAL ACTIVITY ON THE PREVENTION OF SYMPTOM RECURRENCE FOLLOWING LUMBAR SPINE SURGERY: A SYSTEMATIC LITERATURE REVIEW

Rola aktywności fizycznej w zapobieganiu nawrotom bólu pooperacyjnego po zabiegach w odcinku lędźwiowym kręgosłupa: systematyczny przegląd piśmiennictwa

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Abstract

Background: Spinal surgeries are among the most frequently performed procedures in neurosurgery, with discectomies, laminectomies, and decompression operations being the most common. Chronic postoperative pain, which affects 8–40% of patients who have undergone lumbar spine surgery, is a significant clinical issue. Physical activity is one of the key factors preventing postoperative pain recurrence. **Aim:** The aim of this study was to review the literature on the impact of various forms of physical activity on pain recurrence in patients following lumbar spine surgery. **Materials and methods:** This review synthesized evidence from 21 studies (randomized controlled trials, systematic reviews, and meta-analyses from 2005–2024) on exercise-based rehabilitation after lumbar spine surgery. A literature search was conducted in PubMed, Scopus, and Cochrane Library. The included studies focused on adults after disc surgery or spinal fusion and assessed the impact of physical activity on symptom recurrence. **Results:** Early rehabilitation (within 4–8 weeks post-surgery) moderately reduced pain and improved function. Core stabilization, strength, and aerobic exercises helped prevent recurrence. Individualized walking and education programmes enhanced adherence and reduced the risk of relapse, though study protocols and outcomes vary. **Conclusion:** Physical activity plays a crucial role in postoperative rehabilitation of the lumbar spine. It contributes to pain reduction, functional improvement, and decreased risk of recurrence. Early mobilization (within 1–2 months after surgery) and simple interventions, such as walking programmes combined with education, have proven to be effective and safe. The most commonly used exercises include stabilization exercises, deep muscle strengthening, and aerobic training. Despite the lack of standardized protocols, physical activity remains an essential component of patient care following lumbar spine surgery.

Streszczenie

Wprowadzenie: Operacje kręgosłupa należą do najczęściej wykonywanych procedur w neurochirurgii. Do najpoważniejszych z nich zalicza się dyscektomie, laminektomie oraz operacje dekompresyjne. Istotnym problemem klinicznym jest przewlekły ból pooperacyjny, który występuje u 8–40% pacjentów po zabiegach w obrębie odcinka lędźwiowego kręgosłupa. Aktywność fizyczna stanowi jeden z kluczowych elementów zapobiegania nawrotom dolegliwości bólowych po operacji. **Cel pracy:** Celem niniejszej pracy jest przegląd piśmiennictwa dotyczącego wpływu różnych form aktywności fizycznej na występowanie bólu u pacjentów po operacjach w obrębie odcinka lędźwiowego kręgosłupa. **Materiał i metody:** Do przeglądu włączono 21 badań (randomizowane badania kontrolowane, przeglądy systematyczne i metaanalizy z lat 2005–2024) dotyczących rehabilitacji opartej na ćwiczeniach po operacjach kręgosłupa lędźwiowego. Przeszukiwanie piśmiennictwa przeprowadzono w bazach PubMed, Scopus i Cochrane Library. Do analizy włączono badania obejmujące osoby dorosłe po zabiegach dyscektomii lub stabilizacji kręgosłupa, oceniające wpływ aktywności fizycznej na nawrót objawów. **Wyniki:** Wczesna rehabilitacja (rozpoczynana w ciągu 4–8 tygodni po zabiegu) w umiarkowanym stopniu redukuje ból i poprawia funkcję. Ćwiczenia stabilizujące, siłowe

oraz aerobowe sprzyjają zapobieganiu nawrotom objawów. Indywidualnie dostosowane programy marszowe oraz edukacja pacjentów zwiększają przestrzeganie zaleceń i zmniejszają ryzyko nawrotu, choć protokoły badań i oceniane wyniki różnią się między sobą. **Wnioski:** Aktywność fizyczna odgrywa kluczową rolę w pooperacyjnej rehabilitacji odcinka lędźwiowego kręgosłupa. Przyczynia się do redukcji bólu, poprawy funkcji oraz zmniejszenia ryzyka nawrotu dolegliwości. Wczesna mobilizacja (w ciągu 1–2 miesięcy po zabiegu) oraz proste interwencje, takie jak programy marszowe połączone z edukacją, są skuteczne i bezpieczne. Najczęściej stosowane formy aktywności obejmują ćwiczenia stabilizacyjne, wzmacnianie mięśni głębokich oraz trening aerobowy. Pomimo braku ujednoliconych protokołów, aktywność fizyczna pozostaje nieodzownym elementem opieki nad pacjentami po operacjach kręgosłupa lędźwiowego.

Keywords: low back pain; chronic pain; exercise; rehabilitation; pain management

Słowa kluczowe: ból kręgosłupa; ból przewlekły; aktywność fizyczna; rehabilitacja; leczenie bólu

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Introduction

Lumbar pain is a major clinical problem, not only as a symptom, but also as one of the main factors affecting the quality of life of patients [1]. The most common causes of lumbar pain include injuries, intervertebral disc herniation, and age-related degenerative changes [2, 3]. First-line treatment is usually conservative. Non-pharmacological methods include massage, acupuncture, heat and cold therapy, yoga, and tai chi [2, 4]. Pharmacological treatment, including nonsteroidal anti-inflammatory drugs (NSAIDs) and duloxetine, is particularly effective in patients with diffuse pain, high risk of complications, or nociplastic pain [5, 6]. Surgical intervention is considered when conservative management is considered ineffective [7].

Low back pain is often self-limiting, but when symptoms persist beyond the physiological healing time, chronic low back pain (CLBP) may develop. Approximately 85% of CLBP cases are classified as nonspecific, reflecting the absence of a definitive diagnosis and hindering effective treatment. CLBP is currently understood as a multifactorial disorder in which pathoanatomical, neurophysiological, psychological, and social factors contribute to the condition to varying degrees across patients.

Classifying CLBP into subgroups according to the predominant pathophysiological mechanisms is crucial for selecting appropriate treatment. These include pain resulting from pathological processes accompanied by adaptive motor responses, pain centrally modulated by psychological or social factors with maladaptive coping and movement control strategies, and mechanically induced pain associated with impaired movement control and physical and cognitive compensations. For the latter group, targeted physiotherapy interventions addressing both physical and cognitive factors show promising clinical effects, although further research is needed to confirm these findings [8].

Growing evidence also indicates that CLBP patients have significantly reduced aerobic capacity compared to healthy individuals, even at comparable levels of athletic activity, suggesting a clinically significant limitation in physical performance that affects daily functioning [9].

Despite advances in surgical techniques, including the increasing use of minimally invasive methods such as endoscopic spine surgery [10], pain recurrence after spine surgery remains a major clinical challenge. Endoscopic techniques, commonly used in the treatment of lumbar disc herniation and spinal stenosis, aim to limit soft-tissue damage while effectively removing the underlying pathology. Despite these advances, pain recurrence occurs in 8–40% of patients [7]. Preventing pain recurrence is therefore crucial. This review aimed to summarize the current evidence on the role of physical activity in preventing recurrent low back pain after lumbar spine surgery.

Materials and methods

This literature review aimed to synthesize current evidence regarding the role of physical activity in preventing symptom recurrence after lumbar spine surgery. The analysis included randomized controlled trials (RCTs), systematic reviews, and meta-analyses published between 2005 and 2024.

A literature search was conducted in PubMed, Scopus, and Cochrane Library databases using the following keywords and their combinations: “lumbar spine surgery,” “rehabilitation,” “physical activity,” “exercise therapy,” “recurrence,” “low back pain,” and “postoperative recovery.” Boolean operators (AND, OR) were used to narrow the search. Peer-reviewed English-language publications involving adults who had undergone discectomy or lumbar spine stabilization were included if they assessed the effects of physical activity or exercise-based rehabilitation on symptom recurrence or the

progression of CLBP. Only RCTs, systematic reviews, and meta-analyses were included. Case reports, review papers, conference abstracts, and studies that did not report postoperative outcomes or symptom recurrence rates were excluded.

Of the 21 publications ultimately selected, 9 were RCTs, 6 were systematic reviews and meta-analyses, including Cochrane reviews, and 6 were high-quality narrative or clinical reviews. Key sources included Afzal et al. (2022) [11], Hayden et al. (2021, 2005) [1, 12], Oosterhuis et al. (2014) [13], Pocovi et al. (2024) [14], and Foster et al. (2018) [15].

Qualitative assessments were performed with respect to the timing of rehabilitation, types of exercise, functional outcomes, relapse rates, and protocol consistency. Attention was paid to interventions implemented within 1–2 months of surgery, including stabilization exercises, aerobic training, and patient education.

Literature review – results

Early postoperative rehabilitation

A 2022 meta-analysis of 15 RCTs evaluated the efficacy of active rehabilitation initiated within 1–2 months following lumbar discectomy. It demonstrated moderate improvements in functional outcomes and subjective pain perception compared with no-intervention controls [11]. Rehabilitation programmes included motor control exercises, stabilization, strength training, joint and neuromuscular mobilization, as well as educational and psychosocial components [11].

The authors highlighted the significant heterogeneity of protocols in terms of type, intensity, and duration of exercise, as well as the timing of intervention [11]. None of the included studies reported complications related to rehabilitation, supporting the safety of early postoperative mobilization. Early mobilization also helped prevent muscle atrophy and restore normal sympathetic feedback mechanisms [11].

The analysis included a total of 2,188 patients. Active rehabilitation conducted 1–2 months postoperatively was associated with a statistically significant reduction in pain (p = 0.004), improvement in overall functional ability (p = 0.0001), and reduction in pain disability scores (p = 0.002) [11]. Despite moderate heterogeneity across studies, the overall quality of the evidence was rated as moderate to high.

Long-term physical activity

A 2009 Cochrane systematic review included 14 RCTs evaluating the effectiveness of various rehabilitation interventions after initial lumbar spine surgery [16]. Studies demonstrated substantial variability in the timing of rehabilitation initiation, ranging from 2 to more than 12 months postoperatively, as well as in the intensity and duration of exercise programmes [16]. Due to clinical heterogeneity, the meta-analysis could only be performed for three comparisons: exercise programmes vs no treatment, low-intensity vs high-intensity programmes, and home-based exercises vs supervised rehabilitation [16].

The updated review included only RCTs and used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology to assess the quality of evidence [16]. Unlike the earlier classification based on "levels of evidence," the GRADE approach enabled a more precise assessment of the reliability of the findings by considering the risk of bias, consistency, validity, and precision [16]. The findings indicated that intensive exercise programmes initiated 4–6 weeks postoperatively produced moderate improvements in functional outcomes, prompting a revision of earlier conclusions suggesting strong evidence [16].

The review found that exercise initiated 4–6 weeks after surgery was associated with faster pain reduction than no intervention (low-quality evidence), and that lower-frequency programmes were more effective than higher-frequency programmes in reducing disability (moderate-quality evidence) [16]. No increased risk of reoperation was observed, supporting the safety of postoperative physical activity [16].

The effectiveness of supervised rehabilitation compared with home-based exercises was similar in the short term (low-quality evidence), although adherence to home-based programmes was limited [16, 17]. Patient engagement declined to below 60% after two months and below 30% after six months, highlighting the potential need for supervision in long-term rehabilitation programmes to sustain motivation [16].

Biopsychosocial interventions were not shown to be significantly superior to standard physiotherapy, with both forms of therapy considered safe and neither found to affect the reoperation rates [16]. Furthermore, differences in surgical techniques (e.g., open discectomy vs. microdiscectomy) had no significant impact on rehabilitation outcomes [16].

The review authors concluded that there is no justification for avoiding physical activity following lumbar spine surgery. Although the optimal rehabilitation protocol remains unclear, early mobilization and higher-intensity programmes appear beneficial in reducing pain and improving function [16].

These results are consistent with previous observations regarding exercise therapy in patients with nonspecific low back pain. A previous Cochrane review found that although exercise was not superior to other conservative treatments in acute cases, it produced moderate effects in subacute work-related pain and a minor yet significant benefit in chronic cases [12]. It also highlighted limitations in the quality of the studies and the need to standardize both interventions and outcomes [12].

Recent data confirm that early rehabilitation following lumbar spine stabilization, based on strength training and intra-abdominal pressure activation, is safe and may accelerate functional recovery. In a randomized trial, both early training and standard rehabilitation improved functional outcomes; however, only the training group

achieved walking distances close to age-appropriate norms and demonstrated improvements in trunk extension, lateral flexion, and pre-activation patterns [18]. No complications or implant damage were noted despite initiating the programme as early as 3 weeks post surgery, with lower baseline performance associated with greater functional gains. These findings suggest that well-planned, strength-based rehabilitation can improve functional capacity without increasing the risk of complications.

Walking programmes

The randomized WalkBack Trial (2024) showed that an individually tailored, progressive walking programme combined with education significantly reduced the risk of recurrent nonspecific low back pain among previously inactive individuals [14]. This effect was consistent across all three analysed endpoints related to pain recurrence. A significant reduction in pain-related disability was also observed within 12 months of implementing the intervention [14]. Furthermore, the economic analysis demonstrated a high probability of cost-effectiveness from a societal perspective [14].

This study addressed a significant gap in the literature. A 2018 systematic review published in The Lancet highlighted the scarcity of high-quality research on low back pain prevention and emphasized the need to develop effective, accessible preventive strategies [15]. The WalkBack study was the first RCT to evaluate the efficacy of walking as a preventive intervention [14]. The results demonstrated effectiveness comparable to that of more expensive, supervised group programmes, suggesting that large-scale implementation could yield substantial health and economic benefits [14].

The study's strengths included preregistration in a clinical trials database, publication of study protocol and statistical analysis plan, a long follow-up period of 12–36 months, and a high participant completion rate [14]. During the COVID-19 pandemic, the intervention was adapted for remote delivery, enabling participation from rural and geographically isolated areas and thereby improving accessibility and implementation potential [14].

However, the study's generalizability was limited as most participants were women aged 43–66 years with a history of recurrent low back pain [14]. Furthermore, the intervention was delivered by physiotherapists trained in health coaching, which may limit the programme's replicability among other healthcare professionals [14]. Also, the absence of participant blinding may have influenced the subjective assessment of outcomes [14].

The intervention group also reported more lower-limb adverse events compared to controls (100 versus 54 cases) [14]. These findings suggest that similar programmes should include monitoring for signs of overuse or excessive loading, with training intensity increased gradually [14].

Clinically significantly, the preventive effect was achieved with a small number of educational sessions based on the principles of health coaching [14]. The effectiveness of the intervention was likely attributable to the synergistic effects of education, which helped overcome anxiety and activity avoidance, as well as progressive walking training, which supported behavioural changes [14]. It is worth noting that walking intensity initially doubled in the intervention group; however, the differences between the groups were no longer evident after 12 months [14]. This may suggest the need for periodic booster interventions or ongoing therapeutic support to maintain long-term effects [14].

The WalkBack programme has important practical implications: a simple, low-cost, and easy-to-implement walking-based intervention can significantly reduce the risk of low back pain recurrence and the associated burden on the healthcare system [14]. Future studies should evaluate the effectiveness of this approach in physically active individuals and postoperative patients, as well as with alternative forms of physical activity [14].

Types of exercises in postoperative rehabilitation of the lumbar spine

Rehabilitation programmes following lumbar spine surgery typically include three main types of activities: stabilization exercises, core strengthening exercises, and aerobic training [19–21].

Stabilization exercises aim to improve motor control and activation of local muscles, such as the transverse abdominis and multifidus, which are often weakened in patients with low back pain [19, 20]. Core muscle strengthening exercises increase muscle strength and segmental stability of the lumbar spine, which are crucial for improving function and reducing pain [19–21].

Aerobic training improves cardiorespiratory parameters and may also benefit mental well-being, thereby enhancing the overall effectiveness of rehabilitation.

The studies included in this review demonstrated substantial variability in the timing, content, and intensity of postoperative exercise programmes, while the evidence supporting their effectiveness was generally of low to very low quality [13]. Although early postoperative exercise may provide modest improvements in recovery, these findings should be interpreted with caution. Importantly, no association with increased reoperation rates was found, supporting the safety of an early return to activity.

Adherence to home-based exercise recommendations tends to decline over time, highlighting the need for ongoing supervision and support to maintain motivation [13]. Home-based exercise programmes can be effective, particularly when delivered in a group or social setting, which may enhance engagement and adherence. Despite the benefits of supervised and standardized programmes, current evidence remains insufficient to establish the optimal duration and frequency of exercise sessions. Further RCTs are needed to develop optimal practices for home-based rehabilitation following spine surgery [17]. Additionally, patient preferences and expectations may influence adherence, highlighting the importance of individualizing treatment programmes.

Conclusions

Recurrent low back pain following lumbar spine surgery is a major clinical problem that can substantially impair patients' quality of life. Available evidence indicates that physical activity plays a key role in postoperative rehabilitation by reducing pain, improving function, and helping prevent symptom recurrence.

Research suggests that early rehabilitation, initiated within 1–2 months after surgery, provides moderate benefits, including reduced pain and improved functional capacity. Early physical activity not only promotes the recovery of mobility but also helps prevent muscle atrophy and restore neuromuscular control.

However, maintaining patient engagement throughout rehabilitation remains challenging. Therefore, motivational strategies, including regular follow-up, motivational interviewing, and incorporating patient preferences into treatment planning, may help improve adherence.

Simple interventions, such as individually tailored walking programmes combined with education, have been shown to reduce the risk of pain recurrence and promote symptom self-management. These programmes may also be cost-effective for healthcare systems.

Postoperative rehabilitation should include stabilization and core-strengthening exercises alongside aerobic training, as these modalities work together to address different pain mechanisms and provide functional improvement. Despite the absence of standardized protocols, physical activity remains a safe and effective strategy for postoperative management.

Future research should focus on standardizing rehabilitation protocols by defining the optimal duration, intensity, and type of exercise while incorporating psychosocial support. Long-term studies should also evaluate how different rehabilitation strategies affect pain recurrence and functional outcomes across diverse patient populations.

To conclude, incorporating physical activity into postoperative care plans is crucial for optimizing recovery and minimizing the risk of recurrent low back pain. Early mobilization and individually tailored rehabilitation strategies can improve patient outcomes and quality of life. Advancing understanding of the relationship between physical activity and pain mechanisms should prompt healthcare providers to update their approaches to ensure that patient care remains aligned with the latest scientific evidence.

References

1. Hayden JA, Ellis J, Ogilvie R, et al. Exercise therapy for chronic low back pain. Cochrane Database Syst Rev, 2021; 9(9): CD009790. doi: 10.1002/14651858.CD009790.pub2
2. Chenot JF, Greitemann B, Kladny B, et al. Non-specific low back pain. Dtsch Arztebl Int, 2017; 114(51–52): 883–890. doi: 10.3238/arztebl.2017.0883
3. Knezevic NN, Candido KD, Vlaeyen JWS, et al. Low back pain. Lancet, 2021; 398(10294): 78–92. doi: 10.1016/S0140-6736(21)00733-9
4. Beneciuk JM, Robinson ME, George SZ. Low back pain subgroups using fear-avoidance model measures: results of a cluster analysis. Clin J Pain, 2012; 28(8): 658–666. doi: 10.1097/AJP.0b013e31824306ed
5. Maharty DC, Hines SC, Brown RB. Chronic low back pain in adults: evaluation and management. Am Fam Physician, 2024; 109(3): 233–244
6. van de Minkelis J, Peene L, Cohen SP, et al. 6. Persistent spinal pain syndrome type 2. Pain Pract. 2024; 24(7): 919–936. doi: 10.1111/papr.13379
7. Wu Q, Cui X, Guan LC, et al. Chronic pain after spine surgery: Insights into pathogenesis, new treatment, and preventive therapy. J Orthop Translat, 2023; 42: 147–159. doi: 10.1016/j.jot.2023.07.003
8. O'Sullivan P. Diagnosis and classification of chronic low back pain disorders: maladaptive movement and motor control impairments as underlying mechanism. Man Ther, 2005; 10(4): 242–255. doi: 10.1016/j.math.2005.07.001
9. Smeets RJ, Wittink H, Hidding A, Knottnerus JA. Do patients with chronic low back pain have a lower level of aerobic fitness than healthy controls? Are pain, disability, fear of injury, working status, or level of leisure time activity associated with the difference in aerobic fitness level? Spine (Phila Pa 1976). 2006; 31(1): 90–98. doi: 10.1097/01.brs.0000192641.22003.83
10. Shepard NA, Protopsaltis T, Kim Y. Lumbar endoscopic spine surgery: a comprehensive review. Bull Hosp Jt Dis, 2021; 79(1): 35–42
11. Afzal K, Khattak HG, Sajjad AG, et al. Impact of active physiotherapy rehabilitation on pain and global and functional improvement 1-2 months after lumbar disk surgery: a systematic review and meta-analysis. Healthcare (Basel), 2022; 10(10): 1943. doi: 10.3390/healthcare10101943
12. Hayden JA, van Tulder MW, Malmivaara A, Koes BW. Exercise therapy for treatment of non-specific low back pain. Cochrane Database Syst Rev, 2005(3): CD000335. doi: 10.1002/14651858.CD000335.pub2
13. Oosterhuis T, Costa LO, Maher CG, et al. Rehabilitation after lumbar disc surgery. Cochrane Database Syst Rev, 2014; 2014(3): CD003007. doi: 10.1002/14651858.CD003007.pub3
14. Pocovi NC, Lin CC, French SD, et al. Effectiveness and cost-effectiveness of an individualised, progressive walking and education intervention for the prevention of low back pain recurrence in Australia (WalkBack): a randomised controlled trial. Lancet, 2024; 404(10448): 134–144. doi: 10.1016/S0140-6736(24)00755-4
15. Foster NE, Anema JR, Cherkin D, et al.; Lancet Low Back Pain Series Working Group. Prevention and treatment of low back pain: evidence, challenges, and promising directions. Lancet, 2018; 391(10137): 2368–2383. doi: 10.1016/S0140-6736(18)30489-6
16. Ostelo RW, Costa LO, Maher CG, et al. Rehabilitation after lumbar disc surgery: an update Cochrane review. Spine (Phila Pa 1976), 2009; 34(17): 1839–1848. doi: 10.1097/BRS.0b013e3181abbfdf
17. Quentin C, Bagheri R, Ugbolue UC, et al. Effect of home exercise training in patients with nonspecific low-back pain: a systematic review and meta-analysis. Int J Environ Res Public Health, 2021; 18(16): 8430. doi: 10.3390/ijerph18168430

18. Kernc D, Strojnik V, Vengust R. Early initiation of a strength training based rehabilitation after lumbar spine fusion improves core muscle strength: a randomized controlled trial. J Orthop Surg Res, 2018; 13(1): 151. doi: 10.1186/s13018-018-0853-7
19. Fernández-Rodríguez R, Álvarez-Bueno C, Cavero-Redondo I, et al. Best exercise options for reducing pain and disability in adults with chronic low back pain: Pilates, strength, core-based, and mind-body. A network meta-analysis. J Orthop Sports Phys Ther, 2022; 52(8): 505–521. doi: 10.2519/jospt.2022.10671
20. Kostadinović S, Milovanović N, Jovanović J, Tomašević-Todorović S. Efficacy of the lumbar stabilization and thoracic mobilization exercise program on pain intensity and functional disability reduction in chronic low back pain patients with lumbar radiculopathy: A randomized controlled trial. J Back Musculoskelet Rehabil, 2020; 33(6): 897–907. doi: 10.3233/BMR-201843
21. Owen PJ, Miller CT, Mundell NL, et al. Which specific modes of exercise training are most effective for treating low back pain? Network meta-analysis. Br J Sports Med, 2020; 54(21): 1279–1287. doi: 10.1136/bjsports-2019-100886

REVIEW ARTICLE

HIGH-ALTITUDE CEREBRAL OEDEMA (HACE): A HEALTH CHALLENGE IN EXTREME ENVIRONMENTS

Wysokościowy obrzęk mózgu (HACE): wyzwanie zdrowotne w ekstremalnych warunkach środowiskowych

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Abstract

High-altitude cerebral oedema is one of the three forms of altitude sickness and is considered one of its most serious complications. Its incidence is relatively low, but its rapid progression and worsening symptoms make it a life-threatening condition that requires immediate medical attention. The growing popularity of high-altitude tourism means that knowledge about altitude sickness and high-altitude cerebral oedema should be promoted not only among medical professionals but also among ordinary tourists planning high-mountain expeditions. The following paper, which is a narrative review describing high-altitude cerebral oedema, discusses the key pathogenetic elements of this condition, including molecular mechanisms resulting from exposure to hypobaric hypoxia, blood-brain barrier dysfunction, increased vascular permeability, and the development of both vasogenic and cytotoxic oedema. Epidemiological data and risk factors are presented, followed by the spectrum of clinical manifestations, ranging from non-specific, mild symptoms that may coexist with an episode of acute mountain sickness to ataxia, impaired consciousness, and other severe neurological signs. The paper addresses diagnostic issues, with particular emphasis on the usefulness of imaging tests, specifically magnetic resonance imaging, in the process of confirming the diagnosis. Finally, the role of rapid implementation of appropriate therapy, consistent with current medical knowledge and consisting of altitude reduction, oxygen therapy, administration of steroids, and, in difficult conditions, the use of a portable hyperbaric chamber, is emphasised. High-altitude cerebral oedema remains a challenge that should always be managed by an interdisciplinary team; however, further research is needed to deepen our understanding of the pathophysiology, diagnosis, and treatment of this condition.

Streszczenie

Wysokościowy obrzęk mózgu stanowi jedną z trzech form choroby wysokościowej i jest uważany za jedno z jej najpoważniejszych powikłań. Częstość jego występowania jest stosunkowo niska, ale szybka progresja i narastanie objawów sprawiają, że jest to stan zagrażający życiu, wymagający natychmiastowej pomocy medycznej. Ze względu na rosnącą popularność turystyki wysokogórskiej, wiedza na temat choroby wysokościowej i wysokościowego obrzęku mózgu powinna być propagowana zarówno wśród osób związanych z medycyną, jak i wśród turystów planujących wysokogórskie ekspedycje. W niniejszym przeglądzie narracyjnym omówiono kluczowe elementy patogenezy wysokościowego obrzęku mózgu, w tym mechanizmy molekularne wynikające z przebywania w warunkach hipoksji hipobarycznej, dysfunkcji bariery krew–mózg, zwiększonej przepuszczalności naczyń krwionośnych oraz powstawania obrzęku naczyniowego i cytotoksycznego. Przedstawiono dane epidemiologiczne wraz z czynnikami ryzyka, a następnie spektrum objawów klinicznych, od niespecyficznych, łagodnych, które mogą współistnieć z epizodem ostrej choroby wysokogórskiej, po ataksję, zaburzenia świadomości i inne ciężkie objawy neurologiczne. Omówiono również zagadnienia diagnostyczne, ze szczególnym uwzględnieniem przydatności badań obrazowych, zwłaszcza rezonansu magnetycznego, w procesie potwierdzania rozpoznania. Na koniec podkreślono rolę szybkiego wdrożenia odpowiedniej terapii, zgodnej z aktualną wiedzą medyczną i obejmującej obniżenie wysokości, tlenoterapię, podawanie glikokortykosteroidów, a w trudnych warunkach – zastosowanie przenośnej komory hiperbarycznej. Wysokościowy obrzęk mózgu pozostaje istotnym wyzwaniem kliniczym, którym zawsze powinien zajmować się zespół interdyscyplinarny, ale do lepszego poznania jego patofizjologii, diagnostyki i leczenia konieczne są dalsze badania nad tajemnicami, które skrywa przed nami ta jednostka chorobowa.

Keywords: hypobaric hypoxia; acclimatisation; blood–brain barrier; high-altitude cerebral oedema; HACE

Słowa kluczowe: hipoksja hipobaryczna; aklimatyzacja; bariera krew–mózg; wysokościowy obrzęk mózgu; HACE

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Introduction

For hundreds of years, mountains have been a fascinating and intriguing object of human endeavour. These beautiful, expansive landscapes offer space for recreation, rest, and the restoration of well-being. With technological advances, they are becoming increasingly accessible, and what was once the domain of pioneers who made headlines after each expedition is now completely different. For many tourists, crossing the barrier of 4,000 or 5,000 metres above sea level is no longer an extraordinary challenge. This fact should inspire humility towards the mountains, given the physiological consequences they may impose. We must remember that the breathtaking views from high peaks can, under conditions of hypobaric hypoxia, pose a serious and sometimes even fatal threat.

The most common form of altitude illness, typically associated with milder symptoms, is acute mountain sickness (AMS). This syndrome occurs in climbers at altitudes above 2,500 metres above sea level, especially those who ascend too quickly and without proper acclimatisation [1]. Symptoms develop within 6–12 hours and, according to the literature, most commonly include headaches (70–80% of patients), nausea, vomiting (30–50%), insomnia (30–50%), dizziness (50–60%), fatigue (40–60%), and loss of appetite (20–40%) [2]. In the vast majority of cases, mild symptoms resolve spontaneously with acclimatisation or descent. However, if symptoms are ignored and climbing is continued, severe organ complications may develop, including the other two forms of high-altitude sickness: high-altitude pulmonary oedema (HAPE) and high-altitude cerebral oedema (HACE) [3].

This work is a narrative review based on current scientific publications indexed in the PubMed, Scopus, and Web of Science databases. The study includes sources of varying scientific credibility – primarily current guidelines and expert consensus, followed by larger case series, and finally review papers on the pathogenesis, diagnosis and treatment of HACE.

Epidemiology and risk factors

As noted in the introduction, HACE is one of the most dangerous and potentially fatal complications of exposure to a low partial pressure of oxygen. Researchers estimate that the incidence of HACE among individuals travelling above 4,000 metres above sea level ranges from 0.5 to 1% [4]. It should be emphasised that a definitive epidemiological estimate is extremely difficult to obtain, and the literature reports a wide range of values. Studies indicate that differences in incidence may be related to genetic adaptation to hypoxia and more efficient oxygen transport mechanisms [5]. In addition to distinguishing between permanent high-altitude residents and visiting climbers, it is necessary to consider risk factors that help estimate the probability of developing HACE.

Risk factors:

- Climbing speed and acclimatisation – the literature cites fast climbing speed and lack of adequate acclimatisation time as the main risk factors for HACE [6, 7].
- Age and gender – researchers do not list these factors as significant, although some studies indicate that younger men, who may be more likely to ignore early warning signs, i.e., the initial symptoms of AMS, could have a higher incidence of HACE [8].
- Co-existence of HAPE – data show that up to 50% of patients who develop high-altitude pulmonary oedema also develop HACE [6].
- Cardiovascular, respiratory, and neurological diseases – conditions such as congenital heart defects, upper respiratory tract infections, and Parkinson's disease, have been identified as risk factors [9, 10].
- Chronic fatigue and significant exertion at high altitudes – these may contribute to the development of HACE [11].
- Migraine – the occurrence of migraines has been identified in the literature as a risk factor for altitude sickness and, indirectly, for HACE [12].

In light of these findings, HACE remains one of the rarest complications within the spectrum of altitude sickness from an epidemiological point of view, although this fact should not lead to underestimation of the risks associated with the development of this disease.

Notably, HACE does not occur during aircraft cabin depressurisation, as such events involve only short-term hypoxia, even if the equivalent altitude may transiently reach 4,000–7,000 metres. The brief duration of exposure is insufficient to disrupt the blood–brain barrier or trigger the vasogenic cerebral oedema characteristic of HACE. Instead, any neurological disturbances that may appear are more likely related to hypocapnic cerebral vasoconstriction or decompression sickness rather than to high-altitude cerebral oedema [13, 14]. Therefore, the next part of the article addresses the pathogenesis, symptoms, diagnosis, and treatment of HACE.

Pathogenesis

Before discussing the molecular and morphological changes that lead to HACE, it is necessary to understand how oxygen conditions change with increasing altitude:

- 1,500–3,500 metres above sea level – a slight decrease in oxygen saturation (SaO_2) and a decrease in partial oxygen pressure (PaO_2) to approximately 55–75 mmHg.
- 3,500–5,500 metres above sea level – a further decrease in SaO_2 to 75% and a decrease in PaO_2 to 40–60 mmHg.
- 5,500–8,850 metres above sea level – extreme altitudes, with the "death zone" above 8,000 metres. Saturation then drops to as low as 58%, and PaO_2 can fall to about 30 mmHg [15].

These values demonstrate how profoundly the conditions at high altitudes differ from those known from everyday life – at an altitude at or near sea level. High altitude exposes the human body to conditions of hypobaric hypoxia, which in turn, through damage to the blood–brain barrier, vasogenic and cytotoxic oedema, forms the basis for the development of HACE.

Thanks to experimental research conducted in recent years, including studies using animal models, several facts regarding the pathogenesis of HACE have been established:

- Hypoxic hypoxia induces the formation of Caveolin-1 in the endothelium of cerebral vessels, regulated by nuclear respiratory factor-1. This process promotes degradation of proteins such as Claudin-5, which damages endothelial junctions and increases the permeability of the blood–brain barrier [16, 17].
- Hypoxia activates HIF-1α pathways, which affects the synthesis of vascular endothelial growth factor (VEGF). VEGF increases vascular permeability by interfering with the distribution and expression of proteins that form tight junctions, such as occludin and Claudin-5. VEGF may also stimulate the synthesis of metalloproteinases, which further exacerbates damage to the blood–brain barrier [16, 18, 19].
- Blood–brain barrier damage may also result from increased expression of pro-inflammatory cytokines such as TNF-α and IL-1β. By acting through pathways such as MAPK, p38, and NF-κB, these cytokines reorganise intercellular junctions, increasing barrier permeability [4, 13, 20].
- Under conditions of hypoxia, free radicals are formed, which, as studies have shown, damage Na+/K+ ATPase ion pumps. Water and sodium accumulate intracellularly, causing oedema of neurons and astrocytes, followed by cytotoxic oedema, accompanying vasogenic oedema and deepening brain damage [4, 21, 22].
- Individual factors such as skull anatomy, subarachnoid space capacity, compensatory abilities of the circulatory and nervous systems, and adaptation to hypoxic conditions may influence how quickly and to what degree the above mechanisms cause clinically significant brain oedema [16, 21, 23, 24] (Fig. 1).

All the complexities of the processes described above contribute to a cascade of events which, if not interrupted, cause rapid deterioration of the patient's condition, putting them in a life-threatening situation. Despite clear progress in understanding what HACE actually is, many pieces of the puzzle remain unknown, which only emphasises the need for further clinical and experimental research.

Symptoms

Due to its clinical presentation, HACE is a rather heterogeneous set of symptoms that usually develop within 24–48 hours after reaching an altitude of over 4,000 meters above sea level [4].

The first phase consists of symptoms that can be classified as AMS, namely nausea, headache, dizziness, and general weakness. According to the Lake Louise criteria, AMS is diagnosed when the total score reaches three or more points, including at least one point for headache, following recent ascent to high altitude [1, 25] (Tab. 1).

An important moment in the evolution of the disease, when the differential diagnosis should shift towards HACE, is the onset of neurological symptoms. These may manifest gradually or progress rapidly, leading to a life-threatening condition. This is often described as encephalopathy, including ataxia and mental status changes such as increasing somnolence and confusion [1, 26].

Knowledge of the course of this clinical phase should immediately prompt the climber to stop ascending and begin descent, as the further presentation of the disease may become dramatic. Some patients experience loss of consciousness, coma, and seizures [27]. Noteworthy here is the case of a 23-year-old climber who developed a seizure and coma the day after experiencing mild symptoms of AMS. This case also demonstrates the potential reversibility of HACE: with appropriate diagnosis, including MR imaging and hyperbaric treatment, the man regained mobility and the seizures did not return [28].

Table 1. The Lake Louise Acute Mountain Sickness Score

Headache	0 – None 1 – Mild 2 – Moderate 3 – Severe, incapacitating
Gastrointestinal symptoms	0 – No symptoms 1 – Poor appetite/nausea 2 – Moderate nausea/vomiting 3 – Severe nausea/vomiting, incapacitating
Fatigue and/or weakness	0 – Not tired or weak 1 – Mild fatigue/weakness 2 – Moderate fatigue/weakness 3 – Severe fatigue/weakness, incapacitating
Dizziness/ light-headedness	0 – No symptoms 1 – Mild dizziness 2 – Moderate dizziness 3 – Severe dizziness, incapacitating
Stage of the disease: **1. Mild** AMS: 3 to 5 points **2. Moderate** AMS: 6 to 9 points **3. Severe** AMS: 10 to 12 points AMS – acute mountain sickness	

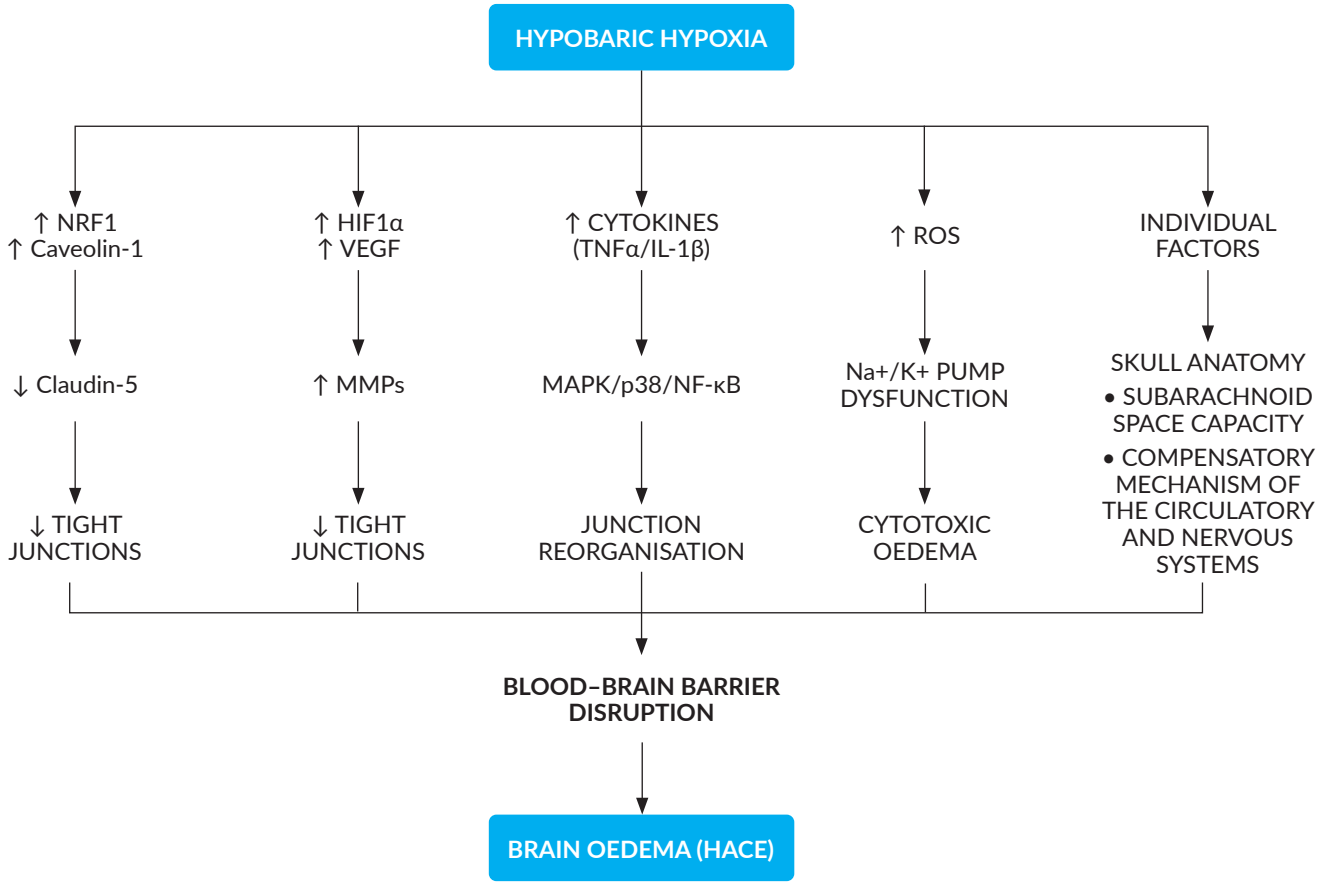

Figure 1. Pathogenesis of high-altitude cerebral oedema (HACE). NRF1 – nuclear respiratory factor 1; VEGF – vascular endothelial growth factor; NF-κB – nuclear factor kappa B; MAPK – mitogen-activated protein kinases; IL-1β – interleukin 1β; TNF-α – tumour necrosis factor α

Descriptions in the literature also include patients presenting symptoms atypical for HACE, such as the case of a 62-year-old patient who, while climbing and ascending to an altitude of about 3,500 metres above sea level, developed hiccups followed by slurred speech, headache, and nausea. After being transported to hospital, HACE was confirmed [29].

Other reviews have described symptoms such as diplopia, which, as shown during examination, was due to paralysis of cranial nerve VI (abducens nerve) and transient paresis of the left upper and lower limbs. The common denominator in both cases was the resolution of symptoms after descent to a lower altitude [30] (Tab. 2).

Diagnostics

The diagnostic process for high-altitude cerebral oedema is based on three pillars: the patient's clinical presentation, a well-collected medical history, and imaging tests (MRI/CT). The aim is to determine whether the presentation is truly consistent with HACE or with another disease producing similar symptoms. The literature states that the following conditions should be considered in the differential diagnosis:

- hypoglycaemia
- hypothermia
- hyponatraemia
- drug/alcohol intoxication
- carbon monoxide poisoning
- ketoacidosis
- cerebrovascular diseases: haemorrhage, stenosis
- meningitis
- epilepsy
- psychosis
- central nervous system tumours [4, 21].

Table 2. Symptoms of high altitude cerebral oedema (HACE) depending on disease phase

Phase of the disease	Symptoms
Prodromal phase/ co-occurrence of acute mountain sickness	• Nausea • Vomiting • Headache • Dizziness • Weakness/fatigue
Early HACE	• Ataxia • Somnolence • Confusion • Behavioural changes
Late HACE	• Loss of consciousness • Seizures • Coma
Atypical symptoms	• Diplopia – VI cranial nerve palsy • Hiccups • Slurred speech • Transient hemiplegia

Table 3. Findings observed depending on the selected imaging method

Head CT without contrast	• Diffuse cerebral oedema • Decreased density of white matter, especially in the corpus callosum region • Compression of the lateral and third ventricles • Blurring of sulci [26, 33]
Magnetic resonance imaging of the head	• Hypointense signal in the T1 sequence • Hyperintense signal in the T2 sequence • Hyperintense signal in the FLAIR and DWI sequences involving the corpus callosum, particularly the splenium, corona radiata, centrum semiovale, and parts of the internal capsule • SWI sequence may reveal microhaemorrhages, most often located in the corpus callosum and subcortically • Decreased ADC value • Indirect signs: narrowing, atrophy of the cerebral ventricles [26, 33–36]

While still in the field, diagnostic possibilities are limited, so attention should be focused on a thorough medical history, which includes questions about the pace and maximum altitude of ascent, chronic diseases, medications or stimulants used, previous episodes of altitude sickness, and the timing and sequence of symptoms [31]. Researchers also note that simple neurological tests assessing coordination or ataxia are extremely useful for evaluating AMS or HACE in mountain conditions: the straight-line walk test [27], the heel–knee test, and the finger–nose test [11].

After hospital admission, specific laboratory tests are performed, although in HACE the most important investigations are imaging tests. So far, no specific laboratory markers for high-altitude cerebral oedema have been identified. Some specialists cite leukocytosis as the only notable change in the patient's results, but this remains controversial, as such an increase may have completely different causes than cerebral oedema itself [4]. Laboratory tests are performed to rule out other causes of the patient's condition and include blood glucose levels, electrolytes, toxicology tests, and blood gas analysis [4, 6, 32]. Magnetic resonance imaging or computed tomography plays a significant role in diagnosis. CT is considered less valuable due to its reduced sensitivity in detecting mild forms of HACE, which may result in diagnostic errors [3, 26] (Tab. 3).

Treatment

The next step in managing HACE is the rapid initiation of treatment, the first stage of which is descending to a lower altitude, which will reduce hypoxia and stop the progression of cerebral oedema. During descent, physical exertion should be minimised as far as possible, as it may worsen the patient's prognosis [37, 38]. If immediate evacuation is not possible, guidelines and studies indicate the need for oxygen therapy (maintaining saturation at >90%) and consideration of a portable hyperbaric chamber (Gamow bag), which simulates descent to a lower altitude. These methods are effective, but not as effective as full evacuation [39, 40].

Another crucial aspect of treatment is the administration of glucocorticosteroids, specifically dexamethasone. Studies have shown that adult patients should be given an initial dose of 8 mg of dexamethasone, followed by 4 mg every 6 hours, administered orally, intravenously, or intramuscularly, depending on the patient's condition and capabilities. The steroid dosage for paediatric patients is 0.15 mg/kg of body weight every 6 hours. The molecular mechanisms of dexamethasone, based on cell membrane stabilisation, inhibition of angiogenesis, and modulation of nitric oxide synthase production, help reduce endothelial damage resulting from hypoxia [4, 15].

Acetazolamide, a carbonic anhydrase inhibitor, is not included in the standard treatment regimen for HACE, although it is used in the prevention of altitude sickness and in the management of mild forms of AMS. The effectiveness of acetazolamide in the treatment of HACE has been demonstrated occasionally, using a dose of 250 mg administered orally twice a day. Its mechanism of action is based on effects on the proximal renal tubules, inducing metabolic acidosis and stimulating ventilation [4, 41].

Researchers have repeatedly emphasised the importance of prevention; however, once cerebral oedema develops, all rescue efforts should be focused on the rapid implementation of the above-described measures, as without them, most patients die within 24 hours. Treatment and appropriate rehabilitation, lasting several days or weeks, significantly increase the chances of survival, reversal of cerebral oedema, and prevention of permanent neurological deficits.

Summary

HACE is one of the most dangerous complications resulting from exposure to high altitudes. It occurs relatively rarely, but its sudden and rapid progression makes it a life-threatening condition that requires immediate medical attention. The pathomechanisms underlying HACE, although not yet fully understood, are quite complex and involve a number of biochemical and molecular processes, including damage to the blood–brain barrier and the development of vasogenic and cytotoxic oedema.

Individual and environmental factors, such as the rate of acclimatisation, underlying disease burden, and previous episodes of altitude illness, should also be taken into account.

The clinical picture may vary from case to case, but typically begins with non-specific, mild symptoms that can quickly evolve into severe neurological disturbances. It is this ambiguity and the dynamic nature of the patient's condition that make proper diagnosis, recogni-

tion, and treatment crucial for determining prognosis. The aforementioned treatment, based mainly on altitude reduction, oxygen therapy, and the administration of dexamethasone in appropriate doses, if implemented promptly, can lead in many cases to complete resolution of symptoms and full recovery.

In summary, high-altitude cerebral oedema remains an interdisciplinary challenge, drawing on knowledge from the fields of neurology, emergency medicine, extreme and travel medicine. Preventive actions, education, and further scientific research into the pathophysiology of the disease are key to improving diagnosis and treatment, and giving patients hope for a full recovery.

References

1. Hackett PH, Oelz O. The Lake Louise consensus on the quantification of altitude illness. In: Sutton JR, Houston CS, Coates G, eds. Hypoxia and Mountain Medicine. Burlington, VT: Queen City Printers; 1992. pp. 327–330
2. Berger MM, Hüsing A, Niessen N, et al. Prevalence and knowledge about acute mountain sickness in the Western Alps. PLoS One, 2023; 18(9): e0291060. doi: 10.1371/journal.pone.0291060
3. Sagoo RS, Hutchinson CE, Wright A, et al.; Birmingham Medical Research and Expedition Society. Magnetic Resonance investigation into the mechanisms involved in the development of high-altitude cerebral edema. J Cereb Blood Flow Metab, 2017; 37(1): 319–331. doi: 10.1177/0271678X15625350
4. Jensen JD, Vincent AL. High Altitude cerebral edema. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 July 17
5. Beall CM. Two routes to functional adaptation: Tibetan and Andean high-altitude natives. Proc Natl Acad Sci U S A, 2007; 104 (Suppl 1): 8655–8660. doi: 10.1073/pnas.0701985104
6. Walsh B, Agrawal S. High-altitude cerebral edema and high-altitude pulmonary edema diagnosed in the desert: a case report. Clin Pract Cases Emerg Med, 2024; 8(3): 202–205. doi: 10.5811/cpcem.3851
7. Basnyat B, Murdoch DR. High-altitude illness. Lancet, 2003; 361(9373): 1967–1974. doi: 10.1016/S0140-6736(03)13591-X
8. Aman M, Alam MS, Khan F, et al. High-altitude cerebral edema manifesting as T2/FLAIR hyperintensity and microbleeds in the white matter on MRI brain. Radiol Case Rep, 2023; 18(5): 1705–1709. doi: 10.1016/j.radcr.2023.01.071
9. Higgins JP, Tuttle T, Higgins JA. Altitude and the heart: is going high safe for your cardiac patient? Am Heart J, 2010; 159(1): 25–32. doi: 10.1016/j.ahj.2009.10.028
10. Falla M, Giardini G, Angelini C. Recommendations for traveling to altitude with neurological disorders. J Cent Nerv Syst Dis, 2021; 13: 11795735211053448. doi: 10.1177/11795735211053448
11. Li Y, Li C, Luo T, et al. Progress in the treatment of high altitude cerebral edema: targeting REDOX homeostasis. J Inflamm Res, 2023; 16: 2645–2660. doi: 10.2147/JIR.S415695
12. Richalet JP, Larmignat P, Poitrine E, et al. Physiological risk factors for severe high-altitude illness: a prospective cohort study. Am J Respir Crit Care Med, 2012; 185(2): 192–198. doi: 10.1164/rccm.201108-1396OC
13. Hackett PH, Roach RC. High altitude cerebral edema. High Alt Med Biol, 2004; 5(2): 136–146. doi: 10.1089/1527029041352054
14. de la Cruz RA, Clemente Fuentes RW, Wonnum SJ, et al. Aerospace decompression illness. [Updated 2024 Jan 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448160/
15. Savioli G, Ceresa IF, Gori G, et al. Pathophysiology and therapy of high-altitude sickness: practical approach in emergency and critical care. J Clin Med, 2022; 11(14): 3937. doi: 10.3390/jcm11143937
16. Xue Y, Wang X, Wan B, et al. Caveolin-1 accelerates hypoxia-induced endothelial dysfunction in high-altitude cerebral edema. Cell Commun Signal, 2022; 20(1): 160. doi: 10.1186/s12964-022-00976-3
17. Wang X, Chen G, Wan B, et al. NRF1-mediated microglial activation triggers high-altitude cerebral edema. J Mol Cell Biol, 2022; 14(5): mjac036. doi: 10.1093/jmcb/mjac036
18. Schoch HJ, Fischer S, Marti HH. Hypoxia-induced vascular endothelial growth factor expression causes vascular leakage in the brain. Brain, 2002; 125(Pt 11): 2549–2557. doi: 10.1093/brain/awf257
19. Shen Y, Gu J, Liu Z, et al. Inhibition of HIF-1α reduced blood brain barrier damage by regulating MMP-2 and VEGF during acute cerebral ischemia. Front Cell Neurosci, 2018; 12: 288. doi: 10.3389/fncel.2018.00288
20. Takata F, Nakagawa S, Matsumoto J, Dohgu S. Blood–brain barrier dysfunction amplifies the development of neuroinflammation: understanding of cellular events in brain microvascular endothelial cells for prevention and treatment of BBB dysfunction. Front Cell Neurosci, 2021; 15: 661838. doi: 10.3389/fncel.2021.661838
21. Hackett PH. High altitude cerebral edema and acute mountain sickness. A pathophysiology update. Adv Exp Med Biol, 1999; 474: 23–45. doi: 10.1007/978-1-4615-4711-2_2
22. Turner REF, Gatterer H, Falla M, Lawley JS. High-altitude cerebral edema: its own entity or end-stage acute mountain sickness? J Appl Physiol (1985), 2021; 131(1): 313–325. doi: 10.1152/japplphysiol.00861.2019
23. Li S, Zhang Q, Yang C, Zhang F. Mechanism of formation of high altitude cerebral edema: recent advances. Discov Med, 2025; 2: 175. doi: 10.1007/s44337-025-00420-8
24. Gallagher SA, Hackett PH. High-altitude illness. Emerg Med Clin North Am, 2004; 22(2): 329–355, VIII. doi: 10.1016/j.emc.2004.02.001
25. Roach RC, Hackett PH, Oelz O, et al.; Lake Louise AMS Score Consensus Committee. The 2018 Lake Louise Acute Mountain Sickness Score. High Alt Med Biol, 2018; 19(1): 4–6. doi: 10.1089/ham.2017.0164
26. Long C, Bao H. Study of high-altitude cerebral edema using multimodal imaging. Front Neurol, 2023; 13: 1041280. doi: 10.3389/fneur.2022.1041280
27. Imray C, Wright A, Subudhi A, Roach R. Acute mountain sickness: pathophysiology, prevention, and treatment. Prog Cardiovasc Dis, 2010; 52(6): 467–484. doi: 10.1016/j.pcad.2010.02.003
28. Chen T, Wu X, Liu X, Luo F. Reversible leukoencephalopathy with seizures: a case of severe high-altitude cerebral edema. Acta Epileptol, 2024; 6(1): 22. doi: 10.1186/s42494-024-00165-4
29. Kaeley N, Datta SS, Sharma A, G J. Hiccups and slurring of speech: atypical presentation of high-altitude cerebral edema. Cureus, 2023; 15(2): e34997. doi: 10.7759/cureus.34997

30. Bhartiya M, Kumar J, Arora R, Dhiman A. Clinical profile of high-altitude cerebral edema: a case series. Ann Indian Acad Neurol, 2025; 28(2): 257–261. doi: 10.4103/aian.aian_921_24
31. Yarnell PR, Heit J, Hackett PH. High-altitude cerebral edema (HACE): the Denver/Front range experience. Semin Neurol, 2000; 20(2): 209–217. doi: 10.1055/s-2000-9830
32. Bolotin T, Prokopakis KE, Becker B. Atypical high-altitude cerebral edema presentation at an altitude of less than 3000 meters elevation: a case report. Open Access Emerg Med, 2022; 14: 119–122. doi: 10.2147/OAEM.S336951
33. Hackett PH, Yarnell PR, Weiland DA, Reynard KB. Acute and Evolving MRI of high-altitude cerebral edema: microbleeds, edema, and pathophysiology. AJNR Am J Neuroradiol, 2019; 40(3): 464–469. doi: 10.3174/ajnr.A5897
34. Kühn S, Gerlach D, Noblé HJ, et al. An observational cerebral magnetic resonance imaging study following 7 days at 4554 m. High Alt Med Biol, 2019; 20(4): 407–416. doi: 10.1089/ham.2019.0056
35. Velasco R, Cardona P, Ricart A, Martínez-Yélamos S. Vasorreactividad cerebral en el edema cerebral asociado a la altura [Cerebral vasoreactivity in high-altitude cerebral edema]. Neurologia, 2008; 23(1): 65–68
36. Bailey DM, Bärtsch P, Knauth M, Baumgartner RW. Emerging concepts in acute mountain sickness and high-altitude cerebral edema: from the molecular to the morphological. Cell Mol Life Sci, 2009; 66(22): 3583–3594. doi: 10.1007/s00018-009-0145-9
37. Armstrong C. Acute altitude illness: updated prevention and treatment guidelines from the Wilderness Medical Society. Am Fam Physician, 2020; 101(8): 505–507
38. Luks AM, Auerbach PS, Freer L, et al. Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Wilderness Environ Med, 2019; 30(4S): S3–S18. doi: 10.1016/j.wem.2019.04.006
39. Zelmanovich R, Pierre K, Felisma P, et al. High altitude cerebral edema: improving treatment options. Biologics, 2022; 2(1): 81–91. doi: 10.3390/biologics2010007
40. Freeman K, Shalit M, Stroh G. Use of the gamow bag by EMT-basic park rangers for treatment of high-altitude pulmonary edema and high-altitude cerebral edema. Wilderness Environ Med, 2004; 15(3): 198–201. doi: 10.1580/1080-6032(2004)15[198:uotgbb]2.0.co;2
41. Wright A, Brearey S, Imray C. High hopes at high altitudes: pharmacotherapy for acute mountain sickness and high-altitude cerebral and pulmonary oedema. Expert Opin Pharmacother, 2008; 9(1): 119–127. doi: 10.1517/14656566.9.1.119

REVIEW ARTICLE

THE IMPACT OF PSYCHOLOGICAL FACTORS ON EJACULATION DISORDERS (PREMATURE EJACULATION)

Wpływ czynników psychologicznych na zaburzenia wytrysku (wytrysk przedwczesny)

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Abstract

Introduction: Premature ejaculation is widely recognized as the most common male sexual dysfunction, affecting up to 30% of the sexually active male population. As a taboo subject, it often goes unreported. Premature ejaculation has a complex aetiology, encompassing both congenital and acquired causes, with psychosocial and biological factors playing a significant role. **Objectives:** The main aim of this article was to analyse the potential psychological factors contributing to the development of premature ejaculation and to emphasize the need for a comprehensive clinical interview to properly differentiate the underlying causes of the dysfunction. **Methods:** This article is a review based on the analysis and synthesis of available scientific literature and clinical guidelines on the epidemiology, aetiology, diagnosis, and treatment of premature ejaculation. The focus was on factors contributing to acquired premature ejaculation, with particular emphasis on psychological mechanisms. **Results:** The aetiology of acquired premature ejaculation has been shown to be multifactorial and characterized by the interaction between biological and psychological factors. Sympathetic nervous system overactivity and an impaired excitation/inhibition balance is the common denominator of these mechanisms. Furthermore, we found a significant correlation between premature ejaculation and poor mental health. Unfortunately, discrepancies in diagnostic timing criteria hinder standardization. Causal treatment should be used for acquired premature ejaculation, and if insufficient, pharmacotherapy should be initiated. **Conclusions:** Premature ejaculation is a sexual dysfunction requiring an interdisciplinary and personalized approach. It is crucial to distinguish acquired from lifelong premature ejaculation based on a detailed clinical interview. Psychotherapy is an essential component of therapy, regardless of the aetiology of the dysfunction. Openness to this topic and interdisciplinary care are key to improving patients' quality of life.

Streszczenie

Wstęp: Wytrysk przedwczesny jest powszechnie uznawany za najczęstszą dysfunkcję seksualną mężczyzn, dotykającą nawet 30% populacji aktywnej seksualnie. Jako problem nadal obciążony tabu często pozostaje nieraportowany. Zaburzenie to ma złożoną etiologię, obejmującą zarówno podłoże wrodzone, jak i nabyte, w którym istotną rolę odgrywają czynniki psychospołeczne i biologiczne. **Cele:** Głównym celem pracy była analiza możliwych czynników psychologicznych, które mogą przyczyniać się do rozwoju nabytego wytrysku przedwczesnego. Ponadto celem było uwrażliwienie klinicystów na konieczność przeprowadzenia szczegółowego wywiadu w celu prawidłowego różnicowania przyczyn dysfunkcji. **Metodyka:** Artykuł ma charakter przeglądowy i opiera się na analizie i syntezie dostępnej literatury naukowej oraz wytycznych klinicznych dotyczących epidemiologii, etiologii, diagnostyki i leczenia wytrysku przedwczesnego. Skoncentrowano się na czynnikach wpływających na nabyty wytrysk przedwczesny, ze szczególnym uwzględnieniem mechanizmów psychologicznych. **Wyniki:** Analiza piśmiennictwa wskazuje, że etiologia nabytego wytrysku przedwczesnego jest wieloczynnikowa i charakteryzuje się wzajemnym oddziaływaniem czynników biologicznych i psychologicznych. Wspólnym mianownikiem tych mechanizmów jest nadaktywność układu współczulnego i zaburzona równowaga między pobudzeniem a hamowaniem. Ponadto stwierdzono istotną korelację wytrysku przedwczesnego ze złym stanem psychicznym. W diagnostyce istnieją rozbieżności w kryteriach czasowych, co utrudnia standaryzację. Leczenie nabytego wytrysku przedwczesnego powinno być ukierunkowane na przyczynę. W przypadku niewystarczającej skuteczności postępowania przyczynowego stosuje się farmakoterapię. **Wnioski:** Wytrysk przedwczesny jest dysfunkcją seksualną, której leczenie wymaga podejścia interdyscyplinarnego i spersonalizowanego. Kluczowe jest rozróżnienie wytrysku przedwczesnego nabytego i wrodzonego na podstawie szczegółowego wywiadu. Psychoterapia stanowi niezbędny element terapii, niezależnie od etiologii dysfunkcji. Otwartość w podejmowaniu tego tematu i interdyscyplinarna opieka są kluczem do poprawy jakości życia pacjentów.

Keywords: sexual health; premature ejaculation; sexology; SSRIs; dapoxetine

Słowa kluczowe: zdrowie seksualne; wytrysk przedwczesny; seksuologia; SSRI; dapoksetyna

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Introduction

Sexuality is an integral aspect of human life. When analysing overall well-being, sexual health cannot be overlooked. However, issues related to sexuality and sexual activity remain taboo in many settings, which may discourage affected individuals from seeking help. Sexual problems should not be underestimated as they may indicate a serious underlying organic disorder. When evaluating sexual difficulties, both somatic and mental health should be considered, as many sexual dysfunctions stem from psychological factors. Premature ejaculation (PE) is one of the most common sexual disorders in men. It may be classified as lifelong or acquired, and its aetiology is multifactorial.

We aimed to investigate the psychological factors that may contribute to the development of acquired premature ejaculation (APE), emphasizing the importance of a comprehensive clinical interview conducted by physicians and psychologists, which may help determine whether the patient's symptoms arise from psychological or genetic factors.

Materials and methods

This narrative review was conducted in accordance with the principles of literature synthesis in biomedical research. A comprehensive search of PubMed, Scopus, and Web of Science databases was performed to identify review papers published between 1998 and 2025. The search strategy combined relevant keywords and Medical Subject Headings (MeSH), including "sexual health," "premature ejaculation," "mental health," "sexology," "selective serotonin reuptake inhibitors (SSRIs)," and "dapoxetine".

Inclusion criteria:
- systematic reviews, meta-analyses and narrative reviews on PE;
- papers presenting data on epidemiology, risk factors, diagnostic methods, screening tools or treatment strategies;
- publications in English in peer-reviewed journals.

Exclusion criteria:
- basic research, case reports and conference abstracts;
- non-peer-reviewed publications and preprints.

Titles and abstracts of all identified records were screened to exclude irrelevant publications. The full texts of articles meeting the eligibility criteria were then reviewed in detail. Data from the included publications were extracted and synthesized narratively, integrating international findings and, where possible, highlighting evidence relevant to the Polish context. No formal tool was used to assess the methodological quality of the included reviews.

Epidemiology

Reliable data on the prevalence of PE remain limited, as sexual problems are often underreported, making it difficult to estimate the actual scale of the condition. Nevertheless, PE is widely regarded as the most common sexual dysfunction among men worldwide. Epidemiological estimates vary, with approximately 30% of men aged 18–59 years reporting PE symptoms [2]. Some studies have reported prevalence rates of up to 75% among sexually active men [3–5]. Although PE can occur at any age, it is most frequently reported by young men aged 18–30 years [6]. However, the majority of epidemiological studies of PE have been criticized for relying on self-reported assessments or diagnostic methods with limited validation. Differences in reported prevalence may therefore reflect variation in study design, assessment instruments, diagnostic criteria, and the age distribution of the study populations [7].

Aetiology

The aetiology of APE is complex and multifactorial, involving interactions among biological, neurophysiological, endocrine, inflammatory, genetic, behavioural, relational, and psychological factors [8].

Among the biological contributors, disturbances in serotonergic neurotransmission appear to play a prominent role. Reduced activity of 5-HT2C and 5-HT1B receptors accompanied by increased activity of 5-HT1A receptors has been linked to a shorter intravaginal ejaculation latency time (IELT) [9]. The ability of selective serotonin reuptake inhibitors (SSRIs) to prolong IELT further supports the role of serotonin in the inhibitory regulation of ejaculation [9].

Endocrine factors are also important players. Clinical studies suggest that hyperthyroidism can shorten ejaculation latency and that appropriate treatment of thyroid dysfunction may restore normal ejaculatory control [10]. Other hormonal abnormalities, including hyperprolactinaemia, low testosterone, and altered pituitary hormone levels, may modulate sympathetic and dopaminergic activity, thereby affecting the ejaculatory threshold [10].

Urological and inflammatory conditions represent another aetiological factor. It has been shown that chronic prostatitis and chronic pelvic pain syndrome can lead to APE due to hypersensitivity of sensory receptors in the prostate, urethra and penis [11]. Persistent stimulation of the afferent pudendal fibres may promote premature activation of the ejaculatory reflex. Consequently, the time required to initiate the emission phase may be reduced.

Metabolic and vascular factors may also contribute to the pathogenesis of APE. Metabolic syndrome, insulin resistance, and obesity have been associated with increased adrenergic activity and endothelial dysfunction, which may impair smooth muscle function within the sperm ducts [12]. Impaired tissue perfusion and endothelial dysfunction, often occurring alongside hypertension and atherosclerosis, may also contribute to erectile dysfunction (ED) and reduced ejaculation latency; however, evidence for their direct impact on PE remains inconclusive [13].

Genetic determinants of PE have also been described, particularly polymorphisms in the serotonin transporter-linked polymorphic region (5-HTTLPR) and genes encoding the 5-HT2C receptor, which may increase susceptibility to PE [14].

From a behavioural perspective, much importance is attributed to masturbation habits and early sexual experiences. Men who developed a habit of rapid masturbation during adolescence, often due to stress, time pressure, or fear of being interrupted, may have conditioned their bodies to reaching ejaculation quickly [15]. This phenomenon can be understood through classical conditioning: sexual stimuli become associated with immediate relief of sexual tension, which may facilitate reflexively accelerated ejaculation during adulthood [15, 16].

Relational factors are another important aspect. Men with PE may be more likely to experience difficulties communicating with their partner, emotional conflicts, reduced intimacy, and perceived partner dissatisfaction with their sexual life [17]. When openness and trust are limited, men may feel pressure to "meet expectations," which increases emotional tension and activates stress responses. Increased sympathetic nervous system activity during intercourse results in a faster emission phase and shorter ejaculation time [18].

Among psychological contributors, fear related to sexual intercourse and performance anxiety may play a central role. Men with APE are more likely to show concern about being judged by their partners and fear of sexual "failure". This anxiety can increase muscle tension, adrenaline and noradrenaline release, as well as activation of spinal pathways involved in the ejaculatory reflex [19, 20]. Studies have shown that intense anxiety about sexual performance may be associated with a shorter IELT and reduced perceived control over ejaculation [20]. Intrapsychic conflicts, such as tension between the desire for control and fear of losing it, as well as guilt, shame, or ambivalence about one's sexuality, may represent additional mechanisms involved in APE [21]. In these circumstances, rapid ejaculation may function as an unconscious means of reducing emotional tension and avoiding prolonged exposure to an anxiety-provoking situation.

Psychosexual literature describes the phenomenon of "rapid ejaculation as an escape from intimacy". This mechanism has been observed particularly in men characterized by excessive emotional control and difficulty communicating emotions [18–21].

Equally important are established cognitive beliefs about sexuality and one's sexual performance. Men with PE may be more likely to exhibit perfectionistic and catastrophic thinking patterns, such as "I must always satisfy my partner" or "If I cannot last long, I have failed." [20–22]. During intercourse, men with PE may focus excessively on monitoring their own sexual responses, a process known as spectatoring, which increases tension, shortens the duration of sexual arousal, and reduces the ability to inhibit ejaculation [22, 23]. This mechanism creates a vicious circle: the greater the expectations and fear, the stronger the physiological tension and the faster the ejaculation.

These biological, hormonal, inflammatory, genetic, behavioural, relational, and psychological factors do not act in isolation but rather interact. Increased sympathetic nervous system activity and an imbalance between excitatory and inhibitory mechanisms regulating ejaculation seem to be a common pathway. However, there is still no clear data defining the relative contribution of individual factors to PE [13]. Table 1 summarizes potential risk factors and their proposed roles in the development of APE.

Diagnostic criteria

According to published studies, PE is the most common sexual dysfunction among men [24]. Its estimated prevalence is approximately 20–30%; however, these figures may vary as definitions and diagnostic terminology differ across studies [25]. In Poland, PE is diagnosed using the World Health Organization's International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Under this classification, premature ejaculation (F52.4) is defined as the inability to control ejaculation sufficiently for both partners to enjoy sexual interaction. In some cases, ejaculation may occur before vaginal penetration or before a full erection is achieved.

Specific diagnostic criteria must be met in order to diagnose PE. Criterion A encompasses some general requirements for sexual dysfunction, including difficulty engaging in sexual activity in a manner consistent with one's desires; recurrent, though not necessarily persistent, pattern of symptoms; symptom duration of at least six months; and the absence of an alternative explanation, such as mental or somatic disorder, or the effects of pharmacotherapy. Criterion B refers to persistent inability to delay ejaculation sufficiently to allow satisfactory sexual activity; ejaculation may occur before or immediately after penetration begins, with the penetration phase lasting no longer than approximately 15 seconds. In some cases, ejaculation may occur despite an erection that is insufficient for penetration. Criterion C specifies that the

Tabela 1. Możliwe czynniki ryzyka i ich wpływ na rozwój nabytego wytrysku przedwczesnego

Factors	Examples	Mechanism underlying APE
Neurophysiological	Dysregulation of the serotonergic system (reduction of 5-HT2C and 5-HT1B receptor activity, increase of 5-HT1A activity)	Imbalance between excitation and inhibition of the ejaculatory reflex; excessive activation of spinal centres shortening IELT
Endocrine	Hyperthyroidism, hyperprolactinemia, low testosterone, pituitary hormone disorders	Excessive adrenergic activity, increased sympathetic stimulation, impaired dopaminergic regulation
Inflammatory and urological	Chronic prostatitis, chronic pelvic pain syndrome	Hypersensitivity of the prostate and urethra sensory receptors; accelerated activation of the ejaculatory reflex arc
Metabolic and vascular	Metabolic syndrome, obesity, insulin resistance, hypertension, atherosclerosis	Increased adrenergic activity, endothelial and perfusion disorders affecting the function of the smooth muscle of the vas deferens; possible co-occurring erectile dysfunction
Genetic (predisposing)	Polymorphisms of the serotonin transporter gene (5-HTTLPR) and 5-HT2C receptors	They may predispose to reduced ejaculatory control by affecting the sensitivity of the serotonergic system; however, they are not a direct cause of APE
Behavioural	Early, rapid masturbation when stressed or in a hurry	Classical conditioning – the consolidation of the pattern of rapid ejaculation in response to sexual stimuli
Relational	Conflicts between partners, lack of intimacy, low sexual satisfaction of the partner	Increased emotional tension and pressure to meet expectations; activation of the sympathetic nervous system and shortening of the emission phase
Psychological – anxiety and tension	Fear of intercourse, performance anxiety	Increased muscle tension, adrenaline and noradrenaline secretion, sympathetic hyperactivity; shortened IELT and loss of control
Psychological – intrapsychic conflicts	Contradiction between the need for control and the fear of losing it, guilt, shame, avoidance of closeness	Ejaculation as an unconscious form of reducing emotional tension; avoiding anxiety-generating situations by quickly ending the sexual intercourse
Psychological – beliefs and attention	Perfectionistic, catastrophic beliefs ("I have to please my partner"), excessive monitoring of reactions ("spectatoring")	Increased self-awareness, increased physiological tension, shortened arousal phase and loss of control over ejaculation
Integrating factors	Interactions between biological, hormonal and psychological factors	Sympathetic nervous system overactivity and an imbalance between the mechanisms of ejaculation stimulation and inhibition

disorder should not be attributable to a prolonged period of sexual abstinence.

ICD-10 classifies PE as a sexual dysfunction not caused by an organic disorder, underscoring the need to consider both psychological and physiological factors during diagnosis [26]. The International Classification of Diseases, 11th Revision (ICD-11), which has not yet been officially translated into Polish, is another relevant classification framework. It provides a similar definition, describing male early ejaculation as ejaculation that happens before or very soon after penetration or other sexual stimulation, with little or no control over when it occurs. The condition may occur sporadically or persist for several years.

Male early ejaculation is classified as a sexual dysfunction and assigned the code HA03.0. For the condition to be diagnosed as a sexual dysfunction, symptoms must persist or recur for at least several months. Cases in which the symptoms are attributable to another condition, such as a spinal cord injury, should be excluded. Symptoms must occur frequently, vary in severity, and be associated with clinically significant distress. PE may be classified as primary (lifelong, LPE) or acquired (when it develops later in life). It may also be categorized as situational (occurring only in specific circumstances), or generalized (occurring consistently regardless of the situation) [27].

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), provides specific time-based criteria for assessing the severity of PE. PE is classified as mild when ejaculation occurs within 30–60 seconds of penetration, moderate when it occurs within 15–30 seconds, and severe when it occurs within 15 seconds. DSM-5 defines PE as a persistent or recurrent pattern of ejaculation occurring within approximately one minute of vaginal penetration during partnered sexual activity, before the individual desires it. Additionally, diagnosis requires that the general criteria for sexual dysfunction be met: symptoms must occur during all or almost all sexual encounters (approximately 75–100%), persist for at least six months, and cause clinically significant distress. Also, the dysfunction cannot be better explained by another mental disorder, relationship difficulties, substantial stressors, substance use, including medications, or a medical condition [28].

Treatment

The choice of treatment for PE should be guided by the underlying cause and mechanisms of the dysfunction. A thorough clinical and psychosexual history can help identify the principal contributing factors and direct the patient toward an appropriate therapeutic approach. Distinguishing between APE and LPE is an essential step. Pharmacotherapy often plays an important role in APE, whereas psychotherapeutic interventions may be particularly useful in LPE.

Available treatment modalities for PE include pharmacotherapy and psychotherapeutic interventions. Selective serotonin reuptake inhibitors (SSRIs) are among the most extensively investigated pharmacological options. SSRIs, which are typically prescribed for the treatment of mood disorders, including depression, prove most effective. Used alone in low doses or in combination with psychosexual counseling, they are widely accepted as first-line treatment for LPE, and are recommended by leading urological guidelines. Dapoxetine fills an important gap in the management of PE, offering a safer and more convenient treatment [29]. Other treatments include topical anaesthetics and tricyclic antidepressants [30]. However, SSRIs generally produce only a temporary extension of IELT, with symptom recurrence shortly after treatment discontinuation [31]. Furthermore, many pharmacological interventions for PE are experimental or prescribed off-label.

Behavioural therapy, sex therapy in particular, is a treatment method for PE characterized by fewer adverse effects and lower costs compared to pharmacotherapy. Its primary goal is to improve self-confidence and reduce anxiety and depression by acquiring sexual skills that may help delay ejaculation. Although behavioural therapy may be effective in 45–65% of patients in the short term, its long-term effects remain uncertain [32].

Psychotherapeutic and behavioural interventions aim to improve ejaculatory control by helping men (and their partners) to achieve the following goals:

- **self-confidence**: gaining confidence in one's sexual performance;
- **anxiety reduction**: reducing sex-related anxiety;
- **changing sexual behaviour patterns**: modifying rigid sexual behaviour patterns;
- **intimacy**: overcoming intimacy barriers;
- **relationships**: resolving interpersonal issues that trigger and maintain dysfunction;
- **emotional acceptance**: coming to terms with feelings and thoughts that interfere with sexual function;
- **communication**: improving communication in a relationship.

In summary, the management of APE requires an individualized approach that considers the aetiology, severity, and coexisting sexual dysfunctions.

Consequences

As the diagnostic criteria outlined above indicate, PE does not necessarily have an organic cause or occur from the beginning of an individual's sexual life. If the dysfunction is acquired or occurs only under specific circumstances, psychological factors potentially associated with its onset and persistence should be considered. Research indicates a significant correlation between PE and poor mental health [33]. Men with PE report significantly higher levels of anxiety and depression compared to healthy controls. High anxiety levels are also associated with greater symptom severity: higher anxiety levels correspond with a shorter ejaculation latency. This suggests a potentially bidirectional relationship between mental health and PE: anxiety may contribute to the development or persistence of PE, while PE itself can intensify anxiety, reduce mental well-being, and create a vicious emotional cycle [19–33].

Mitigating anxiety is therefore important both for lowering the risk of PE and for supporting its treatment. PE can substantially reduce the quality of life for both the affected person and their partner. It is frequently associated with psychological distress, lower self-esteem, and increased anxiety; it may also contribute to ED, decreased libido, and relationship problems [34]. Patients with PE also experience a lack of self-confidence in sexual situations, reduced self-esteem, lack of sexual satisfaction and interpersonal problems.

Despite these far-reaching psychological, emotional, and interpersonal consequences, many men remain reluctant to discuss PE with a healthcare professional. Nevertheless, effective, evidence-based treatments are available and can significantly improve the quality of life of patients with sexual dysfunctions.

Discussion

A key point in the discussion of APE is distinguishing it from the lifelong form. According to the literature, APE is characterized by a sudden or gradual IELT reduction following normal ejaculatory control, typically in association with an identifiable underlying cause [8]. However, standardizing the definition of APE and establishing uniform IELT criteria remain challenging, given the subjective nature of reports from the patient and their partner, as well as the fact that PE often overlaps with other sexual dysfunctions, such as ED [9].

It remains controversial whether APE is invariably secondary to an organic disease or may occur as a primary symptom in the absence of an identifiable somatic cause [7]. Future research should focus on identifying more precise biological markers that could help differentiate, diagnose, and classify this dysfunction.

Particular attention should be paid to the relationship between APE and ED. Many studies suggest that PE may, in some cases, function as a compensatory response, where a man makes an unconscious attempt to ejaculate before losing erection [35]. In such cases, addressing ED often improves or normalizes IELT. The treatment of APE should primarily target the underlying cause. Its diverse aetiologies may require interdisciplinary care involving specialists from different medical fields.

Current guidelines recommend treating PE by eliminating or controlling the underlying cause. If the cause cannot be fully eradicated, or if IELT does not improve sufficiently af-

ter causal treatment, pharmacotherapy similar to that used in congenital PE is initiated. It involves the use of SSRIs, dapoxetine in particular, and topical local anaesthetics.

APE raises several important therapeutic questions. One of these concerns the role of dapoxetine: should this on-demand medication be used as a first-line treatment, or should it be considered an adjunct to causal therapy? Given the sudden onset of PE, the rapid and predictable effect of the drug may have a significant positive psychological impact on the patient by reducing the fear of failure. Second, psychotherapy plays a crucial role. It remains important to determine whether behavioural interventions are equally effective for APE and LPE. Patients with APE often experience increased anxiety and frustration. Therefore, psychosexual counselling should be an integral part of treatment, regardless of the underlying cause.

Conclusions

Premature ejaculation is one of the most common male sexual dysfunctions. It can cause substantial psychological and relationship difficulties by impacting many areas of life. Due to its complex and multifactorial aetiology, the disorder requires an interdisciplinary approach. This is particularly important in APE, which arises from an interaction between psychological (e.g. performance anxiety, internal conflicts, and entrenched behavioural patterns) and biological (e.g. serotonergic dysregulation) factors. The common mechanism may involve sympathetic nervous system overactivity and an imbalance between excitation and inhibition.

PE is strongly linked to anxiety and depression. Performance anxiety and excessive monitoring of a partner's reactions may further worsen symptoms, creating a vicious cycle of distress, lower self-esteem, and relationship problems. Differences in diagnostic criteria, including time-based thresholds, highlight the need to standardize diagnostic assessment tools. A thorough clinical interview is essential to identify the cause of PE. This determines the choice of treatment. Regardless of the aetiology, psychotherapy aimed at reducing anxiety and improving both ejaculatory control and communication within the relationship is an important component of care. PE is one of the few curable sexual dysfunctions. Openness and interdisciplinary care are crucial for improving patients' quality of life.

References

1. Crowdis M, Leslie SW, Nazir S. Premature ejaculation. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK546701/
2. Rosen RC. Prevalence and risk factors of sexual dysfunction in men and women. Curr Psychiatry Rep, 2000; 2(3): 189–195. doi: 10.1007/s11920-996-0006-2
3. Athanasiadis L. Premature ejaculation: Is it a biogenic or a psychogenic disorder? Sex Marital Ther, 1998; 13: 241–255. doi: 10.1080/02674659808406567
4. Patrick DL, Althof SE, Pryor JL, et al. Premature ejaculation: an observational study of men and their partners. J Sex Med, 2005; 2(3): 358–367. doi: 10.1111/j.1743-6109.2005.20353.x
5. Laumann EO, Nicolosi A, Glasser DB, et al.; GSSAB Investigators' Group. Sexual problems among women and men aged 40–80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. Int J Impot Res, 2005; 17(1): 39–57. doi: 10.1038/sj.ijir.3901250
6. Anderson D, Laforge J, Ross MM, et al. Male Sexual dysfunction. Health Psychol Res. 2022; 10(3): 37533. doi: 10.52965/001c.37533
7. El-Hamd MA, Saleh R, Majzoub A. Premature ejaculation: an update on definition and pathophysiology. Asian J Androl, 2019; 21(5): 425–432. doi: 10.4103/aja.aja_122_18
8. Serefoglu EC, McMahon CG, Waldinger MD, et al. An evidence-based unified definition of lifelong and acquired premature ejaculation: report of the second International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. J Sex Med, 2014; 11(6): 1423–1441. doi: 10.1111/jsm.12524
9. Giuliano F, Clément P. Serotonin and premature ejaculation: from physiology to patient management. Eur Urol, 2006; 50(3): 454–466. doi: 10.1016/j.eururo.2006.05.055
10. Coskuner ER, Ozkan B. Premature ejaculation and endocrine disorders. World J Mens Health, 2022; 40(2): 276–285. doi: 10.5534/wjmh.200184
11. Zhao Z, Xuan X, Zhang J, et al. A prospective study on association of prostatic calcifications with sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). J Sex Med, 2014; 11(10): 2528–2536. doi: 10.1111/jsm.12534
12. Ventus D, Jern P. Premature ejaculation. In: Chapple CR, Wein AJ, editors. Primer on Urology. Cham: Springer; 2025. p. 755–770. doi: 10.1007/978-3-031-55405-6_54
13. De Leonardis F, Colalillo G, Finazzi Agrò E, et al. Endothelial dysfunction, erectile deficit and cardiovascular disease: an overview of the pathogenetic links. Biomedicines, 2022; 10(8): 1848. doi: 10.3390/biomedicines10081848
14. Ye N, Huang Y, Zhao H, et al. Association between the serotonin transporter linked polymorphic region and lifelong premature ejaculation: An updated meta-analysis of case–control studies. Medicine (Baltimore), 2020; 99(41): e22169. doi: 10.1097/MD.0000000000022169
15. Waldinger MD. The neurobiological approach to premature ejaculation. J Urol, 2002; 168(6): 2359–2367. doi: 10.1016/S0022-5347(05)64146-8
16. Assalian P. Psychological and interpersonal dimensions of sexual function and dysfunction. Arab J Urol; 2013; 11(3): 217–221. doi: 10.1016/j.aju.2013.07.007
17. Ermeç B, Yucetas U, Güler H, et al. Evaluation of the quality of life of patients with premature ejaculation (lifelong and acquired). Rev Assoc Med Bras (1992), 2022; 68(9): 1303–1307. doi: 10.1590/1806-9282.20220421
18. Althof S. The psychology of premature ejaculation: therapies and consequences. J Sex Med, 2006; 3 Suppl 4: 324–331. doi: 10.1111/j.1743-6109.2006.00308.x
19. Rajkumar RP, Kumaran AK. The association of anxiety with the subtypes of premature ejaculation: a chart review. Prim Care Companion CNS Disord, 2014; 16(4): 10.4088/PCC.14m01630. doi: 10.4088/PCC.14m01630
20. Kempeneers P, Andrianne R, Bauwens S, et al. Functional and psychological characteristics of Belgian men with premature ejaculation and their partners. Arch Sex Behav. 2013; 42(1): 51–66. doi: 10.1007/s10508-012-9958-y
21. Jannini EA, Ciocca G, Limoncin E, et al. Premature ejaculation: old story, new insights. Fertil Steril, 2015; 104(5): 1061–1073. doi: 10.1016/j.fertnstert.2015.08.035

22. Montorsi F. Prevalence of premature ejaculation: a global and regional perspective. J Sex Med, 2005; 2(4): 438–444. doi: 10.1111/j.1743-6109.2005.20369.x
23. Rosen RC, Althof S. Impact of premature ejaculation: the psychological, quality of life, and sexual relationship consequences. J Sex Med, 2008; 5(6): 1296–1307. doi: 10.1111/j.1743-6109.2008.00825.x
24. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA, 1999; 281(6): 537–544. doi: 10.1001/jama.281.6.537
25. Serefoglu EC, Saitz TR. New insights on premature ejaculation: a review of definition, classification, prevalence and treatment. Asian J Androl, 2012; 14(6): 822–829. doi: 10.1038/aja.2012.108
26. World Health Organization. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organization; 1993. Available from: https://www.who.int/publications/i/item/9241544554
27. World Health Organization. International Classification of Diseases, 11th Revision (ICD-11). Geneva: World Health Organization; 2023. Available from: https://icd.who.int/browse11
28. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013. doi: 10.1176/appi.books.9780890425596
29. Vieiralves RR, Favorito LA. Dapoxetine and premature ejaculation. Int Braz J Urol, 2023; 49(4): 511–514. doi: 10.1590/S1677-5538.IBJU.2023.9908
30. Saleh R, Majzoub A, Abu El-Hamd M. An update on the treatment of premature ejaculation: A systematic review. Arab J Urol, 2021; 19(3): 281–302. doi: 10.1080/2090598X.2021.1943273
31. Salonia A, Rocchini L, Saccà A, et al. Acceptance of and discontinuation rate from paroxetine treatment in patients with lifelong premature ejaculation. J Sex Med, 2009; 6(10): 2868–2877. doi: 10.1111/j.1743-6109.2009.01404.x
32. Bao B, Shang J, Wang J, et al. Efficacy and safety of behavioral therapy for premature ejaculation: Protocol for a systematic review. Medicine (Baltimore), 2019; 98(3): e14056. doi: 10.1097/MD.0000000000014056
33. Liu T, Jia C, Peng YF, et al. Correlation between premature ejaculation and psychological disorders in 270 Chinese outpatients. Psychiatry Res. 2019; 272: 69–72. doi: 10.1016/j.psychres.2018.12.038
34. Chung E, Gilbert B, Perera M, et al. Premature ejaculation: A clinical review for the general physician. Aust Fam Physician, 2015; 44(10): 737–743. Available from: https://www.racgp.org.au/afp/2015/october/premature-ejaculation-a-clinical-review-for-the-general-physician/
35. Tang WS, Khoo EM. Prevalence and correlates of premature ejaculation in a primary care setting: a preliminary cross-sectional study. J Sex Med, 2011; 8(7): 2071–2078. doi: 10.1111/j.1743-6109.2011.02280.x

REVIEW ARTICLE

SKIN BARRIER DYSFUNCTION INDUCED BY ENVIRONMENTAL POLLUTANTS: OXIDATIVE STRESS, INFLAMMATION, AND IMMUNE RESPONSE

Dysfunkcja bariery skórnej indukowana przez zanieczyszczenia środowiskowe: stres oksydacyjny, zapalenie i odpowiedź immunologiczna

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Abstract

Environmental pollutants, including particulate matter, ozone, and polycyclic aromatic hydrocarbons, represent significant factors that impair skin function and integrity. Exposure to these substances has been shown to induce reactive oxygen species formation, activate inflammatory pathways, and impair the epidermal barrier. Oxidative stress and chronic inflammation result in lipid imbalance, collagen degradation, increased transepidermal water loss, and dysregulation of immune responses. Clinically, this manifests as accelerated skin aging, pigmentation disorders, and exacerbation of inflammatory dermatoses such as atopic dermatitis, psoriasis, and acne vulgaris. However, the skin has many complex defence mechanisms, including antioxidant systems, lipid barrier repair processes, and immune regulation. The skin microbiome also plays an important role in maintaining homeostasis. Under chronic exposure, these mechanisms gradually become impaired, leading to persistent skin barrier dysfunction. Understanding the molecular basis of these processes is crucial for developing effective preventive and therapeutic strategies, including the use of antioxidants, Nrf2 pathway activators, and interventions that support the skin microbiome. Environmental pollutants should be recognized as an important modifiable risk factor for skin diseases and considered in routine dermatological practice.

Streszczenie

Zanieczyszczenia środowiskowe, w tym pyły zawieszone, ozon i wielopierścieniowe węglowodory aromatyczne, stanowią istotny czynnik wpływający na funkcję i integralność skóry. Wykazano, że ekspozycja na te substancje prowadzi do powstawania reaktywnych form tlenu, aktywacji szlaków zapalnych oraz uszkodzenia bariery naskórkowej. Stres oksydacyjny i przewlekły stan zapalny skutkują zaburzeniem równowagi lipidowej, degradacją kolagenu, wzrostem przeznaskórkowej utraty wody oraz dysregulacją odpowiedzi immunologicznej. Klinicznie manifestuje się to przyspieszonym starzeniem skóry, zaburzeniami pigmentacji oraz nasileniem przebiegu dermatoz zapalnych, takich jak atopowe zapalenie skóry, łuszczyca czy trądzik pospolity. Skóra dysponuje jednak złożonymi mechanizmami obronnymi, obejmującymi system antyoksydacyjny, procesy naprawy bariery lipidowej, regulację immunologiczną oraz udział mikrobiomu w utrzymaniu homeostazy. W warunkach przewlekłej ekspozycji mechanizmy te ulegają stopniowemu osłabieniu, prowadząc do trwałej dysfunkcji bariery skórnej. Zrozumienie molekularnych podstaw tych procesów ma kluczowe znaczenie dla opracowania skutecznych strategii profilaktycznych i terapeutycznych, obejmujących stosowanie antyoksydantów, substancji aktywujących szlak Nrf2 oraz wspierających mikrobiom skóry. Zanieczyszczenia środowiskowe należy uznać za istotny, modyfikowalny czynnik ryzyka chorób skóry, który powinien być uwzględniany w codziennej praktyce dermatologicznej.

Keywords: oxidative stress; epidermal barrier; skin microbiome; environmental pollutants

Słowa kluczowe: stres oksydacyjny; bariera naskórkowa; mikrobiom skóry; zanieczyszczenia środowiskowe

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Introduction

As the body's largest organ, the skin is a highly specialized structure that maintains the barrier between the external and internal environment. The epidermal barrier is essential for homeostasis, as it protects against excessive transepidermal water loss, as well as entry of microorganisms, allergens, and toxins [1, 2]. Recent years have seen a dynamic increase in population exposure to environmental pollutants, particularly in urban and industrialized regions. Air pollutants, including particulate matter ($PM_{2.5}$ and PM_{10}), ozone (O_3), nitrogen oxides (NO_x), sulphur dioxide (SO_2), and polycyclic aromatic hydrocarbons (PAHs), not only can damage skin structures, but they can also induce cellular and molecular changes [1–4].

Epidemiological studies indicate that exposure to environmental pollutants is associated with a higher incidence of dermatological conditions, including atopic dermatitis (AD), psoriasis, acne vulgaris, and pigmentary disorders [5]. Furthermore, chronic exposure to PM and ozone accelerates extrinsic skin aging, contributing to increased wrinkle and lentigo formation [4, 5]. Pollutants may also act synergistically with ultraviolet (UV) radiation, exacerbating oxidative stress and DNA damage [6, 7].

Oxidative stress is a key mechanism underlying pollution-related skin damage. Pollutant-induced reactive oxygen species (ROS) and reactive nitrogen species (RNS) oxidize lipids, proteins, and nucleic acids, thereby disrupting the integrity of epidermal barrier [5, 8]. Excessive ROS production activates the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signalling pathways, promoting the expression of proinflammatory cytokines and matrix metalloproteinases (MMPs), thereby accelerating collagen degradation and skin aging [9].

The aryl hydrocarbon receptor (AhR) is a key player in the skin's response to environmental pollutants. When activated by ligands such as polycyclic aromatic hydrocarbons (PAHs), it modulates the transcription of proinflammatory and detoxification-related genes. AhR overactivation may contribute to skin barrier dysfunction, impaired keratinocyte differentiation, and hyperpigmentation [10, 11].

Environmental pollutants can also affect cutaneous immune function. Activation of Langerhans cells may enhance antigen presentation and shift immune responses toward Th2- or Th17-dominant profiles, accompanied by increased cytokine production [11, 12]. These changes may promote chronic inflammation, as well as increase epidermal permeability and susceptibility to infections and allergens, thereby triggering or exacerbating inflammatory skin conditions such as AD and psoriasis [5, 13].

A growing body of research indicates that air pollution not only compromises the skin barrier but also alters dermal microbiome by reducing its diversity and promoting the growth of potentially pathogenic species. These changes in microflora may further exacerbate inflammation and impair epidermal regeneration [14].

Understanding the molecular mechanisms underlying pollutant-induced skin barrier damage is crucial for developing effective preventive and therapeutic strategies.

Aim

The aim of this paper was to discuss the effects of environmental pollutants on skin barrier function, with particular emphasis on oxidative stress, inflammatory pathways, and immune response modulation.

Materials and methods

As part of this review, a comprehensive search of the scientific literature was conducted using PubMed, ScienceDirect, and Google Scholar databases. Publications in both Polish and English were considered, using keywords related to environmental pollutants, the epidermal barrier, oxidative stress, and the skin microbiome.

The analysis included peer-reviewed original and review papers looking into the effects of pollutants on epidermal barrier function and underlying molecular mechanisms, including oxidative stress, activation of inflammatory pathways, and immune response modulation. Studies addressing clinical implications, such as skin aging, hyperpigmentation, and exacerbation of dermatoses, were also included, along with *in vitro* and *in vivo* research involving both human skin and skin models. Meta-analyses and systematic reviews providing synthesized evidence were likewise considered.

Non-peer-reviewed publications, popular science or marketing reports, duplicate papers, and experimental studies conducted exclusively in animals without explicit relevance to mechanisms in human skin were excluded.

Selection of publications proceeded in three stages: identification and screening of titles and abstracts, followed by full-text assessment for consistency with the review objectives. Of the 68 publications initially identified, 25 papers met the inclusion criteria after duplicate removal and eligibility screening, and were included as the evidence base for this review.

Data from the selected publications were used to provide a synthesized overview of molecular mechanisms, clinical implications, and potential protective and therapeutic strategies.

Discussion

The physiology of skin barrier

The skin barrier is a complex structure encompassing the stratum corneum, intercellular junctions, lipids, and immune components. Its primary role is to protect the body from water loss as well as physical, chemical, and biological stressors while also modulating immune responses [1]. The stratum corneum consists of corneocytes embedded in a lipid matrix rich in ceramides, cholesterol, and free fatty acids; disruption of the balance among these components may increase transepidermal water loss (TEWL) and skin permeability [1, 2]. Structural

proteins, including filaggrin, loricrin, and involucrin, are essential players in keratinocyte differentiation. Filaggrin is involved in the aggregation of keratin filaments and contributes to the generation of natural moisturizing factors; its deficiency is therefore associated with skin barrier dysfunction and AD. Intercellular junction proteins, such as occludin, claudins, and desmogleins, are likewise critical for maintaining epidermal integrity and limiting pathogen penetration [2].

The skin also serves important immunological functions. The epidermis contains Langerhans cells, which initiate immune responses to pathogens and barrier disruption [1, 2]. Keratinocytes actively produce cytokines, chemokines, and antimicrobial peptides, including defensins and cathelicidin (LL-37), thereby modulating inflammation, whereas the papillary dermis contains dendritic cells, tissue-resident memory T cells, and mast cells, which enhance local immune defences [15]. Skin barrier integrity is closely linked to its microbiome. Commensal species, including *Staphylococcus epidermidis* and *Cutibacterium acnes*, compete with pathogens, support immune system maturation, and help regulate inflammatory responses, whereas microbiome dysbiosis may promote overcolonization by pathogens such as *Staphylococcus aureus*, thereby exacerbating inflammation and skin barrier damage [14, 16].

Skin barrier function is also influenced by physiological factors, including dermal pH, hydration, enzymatic activity, and hormones. A slightly acidic skin surface pH of approximately 4.5–5.5 promotes the activity of enzymes involved in epidermal maturation and inhibits pathogen growth [16], while proteolytic enzymes regulate corneocyte desquamation and skin barrier remodelling, with their dysregulation potentially leading to hyperkeratosis or impaired epidermal structure [2, 6].

In summary, the skin barrier is a dynamic, multicomponent system whose proper function depends on the physical integrity of the stratum corneum, stability of the lipid matrix, structural proteins, intact intercellular junctions, balanced microbiome, and appropriately modulated immune responses. Disruption of any of these components may increase dermal susceptibility to environmental stressors, including air pollution, and may contribute to inflammation and the development of dermatological conditions.

Types of environmental pollutants and their interactions with the skin

Environmental pollutants represent a heterogeneous group of natural and anthropogenic substances that can affect the skin through direct contact or systemic exposure. The most important ones include particulate matter (PM), ozone (O_3), nitrogen oxides (NO_x), sulphur dioxide (SO_2), polycyclic aromatic hydrocarbons (PAHs), heavy metals, and tobacco smoke [2]. $PM_{2.5}$ and PM_{10} are complex mixtures of solid and liquid particles classified based on their aerodynamic diameter. PM_{10} particles predominantly deposit on the skin surface, whereas the smaller $PM_{2.5}$ particles can penetrate through hair follicles and sebaceous glands, reaching the viable layers of the epidermis [16]. These particles may contain heavy metals, sulphates, nitrates, oxidized lipids, and toxic organic compounds able to induce oxidative stress and inflammatory responses [16, 17]. Ozone, a potent oxidant formed through photochemical reactions between nitrogen oxides and volatile organic compounds, primarily affects the lipid layer of the stratum corneum, where it induces lipid peroxidation and generates secondary inflammatory mediators. Ozone does not penetrate deeply into the skin; however, its breakdown products can activate keratinocytes and trigger inflammatory responses [5]. Nitrogen oxides, particularly NO_2, react with epidermal lipids and promote RNS formation, thereby increasing oxidative stress and protein nitrosylation. Additionally, NO_2 may activate proinflammatory signalling pathways, including NF-κB, promoting cytokine expression and extracellular matrix degradation [5, 16].

Exposure of the skin to air pollutants, including $PM_{2.5}$, PM_{10}, O_3, NO_2, and PAHs, promotes ROS and RNS generation. The resulting oxidative stress may lead to the oxidization of lipids, proteins, and DNA, thereby contributing to epidermal damage. Activation of NF-κB and MAPK signalling pathways initiates an inflammatory cascade, increasing the expression of proinflammatory cytokines and matrix metalloproteinases, which may in turn promote the degradation of collagen and other extracellular matrix (ECM) components. Prolonged AhR activation may disrupt keratinocyte differentiation and contribute to hyperpigmentation, while alterations in the skin microbiome can further exacerbate inflammation and accelerate environmentally induced skin aging (Fig. 1).

Sulphur dioxide (SO_2) can irritate the skin, disrupt its acid-base balance, and damage the lipid barrier, with chronic exposure associated with increased skin dryness and pruritus [16]. Polycyclic aromatic hydrocarbons are lipophilic compounds that readily penetrate the skin and bind to the aryl hydrocarbon receptor (AhR), the activation of which induces the expression of detoxification-related genes, including *CYP1A1*, as well as proinflammatory and pro-oxidant genes. Prolonged AhR activation may contribute to hyperpigmentation, impaired keratinocyte differentiation, and carcinogenesis [16, 18]. Heavy metals, including arsenic, cadmium, and lead, can bind to structural proteins in the skin and inhibit antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, thereby increasing oxidative stress. Arsenic is a known carcinogen and may contribute to skin cancer by causing DNA damage and disrupting genomic repair mechanisms [18].

Tobacco smoke contains more than 4,000 chemical compounds, including PAHs, heavy metals, and aldehydes, all of which cause damage to the epidermal barrier, accelerate skin aging, and promote pigmentary changes; tobacco smoke components may also activate macrophages and mast cells, thereby increasing inflammation [19, 20]. Some pollutants may act synergistically, thereby amplifying their harmful effects. For example, combined exposure to PAHs and UV has been shown to induce greater ROS generation and DNA damage than either factor alone [20]. A similar synergistic effect has been observed between ozone and PM: ozone causes lipid damage, while PM promotes the production of proinflammatory cytokines [5].

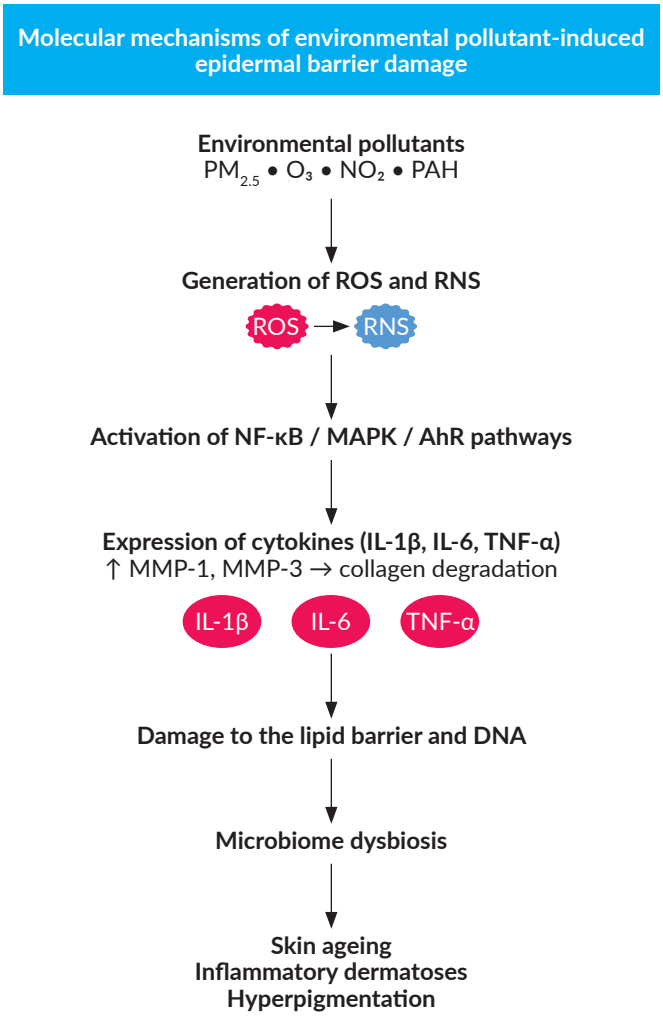

Figure 1. Molecular mechanisms of environmental pollutant-induced epidermal barrier damage

Environmental pollutants may affect the skin both through direct contact, and indirectly, through systemic circulation. PM and PAHs can interact with Toll-like receptors (TLRs) and the aryl hydrocarbon receptor (AhR) on keratinocytes, Langerhans cells, and fibroblasts, activating inflammatory and immune signalling pathways [9, 11]. Additionally, pollutants can alter the skin microbiome by promoting pathogenic colonization, thereby contributing to dysbiosis and chronic inflammation [14].

These findings indicate that, despite their differing chemical properties, environmental pollutants share common effects: they compromise skin barrier function, intensify oxidative stress, promote inflammation, and modulate immune responses, thereby contributing to clinically evident skin changes.

Inflammatory mechanisms and activation of the immune response

Dermal exposure to environmental pollutants triggers a cascade of inflammatory reactions, representing a second major mechanism underlying epidermal barrier dysfunction alongside oxidative stress. This inflammatory process may be initiated through direct activation of pattern-recognition receptors and through secondary oxidative mediators produced during lipid peroxidation [2, 3]. Pollutants such as PM and PAHs can activate Toll-like receptors (TLR2 and TLR4) and AhR, which are expressed on keratinocytes, fibroblasts, and Langerhans cells. TLR activation triggers NF-κB and MAPK signalling pathways, increasing the transcription of genes encoding proinflammatory cytokines. This in turn promotes the local recruitment of neutrophils and monocytes and increases dermal microvascular permeability [11].

AhR activation plays an important role in maintaining cutaneous immune homeostasis; although short-term receptor activation may have protective effects, chronic stimulation by PAHs can promote the overproduction of cytokines and chemokines and disrupt the balance between Th17 and Treg cells, contributing to persistent inflammatory responses observed in conditions such as AD and psoriasis [13]. Ozone and nitrogen oxides can increase local expression of adhesion molecules (ICAM-1 and VCAM-1), on endothelial cells and keratinocytes, thereby promoting leukocyte migration into the skin. Simultaneously, ozone may reduce antioxidant enzyme activity, further amplifying inflammatory responses, while lipid oxidation products (e.g. 4-HNE) can act as ligands for TRPA1 and TLR4, activating neurogenic and immune components of inflammation [5, 11].

Under chronic exposure, inflammatory responses may be sustained by epigenetic mechanisms, including methylation of genes encoding anti-inflammatory mediators and histone acetylation that regulates the expression of proinflammatory cytokines. This may lead to persistent, low-grade subclinical inflammation, causing extracellular matrix damage and accelerated skin aging [9, 21]. Chronic pollutant-induced inflammation can increase the activity of matrix metalloproteinases, which degrade type I and type III collagen in the dermis, contributing to reduced skin elasticity, laxity, and wrinkle formation. Additionally, cytokines such as IL-6 and TNF-α can inhibit collagen synthesis by fibroblasts, further intensifying degenerative changes [9].

Pollution can also affect the skin microbiome – an integral component of innate immunity. PM and ozone may alter commensal flora composition and increase the relative proportion of opportunistic bacteria, such as *Staphylococcus aureus*, thereby impairing immune tolerance and increasing inflammation. Skin dysbiosis may therefore act as a mediator between environmental exposure and the host inflammatory response [2, 6].

In summary, environmental pollutants activate multiple interconnected inflammatory and immunological mechanisms, including stimulation of TLRs and AhR, activation of NF-κB and MAPK signalling pathways, increased expression of proinflammatory cytokines and chemokines, dysregulation of Th17/Treg responses, extracellular-matrix degradation, and disruption of the skin microbiome. These processes contribute to chronic, low-grade inflammation, a key driver of skin barrier dysfunction, loss of epidermal integrity, and the development or exacerbation of environmentally induced dermatoses.

Clinical implications of skin exposure to environmental pollutants

The multifaceted effects of environmental pollutants on the skin are reflected in clinical manifestations such as accelerated skin aging, exacerbation of inflammatory dermatoses, and pigmentary disorders. These symptoms result from chronic oxidative stress, inflammation, and immune dysregulation, with their severity depending on the type and duration of exposure as well as individual susceptibility [2, 11]. Environmental skin aging, which arises from the combined effects of UV radiation, ozone, and PM represents the most extensively documented consequence of cutaneous exposure to air pollution. Epidemiological studies have reported links between higher $PM_{2.5}$ levels and increased wrinkle formation, reduced skin elasticity, and facial hyperpigmentation [4, 16]. Long-term exposure to air pollution can promote collagen fibre degradation by increasing the activity of MMP-1 and MMP-3 while reducing collagen synthesis by fibroblasts. This contributes to skin thinning, reduced firmness, and increased susceptibility to wrinkle formation. The damage may be further exacerbated by the synergistic effects of UV and PAHs [9, 15].

Environmental pollutants may also contribute to the pathogenesis and exacerbation of AD, psoriasis, and acne vulgaris. Upon exposure to $PM_{2.5}$ and NO_2, patients with AD may experience increased epidermal barrier dysfunction due to reduced filaggrin expression and increasing TEWL; these pollutants can also activate Th2 signalling pathways and increase the production of IL-4, IL-13, and IL-31, thereby contributing to pruritus and chronic inflammation [9]. In psoriasis, environmental pollutants can induce oxidative stress and activate the IL-23/Th17 pathway, thereby promoting keratinocyte proliferation and sustained inflammation. In patients with acne vulgaris, pollutants may stimulate sebum production and increase its viscosity, as well as induce inflammatory responses within hair follicles. Ozone and PM may also promote colonization by *Cutibacterium acnes*, contributing to inflammatory lesions [9, 14].

Pollutants, PAHs and ozone in particular, can affect melanocyte metabolism by activating AhR and oxidative pathways. Overproduction of ROSs and increased levels of α-melanocyte-stimulating hormone (α-MSH) may enhance melanogenesis, clinically manifesting as lentigines and uneven facial pigmentation. Population-based studies have reported a relationship between $PM_{2.5}$ exposure and hyperpigmentation, particularly among middle-aged women; additionally, chronic inflammation and epidermal barrier damage may contribute to post-inflammatory hyperpigmentation [19, 22].

Certain pollutant components, including arsenic, cadmium, and PAHs, have carcinogenic potential. Their metabolites can bind to epidermal DNA, causing mutations and impairing genomic repair mechanisms. AhR overactivation and chronic oxidative stress may promote neoplastic transformation and increase the risk of skin cancer, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) in particular. The combined effects of PAHs and UV radiation can upregulate the formation of pyrimidine dimers, thereby intensifying photocarcinogenic processes [1, 3].

Environmental pollutants can also disrupt the balance of the skin microbiome by reducing the diversity of commensal species and promoting pathogenic colonization. These changes may lower the threshold for cutaneous immune reactivity and contribute to the development of allergic contact dermatitis and environmental urticaria. Furthermore, increased epidermal permeability facilitates the penetration of allergens and irritants, promoting contact hypersensitivity [6, 14].

Epidemiological studies in urban populations have demonstrated clear associations between air pollution levels and the incidence and severity of cutaneous conditions, with the strongest correlations reported between exposure to $PM_{2.5}$, NO_2, and ozone and the severity of AD, psoriasis, acne, and hyperpigmentation. Even short-term exposure to elevated $PM_{2.5}$ levels may cause a transient yet measurable increase in TEWL and a reduction in epidermal antioxidant levels [10, 23].

These findings indicate that environmental pollutants constitute an important risk factor for dermatological disorders. Their effects may be both direct and indirect, mediated through oxidative stress, inflammation, immune modulation, and skin microbiome dysbiosis.

Skin adaptive response and defence mechanisms against environmental pollution

Despite harmful effects of environmental pollutants, the skin has a range of adaptive defence mechanisms that help maintain homeostasis and limit exposure-related damage. These mechanisms involve biochemical and molecular responses, as well as structural and microbiological adaptations.

The skin's extensive antioxidant system constitutes its first line of defence against oxidative stress. It comprises both enzymatic and low molecular weight antioxidants. Key antioxidant enzymes include superoxide dismutase (SOD), catalase, and glutathione peroxidase, which neutralize superoxide anions and hydrogen peroxide, thereby limiting the formation of highly reactive hydroxyl radicals. Non-enzymatic antioxidants, including vitamins E and C, glutathione, uric acid, carotenoids, and coenzyme Q10, are also present in the stratum corneum [11, 24]. The skin's response to chronic exposure to environmental pollutants initially involves compensatory increase in the expression of antioxidant enzymes. This mechanism is associated with activation of the transcription factor Nrf2 (nuclear factor erythroid 2–related factor 2), which interacts with antioxidant response elements (AREs) in the promoter regions of genes encoding cytoprotective proteins, including heme oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase 1 (NQO1), and γ-glutamylcysteine synthetase (γ-GCS). The Nrf2/ARE pathway is a central component of the cellular adaptive response to oxidative stress, enabling detoxification of reactive metabolites and the regeneration of glutathione. However, chronic exposure to PM or ozone may deplete these protective mecha-

nisms, resulting in impaired antioxidant defences and persistent epidermal damage [7, 16, 19].

The integrity of the skin barrier also relies on the proper lipid arrangement within the stratum corneum.

In response to irritants and oxidants, keratinocytes initiate repair processes that renew the lipid matrix, with increased expression of ceramide-synthesizing enzymes and lipid transport proteins (ABCA12), further enhancing barrier reconstruction following oxidative stress-induced damage.

This process is modulated by IL-1α and TGF-β, and its effectiveness depends on the metabolic status of epidermal cells and the availability of lipid precursors. It represents an adaptive dermal response that allows for partial restoration of skin barrier function and reduced TEWL once exposure to toxic agents has ceased [15, 20].

The immune system plays a crucial role in the skin's adaptation to environmental exposures. Langerhans cells and keratinocytes exert immunoregulatory effects, among other things, by secreting anti-inflammatory cytokines (IL-10 and TGF-β), as well as by modulating Treg activity, thereby limiting excessive inflammation and maintaining local immune tolerance. In addition to its pro-inflammatory effects, AhR also has some immunomodulatory functions: when activated in a controlled manner, it promotes Treg differentiation and IL-22 production, thereby supporting epidermal barrier regeneration. This phenomenon, which depends on ligand levels and the length of exposure, is often referred to as biphasic AhR response [4, 18].

The skin microbiome functions as a biological barrier by competing with pathogenic microorganisms and modulating local immune responses. In response to environmental pollutants, the commensal skin microbiota may undergo transient adaptive changes, including an increased relative proportion of microorganisms with antioxidant properties (e.g. *Staphylococcus epidermidis* and *Cutibacterium acnes*). These microbes produce metabolites with antioxidant and anti-inflammatory activity, including lactic acid, short-chain fatty acids, and antimicrobial peptides. Maintaining microbiome eubiosis is therefore an important component of the skin's adaptive response to environmental stress [6, 14].

Keratinocytes and fibroblasts can also activate repair mechanisms once pollutant exposure has ceased. These mechanisms include the induction of growth factors (VEGF, EGF, and FGF-2), which promote cell proliferation and differentiation, as well as increase the activity of DNA-repair enzymes (PARP-1, XRCC1), and thus help eliminate oxidative damage and restore normal epidermal cell function. Although these processes are adaptive, their effectiveness declines with age and prolonged exposure to pollution [12, 25].

Together, all the above mentioned mechanisms constitute a complex defence system that protects the skin against environmental pollutants. Their effectiveness determines the ability to maintain cutaneous homeostasis and shapes individual susceptibility to clinically apparent changes. However, chronic exposure can progressively exhaust these protective reserves, ultimately contributing to persistent barrier dysfunction and accelerated skin aging.

Conclusions

Based on the reviewed scientific literature, environmental pollutants are recognized as important risk factors for dermatological disorders. They can induce oxidative stress, inflammatory responses, and epidermal barrier dysfunction. Prolonged exposure may contribute to premature skin aging, pigmentary abnormalities, and exacerbation of inflammatory dermatoses, including atopic dermatitis and psoriasis. The efficacy of skin's antioxidant and immune mechanisms that can partially compensate for pollutant-induced damage may decline as a result of chronic exposure. Therefore, protection against environmental pollutants should be an integral component of dermatological prevention and treatment, particularly in urban settings.

References

1. Lefebvre MA, Pham DM, Boussouira B, et al. Consequences of urban pollution upon skin status. A controlled study in Shanghai area. Int J Cosmet Sci, 2016; 38(3): 217–223. doi: 10.1111/ics.12270
2. Brunekreef B, Holgate ST. Air pollution and health. Lancet, 2002; 360(9341): 1233–1242. doi: 10.1016/S0140-6736(02)11274-8
3. Schikowski T, Hüls A. Air Pollution and skin aging. Curr Environ Health Rep, 2020; 7(1): 58–64. doi: 10.1007/s40572-020-00262-9
4. Park SY, Byun EJ, Lee JD, et al. Air pollution, autophagy, and skin aging: impact of particulate matter (PM_{10}) on human dermal fibroblasts. Int J Mol Sci, 2018; 19(9): 2727. doi: 10.3390/ijms19092727
5. Levy I, Mihele C, Lu G, et al. Evaluating multipollutant exposure and urban air quality: pollutant interrelationships, neighborhood variability, and nitrogen dioxide as a proxy pollutant. Environ Health Perspect, 2014; 122(1): 65–72. doi: 10.1289/ehp.1306518
6. Ali A, Khan H, Bahadar R, et al. The impact of airborne pollution and exposure to solar ultraviolet radiation on skin: mechanistic and physiological insight. Environ Sci Pollut Res, 2020; 27(23): 28730–28736. doi: 10.1007/s11356-020-09280-4
7. Nakamura M, Morita A, Seité S, et al. Environment-induced lentigines: formation of solar lentigines beyond ultraviolet radiation. Exp Dermatol, 2015; 24(6): 407–411. doi: 10.1111/exd.12690
8. Varga R, Gross J. Oxidative stress status and its relationship to skin aging. Plastic and Aesthetic Nursing, 2023; 43(3): 141–148. doi: 10.1097/PSN.0000000000000515
9. Vierkötter A, Schikowski T, Sugiri D, et al. MMP-1 and -3 promoter variants are indicative of a common susceptibility for skin and lung aging: results from a cohort of elderly women (SALIA). J Invest Dermatol, 2015; 135(5): 1268–1274. doi: 10.1038/jid.2015.7

10. Vierkötter A, Schikowski T, Ranft U, et al. Airborne particle exposure and extrinsic skin aging. J Invest Dermatol, 2010; 130(12): 2719–2726. doi: 10.1038/jid.2010.204
11. Widmer R, Ziaja I, Grune T. Protein oxidation and degradation during aging: role in skin aging and neurodegeneration. Free Radic Res, 2006; 40(12): 1259–1268. doi: 10.1080/10715760600911154
12. Li N, Sioutas C, Cho A, et al. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. Environ Health Perspect, 2003; 111(4): 455–460. doi: 10.1289/ehp.6000
13. Valacchi G, Sticozzi C, Pecorelli A, et al. Cutaneous responses to environmental stressors. Ann N Y Acad Sci, 2012; 1271(1): 75–81. doi: 10.1111/j.1749-6632.2012.06724.x
14. Dijkhoff IM, Drasler B, Karakocak BB, et al. Impact of airborne particulate matter on skin: a systematic review from epidemiology to in vitro studies. Part Fibre Toxicol, 2020; 17(1): 35. doi: 10.1186/s12989-020-00366-y
15. Lavker RM. Structural alterations in exposed and unexposed aged skin. J Invest Dermatol, 1979; 73(1): 59–66. doi: 10.1111/1523-1747.ep12532763
16. Ding A, Yang Y, Zhao Z, et al. Indoor $PM_{2.5}$ exposure affects skin aging manifestation in a Chinese population. Sci Rep, 2017; 7(1): 15329. doi: 10.1038/s41598-017-15295-8
17. Hüls A, Vierkötter A, Gao W, et al. Traffic-Related Air Pollution Contributes to Development of Facial Lentigines: Further Epidemiological Evidence from Caucasians and Asians. J Invest Dermatol, 2016; 136(5): 1053–1056. doi: 10.1016/j.jid.2015.12.045
18. Loomis D, Huang W, Chen G. The International Agency for Research on Cancer (IARC) evaluation of the carcinogenicity of outdoor air pollution: focus on China. Chin J Cancer, 2014; 33(4): 189–196. doi: 10.5732/cjc.014.10028
19. Yamada T, Hasegawa S, Inoue Y, et al. Accelerated differentiation of melanocyte stem cells contributes to the formation of hyperpigmented maculae. Exp Dermatol, 2014; 23(9): 652–658. doi: 10.1111/exd.12496
20. Berneburg M, Plettenberg H, Krutmann J. Photoaging of human skin. Photodermatol Photoimmunol Photomed, 2000; 16(6): 239–244. doi: 10.1034/j.1600-0781.2000.160601.x
21. Makrantonaki E, Zouboulis CC; German National Genome Research Network 2. The skin as a mirror of the aging process in the human organism – state of the art and results of the aging research in the German National Genome Research Network 2 (NGFN-2). Exp Gerontol, 2007; 42(9): 879–886. doi: 10.1016/j.exger.2007.07.002
22. Berneburg M, Gattermann N, Stege H, et al. Chronically ultraviolet-exposed human skin shows a higher mutation frequency of mitochondrial DNA as compared to unexposed skin and the hematopoietic system. Photochem Photobiol, 1997; 66(2): 271–275. doi: 10.1111/j.1751-1097.1997.tb08654.x
23. Vierkötter A, Krutmann J. Environmental influences on skin aging and ethnic-specific manifestations. Dermatoendocrinol, 2012; 4(3): 227–231. doi: 10.4161/derm.19858
24. Hüls A, Sugiri D, Fuks K, et al. Lentigine formation in caucasian women-interaction between particulate matter and solar UVR. J Invest Dermatol, 2019; 139(4): 974–976. doi: 10.1016/j.jid.2018.09.034
25. Kosmadaki MG, Gilchrest BA. The role of telomeres in skin aging/photoaging. Micron, 2004; 35(3): 155–159. doi: 10.1016/j.micron.2003.11.002

A REVIEW OF TREATMENT OPTIONS FOR CHRONIC DIABETIC WOUNDS

Przegląd leczenia przewlekłych ran cukrzycowych

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Abstract

Chronic diabetic wounds are one of the main complications of untreated or poorly controlled diabetes. The most common type of chronic diabetic wound is a diabetic foot ulcer. Healing such wounds is extremely difficult and requires diligence on the part of both the physician and the patient. Therefore, it is important to gain a thorough understanding of the available methods for treating diabetic foot ulcers. A literature review was conducted using the PubMed and Google Scholar databases, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following search terms and their combinations in English were used: "chronic diabetic wound", "treatment", "diabetic foot ulcers", "wound healing", "advanced wound care", and the Boolean operator "and". Articles published between 2020 and 2025 were included. Treatment methods were divided into wound bed preparation, oxygen-based therapies, mechanical and biological therapies, tissue engineering approaches, and wound dressings. All therapies were described based on the available information. Chronic diabetic wounds are a serious clinical problem affecting an increasing number of patients. The approach to treatment should be multidisciplinary and individualised to the patient's needs. There are many methods available for treating diabetic foot ulcers. However, not all of them have been sufficiently studied to allow their safe and reliable use in patients.

Streszczenie

Przewlekłe rany cukrzycowe są jednym z głównych powikłań nieleczonej lub niewłaściwie kontrolowanej cukrzycy. Najczęstszym rodzajem przewlekłej rany cukrzycowej jest owrzodzenie stopy cukrzycowej. Gojenie takich ran jest niezwykle trudne i wymaga staranności zarówno ze strony lekarza, jak i pacjenta. Dlatego ważne jest, aby dokładnie poznać dostępne metody leczenia owrzodzenia stopy cukrzycowej. Przegląd literatury przeprowadzono z wykorzystaniem baz PubMed i Google Scholar, zgodnie z wytycznymi Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Podczas przeglądania wyżej wymienionych baz danych użyto następujących haseł i ich kombinacji w języku angielskim: „chronic diabetic wound", „treatment", „diabetic foot ulcers", „wound healing", „advanced wound care" oraz operatora „AND". Uwzględniono artykuły opublikowane w latach 2020–2025. Metody leczenia podzielono na przygotowanie łożyska rany, terapie tlenowe, terapie mechaniczne i biologiczne, a także metody inżynierii tkankowej i opatrunki na rany. Wszystkie terapie opisano na podstawie dostępnych informacji. Przewlekłe rany cukrzycowe stanowią poważny problem kliniczny, dotykający coraz większej liczby pacjentów. Podejście do leczenia powinno być wielodyscyplinarne i zindywidualizowane, dostosowane do potrzeb pacjenta. Istnieje wiele metod leczenia owrzodzenie stopy cukrzycowej. Jednak nie wszystkie z nich zostały wystarczająco przebadane, aby można je było bezpiecznie i niezawodnie stosować u pacjentów.

Keywords: chronic diabetic wound; treatment of chronic wound; diabetic foot ulcer; DFU healing; wound healing

Słowa kluczowe: przewlekła rana cukrzycowa; leczenie przewlekłej rany; owrzodzenie stopy cukrzycowej; gojenie się OSC; gojenie się ran

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Introduction

Diabetes mellitus (DM) is one of the ten leading causes of mortality worldwide and a major contributor to the global demand for medical care. It is estimated that nearly 500 million people worldwide have diabetes [1], with diabetic foot ulcers (DFUs) being one of its major complications [2]. According to statistics, chronic, non-healing wounds develop in approximately one in three to one in five patients with DM, with a recurrence rate of 40% within one year and 65% within five years [1].

Physiological wound healing is defined as a natural process that occurs in response to structural tissue damage, including damage to the skin. This process involves complex and complementary interactions between various cell types, mediated through networks of soluble factors, including cytokines, growth factors, metabolites, and chemokines. Wound healing progresses through four overlapping and sequential phases: haemostasis, inflammation, proliferation, and remodelling (scar maturation). However, in patients with diabetes, wounds exhibit impaired healing, prolonged inflammation, and reduced rates of epithelialisation [3]. Impaired wound healing has an exceptionally complex pathophysiology and is associated with chronic hyperglycaemia, which contributes to numerous systemic complications. This results in a range of local pathological manifestations within the wound microenvironment, including barrier dysfunction and infection, impaired angiogenesis and microvascular complications, atherosclerosis, a suboptimal chronic inflammatory response, and neuropathy [1, 3]. Oxidative stress induced by hypoxia further impairs wound healing, as the partial pressure of oxygen within the wound is often below the critical threshold required for complete tissue repair. All these factors contribute to impaired wound closure, and when combined with inadequate foot care, ultimately lead to the development of diabetic foot syndrome, with ulcers most commonly occurring in areas subject to recurrent trauma and pressure [1]. In many patients with type 2 diabetes, ulcers develop on the lower limbs, representing the most severe form of diabetic wounds (DWs) [3].

The prognosis for patients with DFUs is significantly poor. Approximately 33% of diabetic ulcers fail to heal completely and progress to chronic wounds. Among patients whose ulcers initially heal, 65% experience recurrence within three years, highlighting the chronic and recurrent nature of this condition. Furthermore, around 20% of moderate to severe DFUs result in amputation, and individuals with diabetes are up to 25 times more likely to undergo limb loss than non-diabetic individuals. Moreover, the presence of DFU in diabetic patients is associated with reduced quality of life, decreased physical function, an increased risk of depression and anxiety, and is an independent risk factor for mortality [3].

This study aims to review the available treatment methods for diabetic foot syndrome and to emphasise that, given the prevalence of this condition, the choice of therapy should be individualised for each patient. Treatment decisions should be based on comorbidities, overall health status, and specific patient needs.

Material and methods

The literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two databases, PubMed and Google Scholar, were used for the literature search. The review process began in October 2024 and continued until May 2025. The databases were searched by four independent investigators. None of the investigators was involved in any of the included studies.

The following search terms and their combinations in English were used when searching the aforementioned databases: “chronic diabetic wound”, “treatment”, “diabetic foot ulcers”, “wound healing”, “advanced wound care”, and the operator “AND”. The inclusion criteria were: period of 2020–2025, type of publication (original research, review, systematic review/meta-analysis), subject matter (treatment of chronic diabetic wounds), and English language. The exclusion criteria were: type of publication (case report, editorial, abstract, poster), inappropriate publication period, and language other than English. A total of 668 papers were identified in PubMed and 836 in Google Scholar. Duplicates and irrelevant papers were excluded. A total of 49 papers fulfilled the inclusion criteria. These comprised 24 original studies, 18 review articles, and 7 systematic reviews/meta-analyses. Data were collected on chronic diabetic wounds, established treatments, and future prospects. A flowchart presenting the article search and selection process according to PRISMA guidelines is presented in Figure 1.

Treatment modalities

Wound bed preparation

Debridement

Surgical

- Sharp debridement

Sharp debridement involves the precise excision of devitalised tissue using scalpels, scissors, or curettes. This technique allows for the rapid removal of necrotic mate-

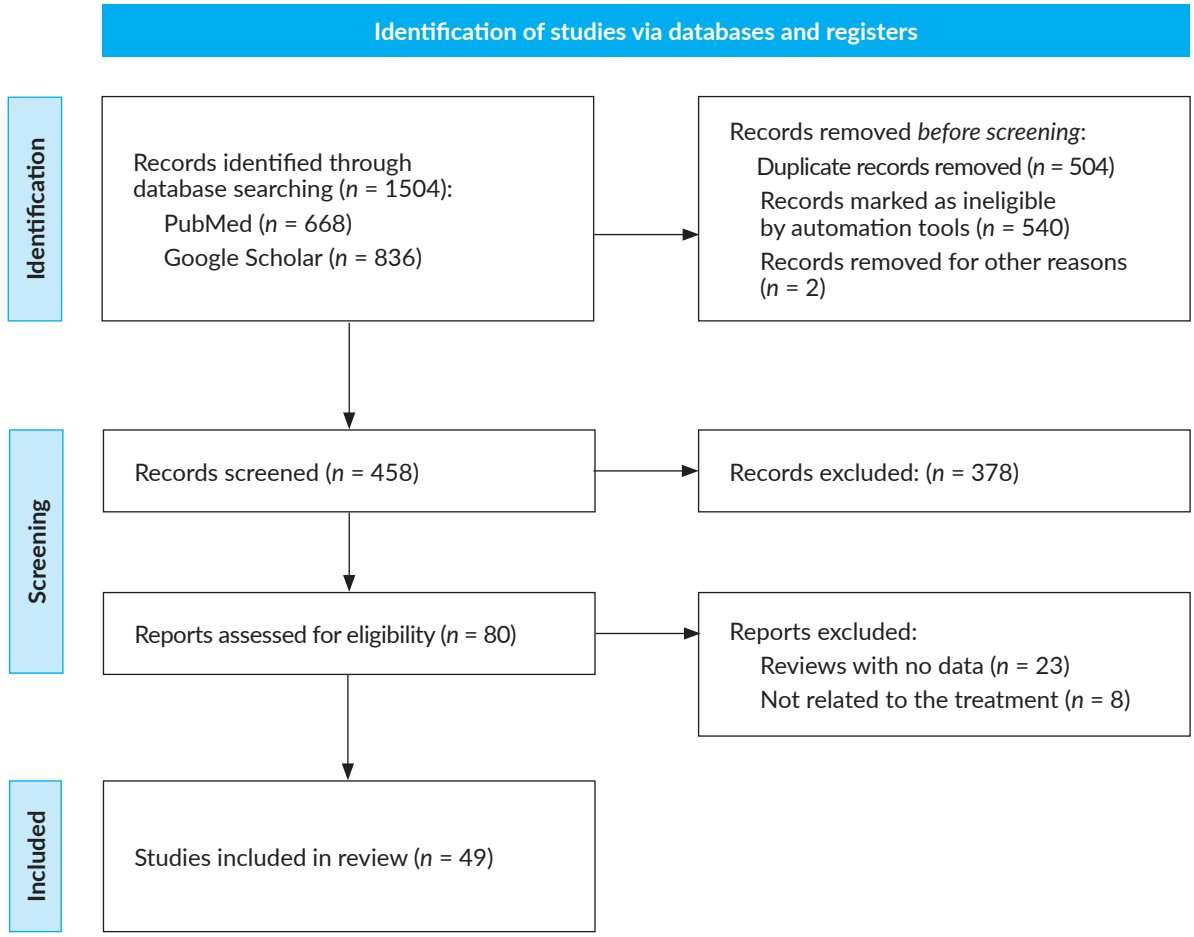

Figure 1. Flowchart of the search and selection of articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

rial, thereby decreasing the bacterial burden and facilitating assessment of the underlying structures. According to Armstrong et al. [4], sharp debridement is considered a first-line therapy in DFU management, emphasising its role in achieving a clean wound bed conducive to healing.

• Surgical debridement in the operating room

For more extensive or deeper wounds, surgical debridement may be performed in an operating room under anaesthesia. This approach is particularly beneficial for patients with significant tissue involvement or those requiring more aggressive intervention. Bandyk highlights that inpatient care, including surgical debridement of infected tissue, is recommended when invasive foot infections develop, particularly when tissue beneath the fascia is involved [5].

The choice of debridement technique is influenced by factors such as the extent of necrosis, presence of infection, patient comorbidities, and overall treatment goals. Boulton et al. emphasise the importance of a multidisciplinary approach, incorporating surgical debridement alongside other interventions, such as off-loading and infection control, to optimise patient outcomes [4].

Autolytic

Autolytic debridement utilises the body's endogenous enzymes and moisture to liquefy and separate necrotic tissue from viable tissue. This process is facilitated by maintaining a moist wound environment, typically achieved through the application of occlusive or semi-occlusive dressings. These dressings retain wound exudate, which contains proteolytic enzymes that break down devitalised tissue, thereby promoting natural tissue regeneration.

One of the primary benefits of autolytic debridement is its selectivity, as it targets only necrotic tissue while preserving healthy tissue, thereby minimising patient discomfort and reducing the risk of bleeding. Additionally, this method is non-invasive and can be easily performed in various settings, including outpatient clinics and home care, thereby enhancing patient compliance. The moist environment created by the dressings not only aids in debridement but also supports cell proliferation and angiogenesis, which are essential components of the healing process.

Despite its advantages, autolytic debridement is generally slower than other debridement methods, such as surgical or enzymatic debridement. It may not be suitable for wounds with extensive necrosis or heavy infection, where more rapid removal of devitalised tissue is necessary. Moreover, maintaining an optimal moist environment requires careful monitoring to prevent maceration of the surrounding skin and to manage exudate levels appropriately [6].

Cleansing solutions

• Superoxidised solutions

Superoxidised solutions, generated through the electrolysis of saline, produce reactive oxygen species with potent antimicrobial properties. A randomised controlled study assessed the efficacy of a neutral-pH superoxidised solution in patients with severe DFUs. The findings indicated significant infection control, a reduction in wound odour, and improvement in the condition of the periwound skin, suggesting its effectiveness as a wound-cleansing agent in DFU management [7].

• Hypochlorous acid (HOCl) solutions

HOCl is recognised for its antimicrobial and anti-inflammatory properties. In a study involving diabetic rats, topical application of HOCl was associated with decreased activity of matrix metalloproteinase-9 (MMP-9), an enzyme linked to delayed wound healing. This reduction in MMP-9 activity correlated with improved histological outcomes, indicating that HOCl may facilitate the healing process in DWs.

The investigation focused on the immersion of debrided DFU tissue in electrochemically generated pH-neutral HOCl. The results demonstrated a significant reduction in microbial bioburden, particularly against *Staphylococcus aureus*, the most prevalent species recovered. This suggests that HOCl can effectively decrease the microbial load in DFUs, potentially reducing the risk of infection [8].

Oxygen-based therapies

Hyperbaric oxygen therapy (HBOT)

HBOT may represent a valuable option for chronic wounds that are unresponsive to standard treatment, as it accelerates healing and modulates oxidative stress and inflammation. During therapy, antioxidant activity increases, while pro-inflammatory markers and MMP-9 levels decline. HBOT also enhances the expression of growth factors such as TGF-β, PDGF, and HIF-1α, which return to normal levels after wound closure, with signalling pathways including NF-κB and MAPKs playing a role in these processes.

Emerging evidence highlights the involvement of adipose tissue in wound repair. Dermal and perivascular adipocytes contribute to healing by releasing fatty acids that support macrophage recruitment, angiogenesis, and vascular remodelling. Although large clinical trials are limited, recent studies indicate that HBOT is effective in patients with advanced diabetic foot ulcers, improving metabolic and inflammatory parameters. Experimental diabetic models further confirm that HBOT accelerates wound closure and reduces MMP-9 expression. Despite these benefits, further research is required to clarify the role of endothelial-derived exosomes in HBOT-mediated diabetic wound healing [9].

Topical oxygen therapy (TOT)

TOT is defined as the topical application of oxygen to a wound, either through continuous diffusion or a pressurised system. There are three types of TOT delivery systems. The first provides continuous delivery of oxygen (CDO), and the second maintains constant low pressure within a contained chamber, and the third uses a cyclically pressurised and humidified contained chamber (TWO2). Until recently, TOT was considered an unproven method of DFU healing, unsupported by clinical evidence. However, a multicentre, open-label, randomised clinical trial conducted by Serena et al. reported the efficacy of TOT in DFU treatment. The study included 145 patients with chronic DFUs. Patients were randomly assigned to a standard-of-care (SOC) group without TOT or an SOC group with TOT. After 12 weeks, 18/64 (28.1%) patients in the SOC group without TOT achieved primary healing, compared with 36/81 (44.4%) patients in the SOC group with TOT (p = 0.044). Subsequently, there was a significant reduction in wound diameter between the SOC group without TOT vs. the SOC group with TOT, with reductions of 40% and 70%, respectively (p = 0.005). Based on these findings, conclusions were drawn about the efficacy of TOT in DFUs [10].

Mechanical therapies

Negative pressure wound therapy (NPWT)

Negative pressure wound therapy facilitates the healing process by applying subatmospheric pressure directly to the wound bed. The system is composed of a foam dressing, a semi-occlusive dressing, and a device for exudate removal. The effectiveness of VAC therapy is attributed to four primary mechanisms: macrodeformation (where applied negative pressure compresses the foam and contributes to wound size reduction), microdeformation (which stimulates cell proliferation, angiogenesis, and the formation of granulation tissue), removal of excess wound fluid (as continuous suction decreases interstitial oedema) and stabilisation of the wound environment (allowing dressing changes to be performed at intervals of approximately 2–3 days).

Vacuum-assisted closure (VAC)

Research by Blume et al. [11] found that complete wound closure was achieved in 43.2% of diabetic foot ulcers treated with VAC, whereas full re-epithelialisation occurred in only 28.9% of cases managed with advanced moist wound therapy. The authors also reported a lower incidence of secondary amputations in the NPWT group (4.1%) than in patients receiving standard wound care (10.2%). Moreover, treatment duration was reduced with the application of VAC therapy. Similarly, Armstrong et al. demonstrated that negative pressure wound therapy led to complete healing in 56% of diabetic foot ulcers, compared with 39% in patients treated with conventional moist wound care methods [12].

Biological therapies

Growth factors

DFUs present significant challenges due to impaired healing processes associated with diabetes. This is corroborated by studies indicating that DFUs are a common complication in patients with diabetes, often lead-

ing to prolonged healing times and an increased risk of infection.

Recent therapeutic approaches have focused on the application of growth factors, such as nerve growth factor (NGF) and becaplermin – a recombinant human platelet-derived growth factor (PDGF-BB) – to enhance wound healing. Research has demonstrated that the topical application of growth factors such as PDGF-BB can accelerate wound healing in patients with DFUs [13].

Nerve growth factor (NGF)

DW, particularly DFUs, pose significant clinical challenges due to delayed healing caused by impaired vascularisation, chronic inflammation, and neuropathy. Standard treatments often fail to restore tissue integrity, necessitating novel therapeutic strategies. One promising approach involves the use of NGF, a neurotrophic factor known for its regenerative properties.

NGF plays a crucial role in skin repair by promoting cellular proliferation and angiogenesis, and modulating the inflammatory response. It interacts with specific receptors, primarily tropomyosin receptor kinase A (TrkA) and the p75 neurotrophin receptor (p75NTR), triggering intracellular signalling pathways essential for wound healing [14].

- Cell proliferation and migration. NGF enhances keratinocyte and fibroblast activity, accelerating the re-epithelialisation process. Studies have demonstrated that NGF-stimulated fibroblasts produce extracellular matrix components that contribute to tissue remodelling and structural integrity.
- Enhancement of angiogenesis. Blood vessel formation is crucial for oxygen and nutrient supply to the wound site. NGF has been shown to upregulate vascular endothelial growth factor (VEGF), leading to improved angiogenesis and enhanced tissue regeneration.
- Inflammation regulation. Chronic inflammation is a major barrier to effective DW healing. NGF modulates the immune response by reducing excessive inflammatory cytokine production while stimulating anti-inflammatory pathways. This effect helps create an environment conducive to wound closure.

Experimental and Clinical Applications of NGF: Recent studies highlight the potential of NGF in DW management [14]:

- Topical NGF application: Clinical trials have shown that NGF-based formulations significantly improve healing rates in DFUs by promoting granulation tissue formation and reducing healing time.
- NGF-loaded hydrogels: Biomaterial research has led to the development of NGF-embedded hydrogels that provide sustained release, enhancing nerve regeneration and reducing inflammation.
- Combination therapies: NGF combined with antioxidant compounds, such as carnosine, has demonstrated enhanced healing outcomes by addressing oxidative stress and neurodegeneration in DW.

Becaplermin (PDGF)

Chronic DWs, particularly DFUs, present a significant challenge in clinical management due to impaired healing processes associated with diabetes. Growth factor therapy has emerged as a promising approach, with becaplermin (recombinant human platelet-derived growth factor-BB, rhPDGF-BB) being the only FDA-approved growth factor treatment specifically designed to enhance wound healing in patients with diabetes. This section explores the mechanism of action, clinical efficacy, and potential risks associated with becaplermin therapy.

Becaplermin, a recombinant form of PDGF-BB, plays a critical role in wound healing by stimulating fibroblast proliferation, collagen synthesis, and angiogenesis. PDGF-BB binds to its receptors on fibroblasts and other mesenchymal cells, promoting cell migration and extracellular matrix production, which are essential for granulation tissue formation and re-epithelialisation. Studies have demonstrated that PDGF-BB also enhances the recruitment of macrophages and neutrophils, facilitating a pro-healing inflammatory response [15].

Clinical trials have evaluated the effectiveness of becaplermin in accelerating DFU healing. A meta-analysis of randomised controlled trials reported that topical application of becaplermin gel significantly increased the rate of complete ulcer closure compared with standard wound care alone. One study demonstrated that becaplermin-treated wounds achieved complete closure approximately 32% faster than those in the control group, reducing the risk of amputation. Furthermore, a long-term observational study suggested that the use of becaplermin in combination with good wound care practices leads to improved limb salvage rates [16].

Despite its efficacy, the use of becaplermin requires careful consideration of potential risks. A retrospective analysis found a slightly increased risk of malignancy among patients who used multiple tubes of becaplermin, prompting a black box warning from the FDA. Although no direct causality relationship has been established, clinicians are advised to avoid using becaplermin in patients with known malignancies or those at high risk of malignancy. Additionally, some studies have reported local adverse reactions, such as erythema, pruritus, and mild pain at the application site [15].

Stem cell therapies

Stem cells obtained from various sources can be used for wound repair and regeneration. These include endothelial progenitor cells (EPCs), bone marrow-derived mesenchymal stem cells (BM-MSCs), adipose tissue stem cells (ASCs), dermal stem cells (DSCs), and induced pluripotent stem cells (iPS). Stem cell transplantation is a promising therapeutic option for treating hard-to-heal wounds, as transplanted cells can differentiate and provide growth factors, leading to improved angiogenesis, lower treatment costs, and an improved quality of life for patients. Recent studies have focused on the mechanism, applications, and clinical trials. Key areas of research include MSCs, exosomes, and biomaterials [17].

MSCs have a multidirectional effect in DFU therapy, contributing to improved blood supply, epidermal regeneration, cell recruitment to the wound, modulation

of the immune response, and reduction of inflammation. However, the efficacy of MSC therapy in DFUs may be limited by hyperglycaemia and chronic inflammation, which can negatively affect the survival and function of MSCs. Therefore, controlling glucose levels and inflammation is an important aspect of DFU therapy with MSCs [18]. MSCs can be obtained from tissues such as bone marrow and umbilical cord, with umbilical cord mesenchymal stem cells (UCMSCs) being obtainable without invasive surgery and having a higher proliferation capacity than bone marrow-derived cells [18].

Apoptotic extracellular vesicles (ApoEVs) of mesenchymal stem cells (MSCs) are extracellular vesicles produced by apoptotic MSCs that can induce tissue regeneration. The mechanism of action of ApoEVs involves inhibition of macrophage pyroptosis at the wound site. A study by Wang et al. showed that ApoEVs-UCMSCs significantly improved wound healing in mice with DM2, as demonstrated by a reduction in wound area and an increased healing rate. Animal studies have confirmed the ability of MSCs to improve blood flow and neovascularisation under ischaemic conditions and to reduce the surface area of chronic lower extremity wounds. Song et al. also tested hydrogel products containing exosomes derived from adipocytes. The hydrogel structure provides a controlled release of exosomes, contributing to a long-lasting therapeutic effect [18]. The mechanisms of action of MSCs are presented in Figure 2.

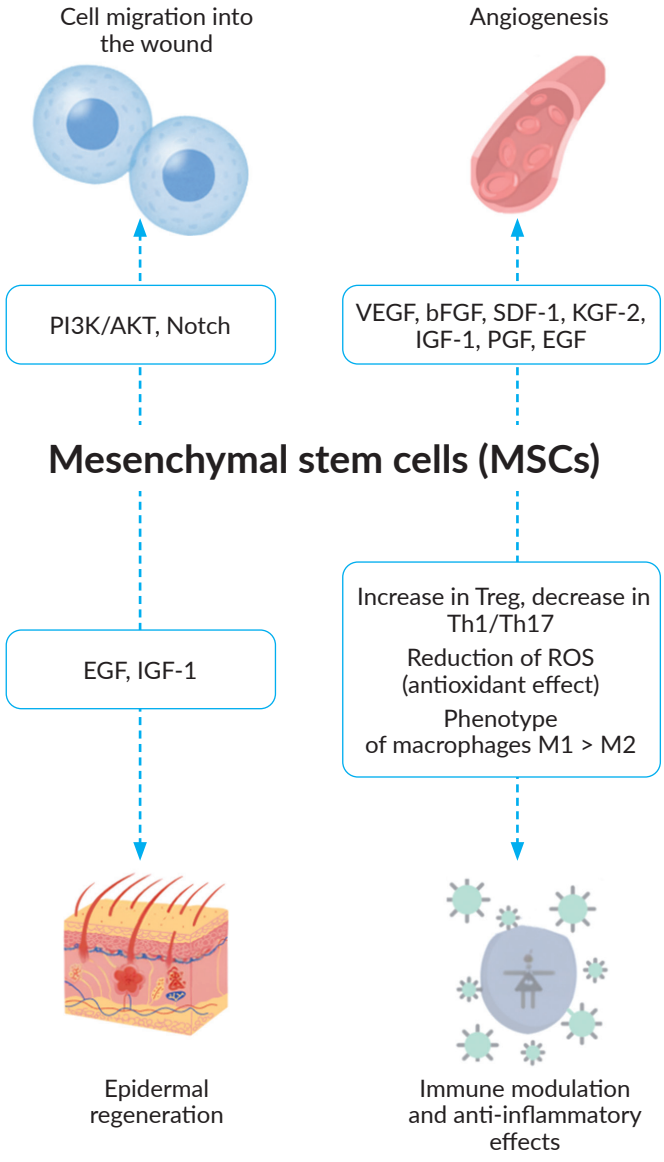

Figure 2. Mechanisms of action of MSCs [18]

Platelet-derived therapies

The International Working Group on the Diabetic Foot (IWGDF) recommends against the use of autologous platelet therapy (including platelets from a blood bank) as an adjunctive therapy to standard care, except for autologous leukocyte-platelet and fibrin patches. This recommendation is based on the high risk of bias and methodological issues identified in studies of platelet gel and PRP, which currently preclude the implementation of these therapies in routine clinical practice [19].

Platelet-rich plasma (PRP)

PRP is a therapeutic method that involves collecting a blood sample by venepuncture and then extracting platelet-enriched plasma, which is subsequently injected intradermally or subcutaneously into the patient. Applied PRP enhances the release of growth factors, cytokines, chemokines and extracellular vesicles (EVs) from platelets, which can subsequently be stimulated using various methods of activation. Unlike the now widespread use of autologous PRP, PRP-derived exosomes obtained from donor mixtures from a pool of healthy individuals with precisely defined biological characteristics may be more effective in treating wounds, particularly those that are difficult to heal, such as diabetic ulcers.

A study investigating the effects of human platelet-rich plasma (hPRP) on canine mesenchymal stem cells (cMSCs) showed that hPRP stimulated the proliferation and migration of cMSCs and increased the levels of phosphorylated ERK, AKT/PKB, and FAK proteins in cMSCs, suggesting that factors released from hPRP activate various cell survival- and migration-related signalling pathways. The study also highlighted that aquaporins (AQP1 and AQP5) play a key role in hPRP-induced cMSC migration. These findings suggest the potential use of hPRPs in regenerative stem cell therapies, including wound healing [20].

Abdel Hafez et al. provided evidence for the beneficial effects of PRP in the treatment of diabetic cardiomyopathy in rats. Treatment with PRP preparations improved biochemical parameters associated with diabetes and cardiac damage, reduced oxidative stress in cardiac tissue, increased cardiomyocyte proliferation, and decreased fibroblast proliferation, potentially reducing fibrosis [21].

Platelet gel

Activated platelet gel (APG) is a preparation made from isolated platelets obtained from blood drawn from a patient or donor. The resulting platelet concentrate is then activated, leading to the release of growth factors and other substances from the platelets that are important for healing and tissue regeneration. Various factors can

be used for activation, such as calcium chloride or thrombin. The activated platelet concentrate is then converted into a gel that can be readily applied to the wound.

Platini et al. showed that APG is an effective and safe adjunctive treatment for DFUs in the elderly, accelerating healing (with a 1.38-fold higher healing rate than conventional treatment), reducing hospitalisation time (by an average of 16.97 days) and potentially reducing the risk of infection and amputation compared with traditional treatments. However, some results were characterised by heterogeneity and a lack of statistical significance for certain parameters, requiring careful interpretation [22].

Olszewska et al. presented an in vitro study of human keratinocytes to assess the effects of PRP and RAPID biodynamic haematogel (RBH) on cell growth. The results showed that both PRP and RBH stimulated the growth of human keratinocytes compared with a negative control (medium without additives), with RBH showing a stronger effect. RBH is an autologous platelet-rich and leukocyte product developed by Biotherapy Services. It is manufactured using a point-of-care (POC) system, allowing clinicians to produce RAPID gel at the bedside. As an autologous product, it minimises safety concerns [23].

Autologous platelet products

- Platelet-rich fibrin (PRF)

PRF is an autologous platelet concentrate consisting of a fibrin matrix rich in platelets and leukocytes. Unlike PRP, PRF is produced without the use of anticoagulants or activating factors of bovine origin (such as thrombin), making it an all-natural, autologous biocomposite. PRF is gaining an advantage over recombinant growth factors in the treatment of musculoskeletal injuries [24].

- Human platelet lysate (hPL)

hPL is a biological compound produced by the disintegration (lysis) of human platelets and the release of their contents.

Unlike PRP or APG, in which platelets are preserved intact and activated, hPL is produced by deliberately disrupting the platelets, as the lysis process releases their entire contents, including growth factors stored in platelet α-granules. Low concentrations of autologous hPL (5% and 10%) are most effective in stimulating the migration of human keratinocytes while having a less inhibitory effect on cell proliferation. Higher concentrations (e.g. 20%) may have a cytotoxic effect [25]. Alhawari et al. showed that treatment efficacy, as measured by wound area reduction, was significantly higher in the hPL group than in the placebo group treated with platelet-poor plasma (PPP). In the hPL group, 9 of 10 patients (90%) achieved complete healing within 12 weeks or sooner [26]. A summary of platelet-derived products used in DW therapy is presented in Table 1.

Tissue engineering approaches

Hydrogels

Stem-cell-loaded hydrogels

DWs are particularly challenging to treat because of the persistent inflammatory state that disrupts normal healing. Various stem cell populations, including embryonic stem cells, induced pluripotent stem cells, and MSCs, have been explored for their regenerative potential. Among these, MSCs support wound repair by reducing oxidative stress and enhancing angiogenesis. However, their therapeutic effectiveness may be limited when administered via direct injection, as this approach can impair cell viability and function.

Hydrogels have therefore gained attention as advanced wound dressings because of their biocompatibility, ability to maintain a moist environment, and structural resemblance to the native extracellular matrix. Their three-dimensional architecture provides a protective niche for stem cells under the hostile inflammatory and oxidative conditions characteristic of diabetic wounds, while also minimising the adverse effects associated with direct cell delivery. Several strategies for hydrogel-based stem cell

Table 1. Summary of platelet-derived products in DW therapy

Product	Characteristics	Mechanism of action	Application	Research and effectiveness
Activated platelet gel (APG)	Gel derived from activated platelets	Releases growth factors to promote healing	Treatment of wounds including diabetic ulcers	Reduces the length of hospitalisation, accelerates wound healing, and may reduce the risk of infection and amputation (Platini et al.) [22].
Platelet-rich plasma (PRP)	Platelet-rich plasma obtained from the patient's blood and administered by injection	Stimulates the secretion of cytokines, chemokines, and growth factors	Tissue regeneration, wound healing, cell therapy	Improves wound healing and muscle regeneration; donor-derived PRP may be more effective in treating hard-to-heal wounds (Abdel Hafez et al.) [21].
Platelet-rich fibrin (PRF)	Natural autologous concentrate of platelets and leukocytes without anticoagulants	Forms a fibrin matrix to promote healing and regeneration	Treatment of musculoskeletal injuries, tissue regeneration	May outperform recombinant growth factors in treating musculoskeletal injuries (Narayanaswamy et al.) [24].
Human platelet lysate (hPL)	Product obtained by the lysis of platelets, resulting in the release of their contents	Stimulates skin cell migration and proliferation	Wound therapy, tissue regeneration	Low concentrations (5–10%) stimulate keratinocyte migration, high concentrations may be cytotoxic (Alhawari et al.) [26].

application have been developed, including preformed hydrogel patches, injectable in situ–gelling systems, and hydrogel microspheres. Of these, microsphere-based hydrogels offer a greater surface area, improved distribution, and enhanced functional versatility, enabling efficient cell delivery to the wound site. Consequently, stem cell–loaded hydrogel microspheres are considered a promising approach for future clinical use.

Although combined hydrogel–MSC therapies show substantial promise in DW management, the high plasticity of MSCs presents clinical challenges. While their multilineage differentiation capacity underpins their regenerative potential, it also raises concerns about possible tumour formation, which must be carefully addressed [27].

Desferrioxamine-laden silk nanofiber hydrogels

Impaired angiogenesis and persistent inflammation are key factors contributing to the development and poor healing of DFUs. Desferrioxamine (DFO), known for its pro-angiogenic properties, has been applied clinically in DFU management, although it typically requires repeated injections. To enhance therapeutic efficacy, sustained-release, biocompatible delivery systems for DFO have been proposed. In vitro studies demonstrated that silk nanofibre-based hydrogels incorporating DFO influence endothelial cell migration and gene expression, while also modulating macrophage inflammatory responses. These findings were further validated in diabetic wound models in vivo, where DFO-loaded hydrogels reduced abnormal vascularisation and chronic inflammation, leading to faster wound closure and enhanced collagen formation [28].

Diabetic wounds are difficult to repair, primarily due to insufficient blood vessel formation within the injured tissue. Increasing evidence indicates that DFO enhances the activity of hypoxia-inducible factor-1α (HIF-1α), which in turn stimulates the production of pro-angiogenic growth factors and supports neovascularisation. Based on this mechanism, a synergistic interaction between BG and DFO has been proposed to further enhance VEGF expression. Studies have shown that sodium alginate hydrogels incorporating both BG and DFO are more effective in promoting diabetic wound closure than formulations containing either component alone. This improved outcome is attributed to the cooperative upregulation of HIF-1α and VEGF, leading to enhanced vascularisation of the wound site [29].

Matrices

Acellular dermal matrix (ADM)

ADM is a biomaterial obtained by removing cells from human skin while preserving its extracellular structure, allowing its use as a scaffold in tissue engineering.

A study published in the *Journal of Surgical Research* in 2022 evaluated the effect of a morphologically transformed decellularised dermal matrix (ADM) on chronic DWs in rats. The results showed that the application of ADM significantly accelerated the wound healing process, increasing the rate of tissue regeneration compared with the control group. Furthermore, an improvement in the quality of newly formed skin tissue was observed, indicating the potential of ADM in the treatment of chronic wounds in diabetic patients [30].

Gormley et al. 2022 evaluated the efficacy of foetal bovine acellular dermal matrix (FBADM) in the treatment of severe DFUs in patients with chronic limb ischaemia. The use of FBADM in the treatment of these wounds contributed to a significant acceleration of the healing process, compared with traditional dressings, which may reduce the risk of amputation. In addition, FBADM showed a positive effect on the reconstruction of the dermal layer, promoting faster wound closure [31].

Bilayer reconstituted matrix

Decellularised, purified, reconstituted bilayer matrix (DPRBM) is a biomaterial derived from animal tissues from which cells, lipids, and antigens have been removed, leaving a protein structure similar to that of the human dermis. It consists of two layers: an upper, compact layer that acts as a barrier and a lower, porous layer that promotes cell migration and proliferation. Thanks to these properties, DPRBM promotes natural wound healing processes by providing an appropriate environment for tissue regeneration [32].

Stromal vascular fraction (SVF) gel

SVF gel is an autologous preparation obtained from adipose tissue that contains concentrated stem cells and natural extracellular matrix. It is used in wound therapy to promote healing and tissue regeneration. A study published in the *Journal of Surgical Research* in 2018 evaluated the therapeutic effects of ECM/SVF gel on wound healing and the mechanisms underlying this process. The gel was shown to promote wound healing by accelerating re-epithelialisation, reducing fibrosis and adhesions, and stimulating cilia formation, suggesting its potential in wound healing [33].

Skin substitutes

An article by Vecin and Kirsner published in 2023 discussed the efficacy of various skin substitutes in the treatment of chronic DW. Biological products, such as Apligraf and Dermagraft, promote regeneration by providing living cells that stimulate angiogenesis. Integra and Matriderm, as acellular matrices, create a temporary scaffold for new tissue formation. Studies indicate that, in certain cases, the best results are obtained with substitutes containing growth factors and stem cells, which significantly accelerate healing and reduce complications [34].

Wound dressings

Sucrose octasulphate (TLC-NOSF) dressings are specialised materials used in the treatment of chronic wounds, such as diabetic and venous ulcers. They work by modulating the wound microenvironment, thereby promoting the healing process and improving patients' quality of life. An article published in the journal *Hautarzt* in 2020 presented evidence for the efficacy of sucrose octasulphate dressings (TLC-SOS) in the treatment of chronic wounds,

including DFUs. The EXPLORER study, involving 240 patients with neurovascular DFUs, found that the use of TLC-SOS dressings significantly accelerated wound healing compared with neutral dressings. Furthermore, an analysis of data from eight observational studies involving a total of 10,220 patients with chronic wounds of various origins showed that TLC-SOS dressings effectively promote the healing process, which may lead to faster tissue regeneration and a reduced risk of complications associated with chronic diabetic ulcers [35].

Discussion

The efficacy of various wound-cleansing solutions compared with normal saline has been the subject of systematic reviews. One such review indicated that solutions like Dakin's solutions and chloramines, as well as hypertonic saline, may enhance ulcer healing compared with normal saline or standard treatment. However, the studies reviewed were of low quality with a high risk of bias, underscoring the need for more rigorous research to draw definitive conclusions [9].

Despite its promising therapeutic benefits, NGF-based treatments face challenges related to stability, effective delivery, and potential side effects. Future research should focus on optimising controlled-release systems, such as nanocarriers or bioengineered scaffolds, to maximise NGF efficacy in wound healing [14].

Although becaplermin remains the most widely used PDGF-based therapy, ongoing research is exploring alternative growth factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), for their potential synergistic effects in wound healing. Combining PDGF with other regenerative approaches, such as stem cell therapy or biomaterial scaffolds, may further optimise outcomes for patients with chronic DWs [15].

Becaplermin represents a significant advancement in the treatment of chronic DWs by leveraging the regenerative properties of PDGF-BB. While clinical evidence supports its efficacy in promoting wound closure, its use should be carefully tailored to individual patient risk profiles. Future research should focus on optimising combination therapies that harness the full potential of growth factors while mitigating potential adverse effects.

Due to IWGDF's position on autologous platelet therapy, researchers are taking steps to improve the quality of research, apply reporting standards, incorporate relevant clinical and economic considerations, and use more innovative research methodologies to generate more reliable and useful evidence on the efficacy and effectiveness of various DFU therapies in the future [19]. Studies of the cost-effectiveness of such therapies are also lacking, but those available indicate that they may not be cost-effective compared with standard therapies [20].

Conclusions

Chronic diabetic wounds are a serious clinical problem affecting an increasing number of patients. The approach to treatment should be multidisciplinary and individualised to the needs of each patient. There are many methods for treating DFUs; however not all of them have been sufficiently studied to support their safe and reliable use in patients.

Author contributions

Dominika Żyła – conceptualisation, original draft preparation, visualisation, investigation, methodology, writing, review, and editing; Katarzyna Zych – visualisation, writing, review, and editing; Jakub Jagiełło – methodology, writing, review, and editing; Milena Krawczyk – writing, review, and editing; Adam Jakubas – writing, review, and editing. All authors have read and agreed to the published version of the manuscript.

References

1. Burgess JL, Wyant WA, Abdo Abujamra B, et al. Diabetic wound-healing science. Medicina (Kaunas), 2021; 57(10): 1072. doi: 10.3390/medicina57101072
2. Oyebode OA, Jere SW, Houreld NN. Current therapeutic modalities for the management of chronic diabetic wounds of the foot. J Diabetes Res, 2023; 2023: 1359537. doi: 10.1155/2023/1359537
3. Holl J, Kowalewski C, Zimek Z, et al. Chronic diabetic wounds and their treatment with skin substitutes. Cells, 2021; 10(3): 655. doi: 10.3390/cells10030655
4. Armstrong DG, Tan TW, Boulton AJM, Bus SA. Diabetic foot ulcers: a review. JAMA, 2023; 330(1): 62–75. doi: 10.1001/jama.2023.10578
5. Bandyk DF. The diabetic foot: Pathophysiology, evaluation, and treatment. Semin Vasc Surg, 2018; 31(2–4): 43–48. doi: 10.1053/j.semvascsurg.2019.02.001
6. Boulton AJM, Armstrong DG, Kirsner RS, et al. Diagnosis and management of diabetic foot complications. Arlington (VA): American Diabetes Association; 2018.
7. Martínez-De Jesús FR, Ramos-De la Medina A, Remes-Troche JM, et al. Efficacy and safety of neutral pH superoxidised solution in severe diabetic foot infections. Int Wound J, 2007; 4(4): 353–362. doi: 10.1111/j.1742-481X.2007.00363.x
8. Grealy L, Wilson P, Gillen C, et al. Immersion of debrided diabetic foot ulcer tissue in electrochemically generated pH neutral hypochlorous acid significantly reduces the microbial bioburden: whole-genome sequencing of Staphylococcus aureus, the most prevalent species recovered. J Hosp Infect, 2023; 138: 42–51. doi: 10.1016/j.jhin.2023.06.006
9. Capó X, Monserrat-Mesquida M, Quetglas-Llabrés M, et al. Hyperbaric oxygen therapy reduces oxidative stress and inflammation, and increases growth factors favouring the healing process of diabetic wounds. Int J Mol Sci, 2023; 24(8): 7040. doi: 10.3390/ijms24087040
10. Serena TE, Bullock NM, Cole W, et al. Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. J Wound Care, 2021; 30(Sup5): S7–S14. doi: 10.12968/jowc.2021.30.Sup5.S7
11. Blume PA, Walters J, Payne W, et al. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes Care, 2008; 31(4): 631–636. doi: 10.2337/dc07-2196
12. Normandin S, Safran T, Winocour S, et al. Negative pressure wound therapy: mechanism of action and clinical applications. Semin Plast Surg, 2021; 35(3): 164–170. doi: 10.1055/s-0041-1731792.

13. Sridharan K, Sivaramakrishnan G. Growth factors for diabetic foot ulcers: mixed treatment comparison analysis of randomized clinical trials. Br J Clin Pharmacol, 2018; 84(3): 434–444. doi: 10.1111/bcp.13470
14. Ji X, Zhou J, Zhou Z, et al. Recovering skin-nerve interaction by nanoscale metal-organic framework for diabetic ulcers healing. Bioact Mater, 2024; 42: 112–123. doi: 10.1016/j.bioactmat.2024.08.024
15. Chen M, Chang C, Levian B, et al. Why are there so few FDA-approved therapeutics for wound healing? Int J Mol Sci, 2023; 24(20): 15109. doi: 10.3390/ijms242015109
16. Loveland JD, McMillen RL, Cala MA. A multicenter, retrospective, case series of patients with charcot neuroarthropathy deformities undergoing arthrodesis utilizing recombinant human platelet-derived growth factor with beta-tricalcium phosphate. J Foot Ankle Surg, 2021; 60(1): 74–79. doi: 10.1053/j.jfas.2020.08.030
17. Ma K, Luo C, Du M, et al. Advances in stem cells treatment of diabetic wounds: A bibliometric analysis via CiteSpace. Skin Res Technol, 2024; 30(4): e13665. doi: 10.1111/srt.13665
18. Song Y, You Y, Xu X, et al. Adipose-derived mesenchymal stem cell-derived exosomes biopotentiated extracellular matrix hydrogels accelerate diabetic wound healing and skin regeneration. Adv Sci (Weinh). 2023; 10(30): e2304023. doi: 10.1002/advs.202304023
19. Chen P, Vilorio NC, Dhatariya K, et al. Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update). Diabetes Metab Res Rev, 2024; 40(3): e3644. doi: 10.1002/dmrr.3644
20. Parascandolo A, Di Tolla MF, Liguoro D, et al. Human platelet-rich plasma regulates canine mesenchymal stem cell migration through aquaporins. Stem Cells Int, 2023; 2023: 8344259. doi: 10.1155/2023/8344259
21. Abdel Hafez SMN, Zenhom NM, Abdel-Hamid HA. Effects of platelet rich plasma on experimentally induced diabetic heart injury. Int Immunopharmacol, 2021; 96: 107814. doi: 10.1016/j.intimp.2021.107814. Erratum in: Int Immunopharmacol. 2024; 133: 112089. doi: 10.1016/j.intimp.2024.112089
22. Platini H, Adammayanti KA, Maulana S, et al. The potential of autologous platelet-rich plasma gel for diabetic foot ulcer care among older adults: a systematic review and meta-analysis. Ther Clin Risk Manag, 2024; 20: 21–37. doi: 10.2147/TCRM.S433033
23. Olszewska A, Duan J, Javorovic J, et al. Manufacture and initial characterisation of RAPID™ biodynamic haematogel, an autologous platelet and leukocyte-rich plasma gel for diabetic foot ulcers. Gels, 2024; 10(9): 572. doi: 10.3390/gels10090572
24. Narayanaswamy R, Patro BP, Jeyaraman N, et al. Evolution and clinical advances of platelet-rich fibrin in musculoskeletal regeneration. Bioengineering (Basel), 2023; 10(1): 58. doi: 10.3390/bioengineering10010058
25. Jafar H, Hasan M, Al-Hattab D, et al. Platelet lysate promotes the healing of long-standing diabetic foot ulcers: A report of two cases and *in vitro* study. Heliyon, 2020; 6(5): e03929. doi: 10.1016/j.heliyon.2020.e03929
26. Alhawari H, Jafar H, Al Soudi M, et al. Perilesional injections of human platelet lysate versus platelet poor plasma for the treatment of diabetic foot ulcers: A double-blinded prospective clinical trial. Int Wound J, 2023; 20(8): 3116–3122. doi: 10.1111/iwj.14186
27. Huang JN, Cao H, Liang KY, et al. Combination therapy of hydrogel and stem cells for diabetic wound healing. World J Diabetes, 2022; 13(11): 949–961. doi: 10.4239/wjd.v13.i11.949
28. Ding Z, Zhang Y, Guo P, et al. Injectable desferrioxamine-laden silk nanofiber hydrogels for accelerating diabetic wound healing. ACS Biomater Sci Eng, 2021; 7(3): 1147–1158. doi: 10.1021/acsbiomaterials.0c01502
29. Kong L, Wu Z, Zhao H, et al. Bioactive injectable hydrogels containing desferrioxamine and bioglass for diabetic wound healing. ACS Appl Mater Interfaces. 2018; 10(36): 30103–30114. doi: 10.1021/acsami.8b09191
30. Kim MJ, Lee WB, Park BY. Effect of morphologically transformed acellular dermal matrix on chronic diabetic wounds: an experimental study in a calvarial bone exposure diabetic rat model. J Surg Res, 2022; 272: 153–165. doi: 10.1016/j.jss.2021.11.009
31. Gormley S, Hart O, French S, et al. The use of fetal bovine acellular dermal matrix in severe diabetic foot ulceration and threatened limbs with tissue loss the use of FBADM as an adjunct for complex wounds. Vascular, 2024; 32(3): 619–625. doi: 10.1177/17085381221141115
32. Armstrong DG, Orgill DP, Galiano RD, et al. Use of a purified reconstituted bilayer matrix in the management of chronic diabetic foot ulcers improves patient outcomes vs standard of care: Results of a prospective randomised controlled multi-centre clinical trial. Int Wound J, 2022; 19(5):1197–1209. doi: 10.1111/iwj.13715
33. Sun M, He Y, Zhou T, et al. Adipose extracellular matrix/stromal vascular fraction gel secretes angiogenic factors and enhances skin wound healing in a murine model. Biomed Res Int, 2017; 2017: 3105780. doi: 10.1155/2017/3105780
34. Vecin NM, Kirsner RS. Skin substitutes as treatment for chronic wounds: current and future directions. Front Med (Lausanne), 2023; 10: 1154567. doi: 10.3389/fmed.2023.1154567
35. Dissemond J, Augustin M, Dietlein M, et al. Sucrose Octasulfat – Evidenz in der Behandlung chronischer Wunden [Sucrose octasulfate-evidence in the treatment of chronic wounds]. Hautarzt. 2020; 71(10): 791–801. German. doi: 10.1007/s00105-020-04637-9

REVIEW ARTICLE

WOUND HEALING, FORMATION OF HYPERTROPHIC SCARS AND KELOIDS, AND THEIR TREATMENT METHODS – A LITERATURE REVIEW

Gojenie ran, powstawanie blizn przerostowych i keloidów oraz metody ich leczenia – przegląd literatury

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Abstract

Background: This article reviews current knowledge on the pathogenesis and process of wound healing, highlighting the differences between scar types. It discusses the pathogenesis and characteristics of hypertrophic scars and keloids, along with therapeutic approaches, including adjuvant, targeted, and non-targeted therapies. Psychological aspects and their impact on patients' lives are also addressed. **Methods:** A comprehensive literature search was conducted in the PubMed and Cochrane databases to identify articles on scar pathogenesis and treatment methods, published between 2007 and 2025. **Results:** The wound healing process is complex and multistage, involving inflammation, proliferation, angiogenesis, and extracellular matrix remodelling. Various cells (including fibroblasts and immune cells) and growth factors such as TGF-β, PDGF, and VEGF, participate in this process. Disruptions to healing can lead to the formation of pathological scars, including keloids and hypertrophic scars. Despite advances in therapeutic approaches, the mechanisms underlying their formation are not fully understood. The best clinical outcomes are achieved through combination therapy. **Conclusion:** A wound represents a disruption of skin integrity, and its healing is a dynamic, multistage process encompassing inflammation, proliferation, cell migration, angiogenesis, remodelling, and extracellular matrix synthesis. Healing engages immune cells, connective tissue, epithelial cells, inflammatory mediators, and the vascular system. Abnormalities can lead to pathological scarring. The mechanisms of scar formation remain unclear, which complicates effective management. Hypertrophic scars and keloids, often occurring in high-tension areas, are particularly challenging. Scars cannot be completely eliminated, and no single therapy is universally effective; combined methods yield the best results.

Streszczenie

Wprowadzenie: Niniejszy artykuł stanowi przegląd aktualnej wiedzy na temat patogenezy i procesu gojenia ran. Omówiono różnice między poszczególnymi rodzajami blizn. Przedstawiono również patogenezę i charakterystykę blizn przerostowych oraz keloidów, a także podejścia terapeutyczne, w tym terapie wspomagające, ukierunkowane i nieukierunkowane. Omówiono także aspekty psychologiczne i ich wpływ na życie pacjentów. **Metody:** Przeszukano literaturę w bazach PubMed i Cochrane w celu zidentyfikowania artykułów dotyczących patogenezy blizn i metod ich leczenia, opublikowanych w latach 2007–2025. **Wyniki:** Proces gojenia jest złożony i wieloetapowy. Obejmuje stan zapalny, proliferację, angiogenezę i przebudowę macierzy zewnątrzkomórkowej. W procesie tym biorą udział różne komórki, w tym fibroblasty i komórki odpornościowe, a także czynniki wzrostu, takie jak TGF-β, PDGF i VEGF. Zaburzenia procesu gojenia mogą prowadzić do powstawania blizn patologicznych, w tym keloidów i blizn przerostowych. Pomimo rozwoju metod terapeutycznych mechanizmy ich powstawania nie są w pełni poznane. Najlepsze wyniki leczenia osiąga się dzięki terapii skojarzonej. **Wniosek:** Rana stanowi uszkodzenie ciągłości skóry, a jej gojenie jest dynamicznym, wieloetapowym procesem, obejmującym stan zapalny, proliferację, migrację komórek, angiogenezę, przebudowę i syntezę macierzy zewnątrzkomórkowej. W procesie

gojenia biorą udział komórki odpornościowe, tkanka łączna, komórki nabłonkowe, mediatory stanu zapalnego i układ naczyniowy. Nieprawidłowości w procesie gojenia mogą prowadzić do powstawania blizn patologicznych. Mechanizmy powstawania blizn pozostają niejasne, co utrudnia ich skuteczne leczenie. Blizny przerostowe i keloidy, często występujące w obszarach o dużym napięciu, stanowią szczególne wyzwanie terapeutyczne. Blizn nie można całkowicie usunąć i nie ma jednej terapii, która byłaby uniwersalnie skuteczna. Najlepsze wyniki daje połączenie różnych metod.

Keywords: keloids; wound healing; scars; hypertrophic scars; scar treatment

Słowa kluczowe: keloidy; gojenie ran; blizny; blizny przerostowe; leczenie blizn

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Wound healing process

The skin, composed of multiple tissues forming the body's outer covering, serves as a barrier against chemical, physical, and biological agents, regulates temperature, prevents water loss, supports immunity, and contributes to hormonal balance. Reparative processes within damaged tissues maintain organismal homeostasis [1]. The skin consists of three layers: the epidermis, dermis, and subcutaneous tissue. The epidermis contains densely packed keratinocytes with little extracellular matrix (ECM), whereas the dermis contains abundant ECM with dispersed fibroblasts as its principal cells, responsible for synthesising collagen that provides elasticity and strength. Type I collagen predominates in the dermis, and type IV collagen is characteristic of the basement membrane. Dermal proteoglycans, composed of glycosaminoglycans and proteins, bind water and interact with hyaluronic acid, maintaining turgor. The ECM is dynamic, undergoing continuous synthesis and degradation by enzymes such as metalloproteinases (MMPs), which are regulated by tissue inhibitors (TIMPs). Imbalance in these processes leads to pathological scarring. Fibroblast migration along the ECM, cell accumulation, and stem cell activity are crucial for wound repair, with cytokines also playing an active role [1–3].

Skin injuries result from physical, chemical, or thermal factors. Wounds, whether traumatic or surgical, trigger complex reparative mechanisms aimed at restoring structure and function [4]. Regeneration restores tissue without scarring, whereas healing replaces it with altered tissue. Wound healing progresses through three overlapping stages: inflammation, proliferation, and remodelling. Inflammation removes necrotic tissue and initiates haemostasis through clot formation [1–3]. Neutrophils and macrophages clear bacteria and release growth factors such as PDGF and TGF-β, which regulate fibroblast activity [1, 2, 5]. Fibroblasts produce collagen and differentiate into myofibroblasts that contract the wound, while epithelialisation restores the surface layer. The remodelling phase, which lasts up to a year, re-establishes tissue architecture [2, 5].

Healing depends on cytokines, growth factors, proteases, and ECM interactions. Disturbances in their balance can result in pathological scarring [2, 5, 6]. Key mediators include CTGF, TGF-β, PDGF, VEGF, IGF, EGF, and TNF-α. VEGF and PDGF initiate granulation and angiogenesis, while TNF-α and FGFs stimulate fibroblast and endothelial proliferation. ECM remodelling involves MMPs, and dysregulation of collagen deposition remains a major cause of impaired healing [5, 6].

Pathogenesis of hypertrophic scars and keloids

Hypertrophic scars and keloids arise from abnormal wound healing, which normally progresses through the inflammation, proliferation, and remodelling phases. Fibroblast migration, regulated by cytokines and stem cells, is a key element of tissue repair [1, 2, 7]. Scars, composed of fibrous connective tissue, replace damaged skin and reflect structural remodelling [2, 3]. Aberrant fibroblast and stem cell activity, along with dysregulated collagen deposition, underlie the development of hypertrophic and keloid scars [2, 5, 7].

An important aspect of scar pathogenesis not fully addressed in the original text is the role of collagen type III. Physiologically, the ratio of collagen I to III is tightly regulated during wound healing, with type III predominating in early proliferation and gradually replaced by type I during remodelling [2, 5, 7]. This transition ensures appropriate tissue elasticity and structural organisation. In hypertrophic scars and keloids, this balance is disrupted: type III collagen remains elevated, contributing to persistent stiffness, a disorganised ECM, and pathological scar maturation [2, 5, 7]. The abnormal persistence of collagen III, combined with excessive fibroblast activity and dysregulated TGF-β signalling, underlies the characteristic rigidity and raised appearance of these scars. TGF-β-activated fibroblasts drive excessive ECM and hypertrophy, while wounds healing without inflammation tend to scar less [5–8].

Mature scars differ from normal skin in elasticity, colour, and structure, lacking rete ridges, glands, and hair follicles,

and retaining capillaries for up to six months. Scarring reflects the balance between regeneration and restoration of the skin barrier [2, 3, 7]. Hypertrophic scars, confined to the wound area, usually develop around four weeks after injury [3, 7, 9]. Their formation involves excessive fibroblast activity, angiogenesis, delayed collagen breakdown, and chronic inflammation, with disorganised collagen and myofibroblast-mediated contracture [2, 5, 6, 8]. TGF-β overexpression, reduced MMP activity, and elevated CTGF and VEGF contribute to hypertrophy and delayed remodelling [5, 6, 10].

Keloids, in contrast, extend beyond the wound borders and do not regress [3, 7, 9, 11]. Their pathogenesis involves dysregulated fibroblast proliferation, impaired apoptosis, and abnormal ECM remodelling. A further critical element in scar pathophysiology is the role of myofibroblasts. These specialised fibroblasts mediate wound contraction through cytoskeletal tension and are normally removed by apoptosis during scar maturation. In hypertrophic scars and keloids, myofibroblasts persist abnormally, contributing to excessive contracture and raised scar morphology [2, 5, 12]. Their activation is strongly influenced by mechanical forces within the wound environment, including tension along skin lines, and is potentiated by TGF-β signalling, linking mechanotransduction to pathological ECM deposition. Dysregulated myofibroblast activity, together with aberrant persistence of collagen type III and fibroblast heterogeneity, underlies the characteristic rigidity, elevated contour, and functional impairment observed in hypertrophic and keloid scars [5, 7, 12]. Genetic predisposition also significantly contributes to keloid formation and abnormal scar healing. Variations in genes involved in TGF-β signalling, including TGF-β1 and TGFBR2, as well as polymorphisms in SMAD proteins and specific HLA alleles, have been associated with enhanced fibroblast proliferation, impaired apoptosis, and excessive ECM deposition. Moreover, keloids occur more frequently in individuals with certain connective tissue syndromes, such as Rubinstein-Taybi, Ehlers-Danlos, and Marfan syndrome, highlighting the influence of inherited abnormalities in collagen metabolism and tissue elasticity [5, 7, 9].

In addition, heterogeneity among keloid fibroblasts has been observed, with distinct subpopulations displaying variable collagen synthesis, cytokine responsiveness, and proliferative capacity, which may explain differences in scar morphology, growth patterns, and treatment response [12]. These genetic and cellular factors interact with environmental and mechanical cues, such as wound tension and local inflammation, to determine the severity and persistence of hypertrophic and keloid scars. Risk is higher in individuals of African, Asian, and Hispanic descent, especially during puberty or pregnancy, and is rare in albinos [7, 9, 11]. Influencing factors include wound tension, pigmentation, immune dysregulation, and genetic background, along with cytokines such as TGF-β, PDGF, VEGF, IL-1, IL-6, and TNF-α [6–9]. Scar formation is also influenced by age, skin type, hormones, nutrition, systemic disease, circulation, infection, and wound depth or location [3, 7, 9]. Remodelling begins around three weeks after wound closure, and mature scars typically become flat and pearly within a year. Hypertrophic and keloid scars are more common in younger patients due to heightened fibroblast activity. A single patient may present with various scar types, classified by shape, cause (surgical, inflammatory, traumatic, burn, or striae), or underlying mechanism [3, 7, 13].

Characteristics of hypertrophic scars and keloids

Hypertrophic scars are thick, red, and raised, but remain confined to the original injury site. They result from prolonged healing and excessive collagen synthesis, often following burns or impaired collagen metabolism, and are more common in individuals genetically predisposed to pathological healing [3, 7, 9]. These scars frequently develop in areas of high skin tension, such as the chest (sternum), shoulder blades, joints, and other regions with steep mechanical force gradients along skin tension lines, which promote excessive fibroblast activity and collagen deposition. High mechanical tension in these anatomical areas contributes to scar formation by stimulating fibroblast proliferation and increasing collagen synthesis, making hypertrophic scars more likely to develop and become pronounced [5–7]. They may negatively affect quality of life due to pain, itchiness, appearance, or functional impairment [4, 9, 11].

Keloids are raised scars that extend beyond the original wound borders and do not regress. They involve excessive deposition of collagen and glycosaminoglycans, and differ in collagen composition (types I and III) from normal skin. Keloids may form after injury or spontaneously, appearing as protruding nodules that grow from a central core and may reach several centimetres. Common symptoms include burning, itching, redness, tension, pain, and impaired mobility. Keloids typically occur on the chest, back, shoulders, and earlobes, and may also arise from minor injuries such as insect bites or injections. They are more frequent in younger individuals due to active fibroblast proliferation. Similar to hypertrophic scars, areas subjected to high mechanical forces and tissue tension, such as the chest, back, and joints, are particularly predisposed to keloid formation [5, 7, 9, 11, 14]. Mechanical stress in these regions amplifies fibroblast activity and excessive collagen deposition, contributing to the aggressive growth and protrusion characteristic of keloids [5–7].

Acne keloidalis increases the risk of both keloid and hypertrophic scarring. These lesions lack hair follicles, sebaceous glands and sweat glands, and show abnormal fibroblast activity, with increased synthesis of elastin, fibronectin, and proteoglycans, as well as an aberrant cytokine response. The overlying epidermis may appear normal or atrophic [8, 9]. A spontaneous form of keloid occurs in predisposed individuals, presenting with multiple foci and rich vascularisation during the growth phase, giving a pink or red appearance that gradually fades over time [9, 11].

Hypertrophic scars and keloids differ in their response to light- and energy-based treatments. Keloids, with higher vascularity and fibroblast activity, exhibit more pronounced inflammatory reactions, whereas hypertrophic scars are more localised [10, 15, 16]. In patients with darker skin phototypes (Fitzpatrick IV–VI), post-inflammatory hyperpigmentation is a common and clinically relevant complication, limiting the use of aggressive

laser modalities and medium- to deep-depth chemical peels [11, 15, 16]. Consequently, current reviews and clinical guidelines emphasise cautious patient selection, preference for less aggressive or fractional approaches, and individualised treatment protocols adjusted to scar type, anatomical location, and skin phototype to balance therapeutic efficacy with safety [11, 16].

According to Mustoe's classification, scars are divided as follows:
- Normal scar – pale, flat;
- Abnormal scar – painful, red, slightly raised above the surrounding skin;
- Linear hypertrophic scar – red, confined to the area of surgical incision, may be painful;
- Widespread hypertrophic scar – large, raised, flat, sometimes itchy;
- Small keloid – raised, localised, itchy, extends beyond the original wound;
- Large keloid – itchy or painful, large, raised, extends beyond the wound margins [14].

Scars can also be classified based on shape:
- Linear scars – the least visible, tend to fade quickly, typically occurring at surgical or traumatic incision sites;
- Atrophic scars – result from skin thinning; often caused by inflammation such as acne or chickenpox; may be singular or numerous;
- Hypertrophic scars – raised, firm, fibrotic thickening of various shapes and sizes, confined to the original area of trauma, surgery, inflammation, or burn;
- Keloids – typically occurring at sites of skin damage such as injections, surgeries, burns, or post-inflammatory lesions.

Scars may also be categorised by injury mechanism: post-surgical, post-burn, post-acne, post-traumatic, or striae. Another classification is based on aetiology: post-surgical, post-burn, post-inflammatory, or post-traumatic [3, 9, 14, 17].

Two main types of factors influence scar appearance:
- General factors: Fitzpatrick skin type, patient age, kidney or liver disease, diabetes, overall health, comorbidities, hormonal imbalances, nutrition, circulatory disorders, vitamin deficiencies.
- Local factors: neuropathy, impaired wound perfusion, wound infection, and the location, shape, depth, and width of the wound [7, 9, 11, 13].

In clinical practice and research, scar severity and treatment outcomes are commonly assessed using validated scar assessment scales. The Vancouver Scar Scale (VSS) focuses on observer-based evaluation of vascularity, pigmentation, pliability, and scar height, providing an objective measure of scar maturity and severity. In contrast, the Patient and Observer Scar Assessment Scale (POSAS) incorporates both clinician-rated parameters (including vascularity, pigmentation, thickness, surface roughness, and pliability) and patient-reported symptoms such as pain, pruritus, stiffness, and overall scar perception. The combined use of observer- and patient-based assessments allows for a more comprehensive evaluation of hypertrophic scars and keloids, particularly when monitoring therapeutic efficacy and impact on quality of life [14, 18, 19].

Therapeutic methods

Adjunctive therapy

Scar treatment depends on scar type, characteristics, and time since healing. Surgical correction is usually avoided during the first year, with conservative approaches such as massage, emollients, or specialised ointments used instead [4, 7, 13]. Recurrence rates are high with monotherapy. The aim of treatment is to reduce scar prominence and symptoms (e.g. pain, burning, restricted movement), particularly in visible areas that affect quality of life [7, 11, 18].

Flavonoids are plant-derived compounds used to prevent severe scar formation. Products such as gels and ointments containing flavonoids have shown variable efficacy. Quercetin, a flavonoid, may act by inducing MMP-1 or inhibiting SMAD2/3/4 expression [20].

Deep oscillation is a non-invasive technique using electrostatic fields to generate deep tissue vibrations that enhance fluid transport and tissue healing. Effective in early scar remodelling, it uses frequencies between 5 and 250 Hz. Reported benefits include improved blood flow, scar pigmentation, and elasticity. It is particularly useful after grafts, surgery, or trauma, and in cases where conventional mechanical therapy is contraindicated [21].

Laser therapy

Laser therapy has become the gold standard in scar management, used either alone or in combination with other modalities [4, 11, 16]. Ablative lasers (e.g. Er:YAG, CO_2) remove the epidermal and upper dermal layers, whereas non-ablative lasers (e.g. Er:Glass, PDL, diode, Nd:YAG) remodel collagen without disrupting the epidermis [11, 15, 16]. The Er:YAG laser (2940 nm) corresponds to the peak absorption coefficient of water, producing a superficial and precisely controlled ablative effect with minimal thermal injury and fewer adverse effects. In contrast, CO_2 lasers penetrate more deeply, generating a broader zone of thermal impact that induces more pronounced collagen remodelling but carries a higher risk of side effects.

Skin phototype, commonly classified according to the Fitzpatrick scale, is an important clinical factor influencing both the selection and safety of therapeutic modalities for hypertrophic scars and keloids. Several reviews and clinical guidelines emphasise that darker skin phototypes are associated with an increased risk of pigmentary complications, particularly post-inflammatory hyperpigmentation (PIH), when treated with laser- and energy-based devices. Consequently, treatment strategies should be individualised according to skin phototype, with careful adjustment of laser parameters, preference for less aggressive modalities, and increased caution in patients with higher Fitzpatrick phototypes to optimise outcomes and minimise adverse effects.

Laser therapy therefore carries a higher risk of PIH in individuals with darker skin phototypes (Fitzpatrick IV–VI), making careful selection of laser type, wavelength, and fluence essential. The absorption characteristics of different lasers influence their safety and efficacy: Er:YAG

(2940 nm) energy is strongly absorbed by water, resulting in a superficial and highly controlled ablative effect with minimal thermal spread, whereas CO_2 lasers (10,600 nm) penetrate more deeply, producing a broader zone of thermal impact and more extensive collagen remodelling, but with a higher risk of PIH, scarring, or delayed healing, particularly in dark-skinned patients. For hypertrophic scars and keloids, lower fluences are generally recommended to reduce the risk of adverse effects while still promoting collagen remodelling.

Fractional non-ablative lasers are often preferred in darker skin types because they deliver energy in microthermal zones, allowing surrounding tissue to remain intact and promoting faster re-epithelialisation. Pre-treatment skin preparation, including topical depigmenting agents or careful photoprotection, may further reduce the risk of hyperpigmentation and optimise outcomes, particularly in individuals prone to abnormal pigmentary responses.

The fractional Er:Glass laser (1550 nm) creates microthermal zones that stimulate collagen regeneration, reducing scars and stretch marks with minimal discomfort and rapid recovery [11, 15, 16]. PDL (585–600 nm) targets haemoglobin to treat the vascular components of scars. Compared with other methods, such as microneedling or CO_2 lasers, non-ablative lasers offer lower pain and shorter downtime. Lasers generally outperform IPL (intense pulsed light) devices in pain relief, anti-inflammatory action, and wound healing [10, 11, 16].

IPL enhances microcirculation, stimulates fibroblasts, and improves oxygen exchange through low-energy electromagnetic radiation (500–2500 nm), leading to reduced scar thickness, greater elasticity, and improved appearance. However, IPL delivers broad-spectrum, non-coherent light with limited penetration and selectivity, restricting its ability to target deeply located fibroblasts and the excessive collagen production characteristic of keloids. Consequently, IPL may improve scar appearance and vascularity but has limited impact on the key pathophysiological mechanisms underlying keloid formation and persistence [20, 22].

Fractional lasers, used in atrophic acne scars, hypertrophic scars, and stretch marks, create micro-injuries while sparing surrounding tissue, enabling rapid re-epithelialisation and a lower risk of post-inflammatory hyperpigmentation. Fractional laser therapy is indicated for atrophic acne scars, remodelling hypertrophic surgical and traumatic scars, and improving stretch marks. Contraindications include the use of skin-sensitising medications, and potential adverse effects comprise scarring, depigmentation, hyperpigmentation, and blistering. In clinical practice, individualised treatment protocols that consider skin phototype, scar type, and anatomical location are essential for maximising efficacy and minimising complications, particularly when treating dark-skinned patients with hypertrophic or keloid scars [11, 15, 16, 20, 22].

Acids peels

Chemical peels are classified by depth: superficial (stratum corneum to spinous layer), medium and deep (epidermis to reticular dermis). Acid strength depends on pH and pKa, and treatment choice is guided by photodamage, skin type, scar characteristics, and therapeutic goals. Agents such as trichloroacetic acid (15–40%), pyruvic acid, salicylic acid, glycolic acid, lactic acid, mandelic acid, Jessner's solution, and phenol are used to reduce scars. Combined peels may reduce adverse effects [23–25].

Hydroxy acids (AHAs and BHAs) provide gentle exfoliation at concentrations below 5%. Mandelic acid is notable for its antibacterial properties and suitability for all skin types. BHAs such as salicylic acid have anti-inflammatory benefits. Newer agents, including gluconic acid and polyhydroxy acids (PHAs) such as lactobionic acid, provide gentle exfoliation, antioxidant effects, and suitability for sensitive skin [23–25].

Special caution is required in patients with darker skin phototypes (IV–VI), who are particularly susceptible to complications. High-concentration formulations, especially trichloroacetic acid (TCA) 35–40%, may induce PIH, exacerbate scarring, prolong inflammation, and potentially worsen the overall appearance of scars. For this reason, pre-treatment prior to chemical peeling is particularly important in patients with Fitzpatrick skin types IV–VI and in the management of hypertrophic scars and keloids, as it helps reduce the risk of PIH and excessive inflammatory response. Recommended pre-treatment for a period of 2–4 weeks includes hydroquinone at a concentration of 2–4% to inhibit melanogenesis, cautious use of a retinoid to normalise keratinisation, mandatory application of broad-spectrum SPF 50+ sunscreen, and avoidance of skin irritation.

Acid peels are used primarily for acne scars and atrophic scars rather than hypertrophic scars or keloids. They are not first-line therapy, should be applied with caution, and are mainly used as adjunctive treatment [17, 26, 27].

Chemotherapeutic agents

Main chemotherapeutic agents used in scar management include antimetabolites and steroids, such as 5-fluorouracil (5-FU), mitomycin C, bleomycin, and corticosteroids, which inhibit fibroblast proliferation by disrupting cell cycles [28].

5-FU blocks thymidylate synthase and suppresses TGF-β-induced collagen expression, showing particular efficacy when combined with other therapies. Weekly or biweekly intralesional injections are effective, with adverse effects including pain, ulceration, and hyperpigmentation, although systemic toxicity has not been reported [11, 28].

Mitomycin C inhibits nucleic acid and protein synthesis, reducing fibroblast activity, but topical use application has not prevented keloid recurrence and may delay wound healing, indicating the need for further research.

Bleomycin reduces collagen and lysyl oxidase (LOX) synthesis, and may induce fibroblast apoptosis, with similar side effects and rare systemic toxicity [11, 28].

Corticosteroids, particularly triamcinolone acetonide (TAC), are widely used for their anti-inflammatory and

antifibrotic effects. They reduce collagen and glycosaminoglycan synthesis, and modulate growth factors such as TGF-β, IGF-1, and VEGF. TAC (10–40 mg/ml) is injected intralesionally every 4–6 weeks, inhibiting TGF-β1 and increasing bFGF expression. When combined with surgery, recurrence rates drop to 10–30%, making TAC the current gold standard [11, 29]. Monotherapy with TAC achieves a 50–100% response rate, but combining it with agents such as 5-FU, interferon-α2b, or pulsed dye laser further improves scar outcomes.

Dexamethasone also slows fibroblast proliferation and reduces VEGF expression, whereas topical corticosteroids alone are ineffective for prevention. Adverse effects such as atrophy, pigment changes, telangiectasia, pain, and ulceration may be reduced by combining low doses with 5-FU [11, 29].

Targeted therapy

Targeted therapies aim to block specific factors involved in pathological scar formation, particularly those driving fibrosis. Key targets include fibronectin (FnEDA), cytokines, and enzymes involved in collagen cross-linking. Antisense oligonucleotides (ASOs) directed against TGF-β mRNA have shown promise in vitro by downregulating fibrosis-related markers such as MMP-9, SMAD2, and SMAD4. ASOs targeting HIF-1α reduce PAI-1 levels. However, these therapies remain experimental and are not yet applicable in clinical practice.

Collagen cross-linking inhibitors such as beta-aminopropionitrile (BAPN) inhibit LOX, an enzyme responsible for collagen fibre stabilisation. BAPN has shown efficacy in reducing severe scarring following keloid excision. Other agents, including copper chelators (e.g. D-penicillamine) and proline analogues, also aim to reduce collagen deposition but require further study before clinical use [5, 30].

Surgical treatment

Every surgical intervention results in scar formation as a normal component of wound healing, and even well-healed scars differ structurally from normal skin [3, 6]. Excision of hypertrophic scars may improve aesthetic outcomes but carries a risk of recurrence; a scar is generally considered successfully treated if no recurrence occurs within two years. Importantly, surgical excision itself may trigger recurrence of hypertrophic scars and keloids, occasionally producing lesions larger than the original, and should therefore be undertaken with caution, except in cases of minor hypertrophic scars.

The first-line surgical approach involves scar excision combined with modification of scar shape, most commonly through Z- or W-plasty, to reduce linear tension. Effective recurrence prevention relies on tension-minimising strategies, including subcutaneous or fascial tension-reduction sutures, which address the dermal origin of pathological scarring. Dermal sutures alone are insufficient to offload dermal tension, whereas engagement of the superficial and deep fascia enables effective stress redistribution and controlled approximation of wound edges, a key factor in preventing postoperative pathological scarring. Zig-zag techniques, including Z-plasty, further facilitate release of linear contractures, accelerate scar maturation, and reduce pathological scarring, particularly when scars cross joints.

Surgical management is commonly complemented by adjuvant therapies, including 5-fluorouracil, corticosteroids, laser therapy, topical steroids, and silicone-based products, to limit excessive connective tissue proliferation. Local flap techniques may be employed in selected cases, particularly for elevated scars or those that restrict movement [6, 31–33]. Compared with skin grafts, which frequently result in secondary circumferential contractures, local flaps offer better postoperative adaptability and a lower risk of contracture formation. Although historically avoided due to concerns about donor-site keloid formation, multimodal strategies incorporating tension-reduction sutures and radiotherapy can mitigate these risks, rendering flap reconstruction a viable option for severe keloids. In patients predisposed to keloid formation, surgical incisions should be oriented along relaxed skin tension lines and performed using atraumatic techniques. Despite appropriate management, keloids frequently recur following excision and may increase in size [6, 31–33].

Radiotherapy

Superficial X-ray therapy, low- or high-dose-rate brachytherapy, and electron-beam irradiation have demonstrated favourable outcomes in scar-reduction protocols, most commonly as adjuncts to surgical excision of keloids. The therapeutic and preventive effects of radiotherapy are mediated through suppression of neovascular sprouting and inhibition of fibroblast proliferation, leading to reduced collagen synthesis and, consequently, decreased inflammation. Radiotherapy used as monotherapy should be reserved for elderly patients or those with very large keloids, as effective treatment requires relatively high radiation doses. This approach provides rapid relief from pain and pruritus, while gradual improvements in scar pigmentation and thickness are typically observed over the following year. Radiotherapy is particularly effective when combined with surgical excision, with combined therapy associated with lower recurrence rates than radiotherapy alone. Advances in surgical techniques, radiation delivery, and postoperative management likely contribute to these improved outcomes.

Although superficial or orthovoltage x-rays (photons) were previously employed, many centres now favour electron-beam (β-ray) therapy because of its reduced impact on internal organs. High-dose-rate brachytherapy, primarily using γ-rays, is increasingly utilised; however, further evaluation of its safety with respect to internal organs is required [6, 31–34]. Electron-beam irradiation is typically initiated 24–48 hours after keloid excision. The maximum biologically effective dose for keloid treatment is 30 Gy, as higher doses do not improve efficacy and instead increase the risk of secondary carcinogenesis and adverse effects, including hypo- and hyperpigmentation, erythema, telangiectasia, and tissue atrophy. Because recurrence risk varies by anatomical location, a biologically effective dose of 30 Gy is not always necessary. To further reduce carcinogenic risk, postoperative irradiation may be tailored to the treated site, with

protocols including 18 Gy in three fractions over three days for high-recurrence areas, 8 Gy in a single fraction for earlobes, and 15 Gy in two fractions over two days for other body sites. Over the past 70 years, only a limited number of cases of malignant transformation following keloid radiotherapy have been reported. Nevertheless, as radiation carries an inherent carcinogenic risk, particularly in sensitive regions such as the breast and thyroid, its use should be approached with appropriate caution [31, 33, 34].

Pressure therapy

Pressure therapy employs mechanical compression using garments, cuffs, or clips [3, 6]. Treatment duration ranges from 6 to 24 months. This method is widely recommended for post-burn scars to prevent the formation of contractile fibrous bands, also known as "bridges". It requires the continuous use of custom-made compression garments, worn for 23 hours per day with a one-hour break for hygiene and skincare routines [13, 22, 31]. The mechanism of action involves inducing tissue hypoxia (limiting the supply of blood and oxygen), modulating fibroblast activity, and promoting collagen breakdown [5, 13, 31].

Post-surgical scar care follows three phases. Phase 1: no scar manipulation; dressings and manual lymphatic drainage (MLD) support healing. During the first 7 days, a mature scar has not yet formed, and the wound remains protected under a dressing. This first week is critical for the development of postoperative adhesions. By 6 to 8 weeks post-surgery, Phase 2 begins: MLD continues, with scar-area treatments and dynamic taping to minimise tension. Phase 3: scar management occurs from approximately 6–8 weeks to 0.5–2 years post-operation, and focuses on scar remodelling. A mature scar should move freely; adhesions indicate abnormal healing [21, 31]. Therapeutic techniques applied during this phase are significantly more intensive than in earlier stages.

Current guidance on pressure levels and treatment duration is largely derived from empirical experience and recommends sustained compression in the range of 15–40 mmHg; however, pressures between 15 and 25 mmHg are generally considered therapeutic, whereas higher values approaching 40 mmHg are associated with an increased risk of tissue ischaemia and adverse effects [13, 21, 22, 31].

Silicone

Silicone, a biomedical polymer, is applied topically in the form of gels or dressings that remain on the skin surface. Available formulations include gels, oils, elastomers, rubbers, and resins, with their properties influenced by polymerisation processes and alkylsiloxane content. Silicone reduces itching and pain, maintains hydration, and improves scar texture and colour. It conforms well to scar contours and is non-invasive. Gels create a transparent occlusive layer suitable for visible scars, whereas creams are more appropriate for small, fresh lesions. Silicone elastomer patches adhere through Van der Waals forces and may remain in place for up to a month.

Silicone increases skin temperature by approximately 1.7°C, potentially activating collagenase and altering fibroblast activity, although its exact mechanism is unclear due to the absence of systemic absorption. Silicone gels and patches demonstrate better efficacy for hypertrophic scars than keloids. However, occlusion may still reduce keloid density, pain, and pruritus [22]. This approach is primarily used as a preventive measure against the formation of hypertrophic scars and keloids and has not been shown to be effective in the treatment of established or mature lesions. In high-risk patients, early initiation of silicone therapy is a key preventive strategy. Silicone may also help with neurogenic inflammation and stabilise scars by addressing mechanotransduction.

Therapy may be initiated approximately two weeks after complete wound closure. Silicone sheets should be worn for a minimum of 12 hours per day, and preferably continuously, for at least two months. In anatomical regions with frequent movement or poor adherence of sheets, silicone gel is the preferred option and should be applied twice daily [18, 22].

Therapeutic algorithms for hypertrophic scars and keloids

Management of hypertrophic scars and keloids requires a stepwise, individualised approach that integrates scar type, stage, anatomical location, patient-specific risk factors, and prior treatment response [7, 18]. Both Ogawa and Mustoe emphasise prevention as the initial step, including meticulous wound closure, minimisation of mechanical tension, early silicone therapy, and pressure application to high-risk areas. Ogawa's algorithm combines preventive measures with active interventions tailored to scar severity and recurrence risk. Initial therapy for established scars commonly involves intralesional corticosteroids, frequently combined with 5-FU or laser therapy, to reduce fibroblast proliferation and abnormal ECM deposition. Surgical excision is reserved for refractory, functionally limiting, or cosmetically significant scars, and must be accompanied by adjuvant therapy to prevent recurrence.

Novel approaches, including stem cell modulation, growth factor targeting, and biologics, aim to normalise collagen deposition and TGF-β-mediated signalling. Treatment decisions are guided by scar location, size, patient age, skin type, and the heterogeneity of fibroblast subpopulations. Mustoe's algorithm similarly emphasises classification by scar type (hypertrophic versus keloid), stage (proliferative versus mature), and risk profile. Preventive strategies include silicone sheeting, pressure therapy, and early recognition of high-risk wounds [13, 22, 29]. Active scars are primarily managed with intralesional corticosteroids, with adjunctive therapies such as cryotherapy, laser therapy, and superficial chemical peels selected according to scar morphology and patient tolerance [11, 18, 29]. Surgery is considered for scars resistant to conservative measures, again followed by adjuvant therapy to minimise recurrence [11, 18]. Mustoe highlights the importance of continuous monitoring using validated assessment tools, such as the Vancouver Scar Scale (VSS) and Patient and Observer Scar Assessment Scale (POSAS), to guide ongoing therapy and optimise functional and aesthetic outcomes [14, 18, 19]. In practice, both algorithms underscore that scar treatment should be individualised,

combining preventive and active interventions and guided by pathophysiological understanding, including fibroblast heterogeneity, persistent myofibroblast activity, collagen type III dysregulation, mechanical tension, and genetic predisposition [5, 7, 12, 18].

Combined therapy

Combining surgical excision with adjunctive therapies such as pulsed dye laser, radiotherapy, CO_2 laser, or pressure therapy reduces recurrence rates and underscores the need for personalised treatment plans that account for individual scar-risk factors. Patients prone to dystrophic scarring should avoid procedures that disrupt skin integrity, and no single modality guarantees success, making combined therapies preferable. Hypertrophic scars are often managed in stages, beginning with pressure therapy – frequently combined with corticosteroids – and, in some cases, skin expansion to facilitate closure. Keloid treatment is more challenging and may involve corticosteroid injections, vitamin A, surgery, or radiotherapy [18, 32, 35]. Because keloid pathophysiology remains incompletely understood, prevention is essential.

Monotherapies (e.g. excision, intralesional chemotherapy, laser, cryotherapy, silicone, pressure) yield variable and often temporary results with high recurrence rates (≈50–70%). Intralesional corticosteroids, commonly used alongside surgery, reduce collagen synthesis and fibroblast activity, and suppress pro-inflammatory mediators, although they typically soften rather than eliminate keloids. Combined treatments generally produce superior outcomes. When prophylaxis fails, options include corticosteroids, 5-FU, radiotherapy, laser therapy, or surgery, ideally applied in a tailored, combinatorial manner. Emerging techniques such as laser-assisted drug delivery or advanced topical formulations may benefit refractory cases. Microdermabrasion combined with AHA/BHA peels can improve texture and regeneration via stimulation of collagen, elastin, and glycosaminoglycan synthesis, and is more effective when performed in series than as a standalone treatment [23, 26]. Although standardised guidelines are lacking, evidence supports that combining excision with triamcinolone (TAC), pulsed dye laser, or 5-FU reduces recurrence and side effects. Treatment should remain flexible and tailored to each patient's response [29, 35].

Psychological aspects

Smooth skin is a key component of aesthetic appearance and self-esteem, and a clear link exists between dermatological conditions and mental health. Scars pose cosmetic, psychological, and physical challenges. Keloid lesions may cause functional impairment and significant psychosocial burden. They can be hypersensitive to touch and may represent a significant clinical problem [9, 34]. Scars, especially extensive ones, often serve as reminders of traumatic or unfortunate life events, and scarring in visible areas may provoke negative reactions from others. Scars in conspicuous places, such as the face, are particularly difficult for patients to accept. Scars are frequently perceived as disfiguring; individuals with visible scarring may be judged less attractive, which can lead to psychological distress. Scars can also be a source of anxiety, sleep problems, and even depression. Patients with scars should therefore be provided with optimal holistic treatment [33, 34].

Summary

Because of the complexity of the healing process, disturbances may occur, leading to the formation of various types of pathological scars. These lesions are characterised primarily by increased collagen synthesis and decreased collagen degradation. Scars have a diverse morphological presentation. Despite significant advances in medicine and aesthetic dermatology in recent years, the mechanisms involved in scar pathogenesis have not been fully elucidated, which complicates therapy.

Scar treatment is a challenging clinical problem. The complexity of scar pathogenesis, encompassing dysregulated fibroblast activity, excessive collagen deposition, and altered extracellular matrix remodelling, makes it unlikely that any single therapy can address all pathological mechanisms. Treatment often relies on direct and indirect modulation of skin fibroblast proliferation and collagen synthesis. Hypertrophic scars and keloids, most commonly located in areas of increased tissue tension, represent a distinct subgroup. It should be emphasised that only improvement in scar appearance and reduction in size are achievable. No currently available method is effective for all patients, regardless of differences in therapeutic goals and levels of invasiveness. Clinical studies have consistently shown that monotherapies, whether surgical, pharmacological, or physical, often result in incomplete resolution or high recurrence rates, particularly in hypertrophic scars and keloids. Complete scar removal is not achievable.

The most commonly used therapeutic approaches include pharmacological methods (local corticosteroid injections, systemic and topical preparations), surgical treatment, and physical modalities including laser therapy and pressure therapy. Each therapeutic method can be used as monotherapy; however, combining multiple methods yields significantly better therapeutic outcomes.

Combination therapy leverages complementary mechanisms: for example, surgery can remove bulky scar tissue, corticosteroids reduce fibroblast proliferation, and physical modalities such as laser or pressure therapy remodel collagen and improve vascularisation. This multimodal approach addresses multiple aspects of scar pathophysiology, leading to improved functional and aesthetic outcomes.

Therefore, for most patients, multiple methods should be combined to achieve the most effective treatment. Personalised multimodal strategies should be planned for each patient, taking into account scar type, anatomical location, and risk of recurrence, to optimise therapeutic efficacy and minimise complications. Patients should be informed that the goal of treatment is to reduce aesthetic and physical impairment rather than achieve complete scar elimination.

References

1. Pikuła M, Langa P, Kosikowska P, Trzonkowski P. Komórki macierzyste i czynniki wzrostu w gojeniu ran [Stem cells and growth factors in wound healing]. Postepy Hig Med Dosw (Online), 2015; 69: 874–885. Polish. doi: 10.5604/17322693.1162989
2. Gauglitz GG, Korting HC, Pavicic T, et al. Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. Mol Med, 2011; 17(1–2): 113–125. doi: 10.2119/molmed.2009.00153
3. Bharadia SK, Burnett L, Gabriel V. Hypertrophic Scar. Phys Med Rehabil Clin N Am, 2023; 34(4): 783–798. doi: 10.1016/j.pmr.2023.05.002
4. Frech FS, Hernandez L, Urbonas R, et al. Hypertrophic scars and keloids: advances in treatment and review of established therapies. Am J Clin Dermatol, 2023; 24(2): 225–245. doi: 10.1007/s40257-022-00744-6
5. Andrews JP, Marttala J, Macarak E, et al. Keloids: the paradigm of skin fibrosis – Pathomechanisms and treatment. Matrix Biol, 2016; 51: 37–46. doi: 10.1016/j.matbio.2016.01.013
6. Chiang RS, Borovikova AA, King K, et al. Current concepts related to hypertrophic scarring in burn injuries. Wound Repair Regen, 2016; 24(3): 466–477. doi: 10.1111/wrr.12432
7. Ogawa R, Akaishi S, Kuribayashi S, Miyashita T. Keloids and hypertrophic scars can now be cured completely: recent progress in our understanding of the pathogenesis of keloids and hypertrophic scars and the most promising current therapeutic strategy. J Nippon Med Sch, 2016; 83(2): 46–53. doi: 10.1272/jnms.83.46
8. Ogawa R. Keloid and hypertrophic scars are the result of chronic inflammation in the reticular dermis. Int J Mol Sci, 2017; 18(3): 606. doi: 10.3390/ijms18030606
9. Knowles A, Glass DA 2nd. Keloids and hypertrophic scars. Dermatol Clin, 2023; 41(3): 509–517. doi: 10.1016/j.det.2023.02.010
10. Zhu R, Yue B, Yang Q, et al. The effect of 595 nm pulsed dye laser on connective tissue growth factor (CTGF) expression in cultured keloid fibroblasts. Lasers Surg Med, 2015; 47(2): 203–209. doi: 10.1002/lsm.22334
11. Ekstein SF, Wyles SP, Moran SL, Meves A. Keloids: a review of therapeutic management. Int J Dermatol, 2021; 60(6): 661–671. doi: 10.1111/ijd.15159
12. Limandjaja GC, van den Broek LJ, Waaijman T, et al. Reconstructed human keloid models show heterogeneity within keloid scars. Arch Dermatol Res, 2018; 310(10): 815–826. doi: 10.1007/s00403-018-1873-1
13. Marini L, Odendaal D, Smirnyi S. Importance of scar prevention and treatment – an approach from wound care principles. Dermatol Surg, 2017; 43(Suppl 1): S85–S90. doi: 10.1097/DSS.0000000000001001
14. Berman B, Maderal A, Raphael B. Keloids and hypertrophic scars: pathophysiology, classification, and treatment. Dermatol Surg, 2017; 43(Suppl 1): S3–S18. doi: 10.1097/DSS.0000000000000819
15. Ogawa R. Long-pulsed 1064 nm Nd\:YAG laser treatment for keloids and hypertrophic scars. In: Téot L, Mustoe TA, Middelkoop E, Gauglitz GG, eds. Textbook on Scar Management: State of the Art Management and Emerging Technologies. Cham (CH): Springer; 2020. Chapter 32
16. Leszczynski R, da Silva CA, Pinto ACPN, et al. Laser therapy for treating hypertrophic and keloid scars. Cochrane Database Syst Rev, 2022; 9(9): CD011642. doi: 10.1002/14651858.CD011642.pub2
17. Fife D. Practical evaluation and management of atrophic acne scars: tips for the general dermatologist. J Clin Aesthet Dermatol, 2011; 4(8): 50–57
18. Ogawa R. The most current algorithms for the treatment and prevention of hypertrophic scars and keloids: a 2020 update of the algorithms published 10 years ago. Plast Reconstr Surg, 2022; 149(1): 79e–94e. doi: 10.1097/PRS.0000000000008667
19. Kafka M, Collins V, Kamolz LP, et al. Evidence of invasive and noninvasive treatment modalities for hypertrophic scars: a systematic review. Wound Repair Regen, 2017; 25(1): 139–144. doi: 10.1111/wrr.12507
20. Lee HJ, Jang YJ. Recent understandings of biology, prophylaxis and treatment strategies for hypertrophic scars and keloids. Int J Mol Sci, 2018; 19(3): 711. doi: 10.3390/ijms19030711
21. Lubczyńska A, Garncarczyk A, Wcisło-Dziadecka D. Effectiveness of various methods of manual scar therapy. Skin Res Technol, 2023; 29(3): e13272. doi: 10.1111/srt.13272
22. Jiang Q, Chen J, Tian F, Liu Z. Silicone gel sheeting for treating hypertrophic scars. Cochrane Database Syst Rev, 2021; 9(9): CD013357. doi: 10.1002/14651858.CD013357.pub2
23. Măgerușan ȘE, Hancu G, Rusu A. A comprehensive bibliographic review concerning the efficacy of organic acids for chemical peels treating acne vulgaris. Molecules, 2023; 28(20): 7219. doi: 10.3390/molecules28207219
24. Samargandy S, Raggio BS. Chemical peels for skin resurfacing. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2026 Jan
25. Lee KC, Wambier CG, Soon SL, et al.; International Peeling Society. Basic chemical peeling: Superficial and medium-depth peels. J Am Acad Dermatol, 2019; 81(2): 313–324. doi: 10.1016/j.jaad.2018.10.079
26. Gozali MV, Zhou B. Effective treatments of atrophic acne scars. J Clin Aesthet Dermatol, 2015; 8(5): 33–40
27. Al-Talib H, Al-Khateeb A, Hameed A, Murugaiah C. Efficacy and safety of superficial chemical peeling in treatment of active acne vulgaris. An Bras Dermatol, 2017; 92(2): 212–216. doi: 10.1590/abd1806-4841.20175273
28. Jones CD, Guiot L, Samy M, et al. The use of chemotherapeutics for the treatment of keloid scars. Dermatol Reports, 2015; 7(2): 5880. doi: 10.4081/dr.2015.5880
29. Wong TS, Li JZ, Chen S, et al. The efficacy of triamcinolone acetonide in keloid treatment: a systematic review and meta-analysis. Front Med (Lausanne), 2016; 3: 71. doi: 10.3389/fmed.2016.00071
30. Wu Y, Peng Y, Gao D, et al. Mesenchymal stem cells suppress fibroblast proliferation and reduce skin fibrosis through a TGF-β3-dependent activation. Int J Low Extrem Wounds, 2015; 14(1): 50–62. doi: 10.1177/1534734614568373
31. Zebrowska A, Trybulski R, Roczniok R, Marcol W. Effect of physical methods of lymphatic drainage on postexercise recovery of mixed martial arts athletes. Clin J Sport Med, 2019; 29(1): 49–56. doi: 10.1097/JSM.0000000000000485
32. Schønfeldt T, Andersen PS. [Prevention and treatment of keloids]. Ugeskr Laeger, 2022; 184(25): V05210395. Danish
33. Tan J, Beissert S, Cook-Bolden F, et al. Impact of facial atrophic acne scars on quality of life: a multi-country population-based survey. Am J Clin Dermatol, 2022; 23: 115–123. doi: 10.1007/s40257-021-00628-1
34. Mathew M, DiBartolomeo G, Stone RC. Biopsychosocial impact of keloids on quality of life. JAAD Rev, 2024; 2: 13–19. doi: 10.1016/j.jdrv.2024.08.010
35. Sabetghadam M, Farahani Nik Z. Multimodal approach in the treatment of recurrent keloids: Surgery, triamcinolone and 5-FU injections, and PLT, a case-report. Int J Surg Case Rep, 2025; 135: 111931. doi: 10.1016/j.ijscr.2025.111931

BMI AND THE RISK OF AXILLARY FAT INFILTRATION IN PRIMARY CN0 BREAST CANCER PATIENTS – A SINGLE-CENTRE, SMALL-COHORT, RETROSPECTIVE ANALYSIS

BMI a ryzyko infiltracji tłuszczu pachowego u pacjentek z pierwotnym rakiem piersi cN0 – jednoośrodkowa analiza retrospektywna w małej kohorcie

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Abstract

Introduction and objective: The status of regional lymph nodes is one of the most important prognostic factors in breast cancer. Massive extracapsular extension of breast cancer metastasis carries a high risk of disease recurrence. A fairly high rate of false-negative clinical diagnoses of the N trait is observed during preoperative breast cancer staging. This may expose patients to prolonged therapeutic management. In this analysis, it was determined whether there is any correlation between body weight, BMI, age, and axillary fat infiltration in a population of patients who underwent both procedures – sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) – and were not originally suspected of having nodal metastases at all (cN0). **Material and methods:** A single-centre retrospective analysis of medical records was conducted in women treated between 2015 and 2019 for newly diagnosed cN0 breast cancer who ultimately underwent both procedures: SLNB followed by ALND as a separate procedure due to axillary node involvement confirmed on SLNB. A paired Student's t-test was used (confidence interval 95%). **Results:** A statistically significant association (p <0.001) between body weight and axillary fat infiltration was observed, but the linear correlation was not statistically significant. The second association – between age and axillary fat infiltration – was also statistically significant (p <0.001), while the linear correlation was not statistically significant. The association between BMI and nodal axillary fat infiltration was statistically significant (p <0.001), and unlike the previous two variables, the linear correlation was also statistically significant (p = 0.046); Pearson's correlation coefficient was r = +0.329, indicating a sufficient positive correlation. **Conclusions:** A statistically significant, sufficient, positive, linear correlation was found between BMI and nodal metastases with axillary fat involvement in women with breast cancer, initially staged as cN0.

Streszczenie

Wprowadzenie i cel: Status regionalnych węzłów chłonnych jest jednym z najważniejszych czynników prognostycznych w raku piersi. Masowe przejście przerzutu przez torebkę węzła chłonnego wiąże się z wysokim ryzykiem nawrotu choroby. Podczas diagnostyki przedoperacyjnej raka piersi obserwuje się dość wysoki wskaźnik fałszywie ujemnych rozpoznań cechy klinicznej N. Może to narażać pacjentów na przedłużone postępowanie terapeutyczne. Celem niniejszej analizy była ocena, czy istnieje jakakolwiek korelacja między masą ciała, BMI, wiekiem pacjentek a infiltracją nowotworową tłuszczu pachowego w populacji chorych, u których wykonano oba zabiegi – biopsję węzła wartowniczego (SLNB) oraz limfadenektomię pachową (ALND) – i u których pierwotnie nie podejrzewano obecności przerzutów do węzłów chłonnych (cN0). **Materiał i metody:** Przeprowadzono jednoośrodkową retrospektywną analizę dokumentacji medycznej kobiet leczonych w latach 2015–2019 z powodu nowo zdiagnozowanego raka piersi z cechą cN0, które ostatecznie przeszły obie procedury: najpierw SLNB, a następnie ALND (jako odrębny zabieg operacyjny) z powodu zajęcia pachowych węzłów chłonnych przez nowotwór. Zastosowano test t-Studenta dla par zależnych (przedział ufności 95%). **Wyniki:** Stwierdzono statystycznie istotny związek pomiędzy masą ciała a naciekaniem tłuszczu pachowego (p <0,001), jednak korelacja liniowa nie była istotna statystycznie. Również związek między wiekiem a infiltracją tłuszczu pachowego był istotny statystycznie (p <0,001), przy czym korelacja liniowa nie była istotna statystycznie. Związek między BMI a infiltracją tłuszczu pachowego był istotny statystycznie (p <0,001), a korelacja liniowa, w przeciwieństwie do dwóch poprzednich par, również była istotna statystycznie (p = 0,046). Współczynnik korelacji Pearsona wyniósł r = 0,329, co wskazuje na dodatnią i wystarczającą korelację. **Wnioski:** Stwierdzono statystycznie istotną, wystarczającą, dodatnią korelację liniową między BMI a obecnością przerzutów do węzłów chłonnych z zajęciem tłuszczu pachowego u kobiet z rakiem piersi, u których początkowo rozpoznano cechę cN0.

Keywords: breast cancer; axillary fat infiltration; BMI and breast cancer; lymph node metastasis

Słowa kluczowe: rak piersi; naciek tłuszczu pachowego; BMI a rak piersi; przerzuty do węzłów chłonnych

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Introduction

A fairly high rate of false-negative clinical N staging occurs during preoperative breast cancer diagnosis. This may expose patients to prolonged therapeutic management and involve malpractice claims, particularly directed at radiologists. According to Whang et al., the most frequent cause of medical malpractice claims in the United States related to procedures performed by radiologists involves errors made during breast cancer diagnosis [1].

The diagnostic procedure in breast cancer staging requires radiological examinations of the breast and regional lymphatic system (mammography (MMG) and ultrasound (US)), in addition to physical examination. Magnetic resonance imaging (MRI) is also used in selected cases, especially in younger patients.

Regional lymph nodes metastatic status remains one of the most important prognostic factors. Massive extracapsular extension of breast cancer metastasis carries a high risk of disease recurrence [2].

During the reviewed period, the available randomised trial data were insufficient to recommend omitting completion axillary lymph node dissection (ALND) in T1/T2 breast cancer with fewer than three involved sentinel lymph nodes (SLNs) in patients undergoing lumpectomy and whole-breast irradiation. Longer follow-up was then necessary to confirm that omitting ALND was safe and that distant outcomes were equivalent in patients with luminal A breast cancer presenting with more advanced disease, e.g. in patients with T2 tumours and two positive SLNs [3].

The subjectivity of ultrasound and physical examination is their main disadvantage. US, which plays a significant role in assessing axillary lymph node status, demonstrates 77% sensitivity and 80% specificity [4]. Other authors report a specificity of 95% in vivo, with only 36% sensitivity [5]. A sensitivity below 40% may raise doubts about the clinical utility of US in breast cancer staging.

Axillary lymph nodes metastatic involvement may be very subtle [6].

The criteria for suspecting a metastatic lymph node are:
- the longest dimension greater than 1 cm or more than 5 mm in the short axis,
- asymmetry compared with the contralateral side (both in the number of lymph nodes and in size, even if within normal limits),
- loss or blurring of the nodal margin,
- infiltration of axillary fat,
- thickening of the cortical layer of more than 3 mm,
- obliteration of the fatty hilum,
- significant enlargement, especially when the node assumes a spherical shape [6, 7].

A preserved nodal hilum has limited prognostic value. The tumour and the visible interstice in the hilum are, on the other hand, late signs of massive metastatic lymph node involvement [8].

In 2016, researchers published a paper describing 5,142 cN0 patients who underwent 5,262 sentinel lymph node biopsy (SLNB) procedures. Overall, 28% of the patients had body mass index (BMI) >30 kg/m^2. Larger tumour size, younger age, multifocality, lymphovascular invasion, and high nuclear grade were the most common predictors of SLN positivity. They found no correlation (p = 0.6) between increased BMI and an increased likelihood of SLN metastasis. There was a 4% overall burden of axillary metastases in cN0 patients. Physical examination, according to the authors, is both appropriate and sufficient for preoperative axillary staging regardless of patient BMI [9].

In a retrospective study of 188 women who underwent screening mammography, the length and width of the lymph node, as well as the size of the hilum in the largest visible axillary node, were measured. The authors of this study found a significant association between increased BMI and the dimensions of axillary lymph nodes (caused by fatty infiltration), independent of age or breast density [10].

Conversely, the absence of suspicious changes on mammography, ultrasound, or MRI does not exclude the presence of lymph node metastases – especially micrometastases (i.e. metastases smaller than 2 mm) [11].

In this analysis, it was determined whether there is any correlation between body weight, BMI, patient age, and axillary fat infiltration in a cohort of patients who underwent both procedures – SLNB and ALND – and who were not originally suspected of having nodal metastases at all (cN0). The research hypothesis investigates whether an association exists between body weight, BMI, or age of cN0 breast cancer patients and axillary fat infiltrating lymph node metastases.

Material and methods

A retrospective analysis of medical records was conducted among female patients with cN0 breast cancer treated at the St. John of Dukla Oncology Centre in Lublin, Poland. There were 37 women operated on between 2015

and 2019 for newly diagnosed cN0 breast cancer who underwent both procedures: SLNB followed by ALND as a separate procedure due to axillary node involvement found on SLNB. Micrometastases were not considered.

The axillary nodes were initially assessed as clinically non-suspicious – cN0. Clinical staging was determined by physical examination, mammography, and ultrasound only.

Homogeneity of variance was evaluated by Levene's test; statistical significance was assessed at a 95% confidence interval (CI) using a paired Student's t-test; and internal consistency was evaluated using Cronbach's alpha test. GNU PSPP ver. 2.0.0-g5b54d1 statistical software was used.

The mean age of patients was 56.1 years; median age: 44 years; mean body weight: 72.2 kg; median body weight: 73 kg; mean BMI: 28.2 (kg/m^2); and median BMI was 28 (kg/m^2) (Tab. 1).

The number of women with metastases to the adipose tissue surrounding a sentinel lymph node with node diameter = <10 mm was 9 (24.3%); and with node dimension >10 mm it was also 9 (24.3%). There were 6 (16.2%) women with metastases to perinodal adipose tissue (excluding micrometastases) revealed during the ALND procedure (Tab. 2).

As many as 26 (70.2%) women did not have any further metastases identified on ALND.

Statistical analysis for the body weight and axillary infiltration pair yielded: homogeneity of variance using Levene's test = 0.28, p = 0.597; paired t-test: p <0.001; Pearson's correlation r = +0.315, p = 0.058.

For the age and lymph axillary infiltration pair: Levene's test = 1.59, p = 0.215; paired t-test: p <0.001; Pearson's correlation r = −0.103; p = 0.543.

Finally, for the BMI and axillary infiltration pair: Levene's test = 0.27, p = 0.681; paired t-test: p <0.001; and Pearson's correlation r = +0.329, p = 0.046 (Fig. 1).

Scale reliability measured using Cronbach's alpha was 0.75 (N = 6 items).

A comprehensive summary of the statistics is presented in Table 3.

Results

The tests showed a statistical significance (p <0.001) between body weight and axillary fat infiltration, but the linear correlation (moderate and positive) was not statistically significant.

The second association – between age and axillary fat infiltration – also demonstrated statistical significance (p <0.001), but the linear correlation was weak, negative – and not statistically significant.

Evaluating the paired t-test for dependent pairs revealed that the association between BMI and nodal axillary fat infiltration was also statistically significant (p <0.001) and, importantly, the linear correlation was statistically significant here (p = 0.046); Pearson r = +0.329 (sufficient and positive).

Discussion

The aim of this study was to evaluate potential correlations between body weight, BMI, age of women with

Table 1. Patient characteristics

Number of cases	Mean age (y)	Median age (y)	Mean body weight (kg)	Median body weight (kg)	Mean Body Mass Index (BMI) (kg/m^2)	Median BMI (kg/m^2)
37	56.1	44	72.2	73	28.2	28

Table 2. Number of patients with metastases to the perinodal adipose tissue of the sentinel lymph node

Sentinel Lymph Node (SLN) dimension =<10mm (excluding micrometastases)	SLN dimension >10mm (excluding micrometastases)	Lymph nodes after Axillary Lymph Node Dissection (ALND), no sentinel dimension data in pathological report (excluding micrometastases)	Lymph nodes after Axillary Lymph Node Dissection (ALND), no sentinel dimension data in pathological report) (micrometastases)	No metastases found after ALND
9	9	6	5	26
24.3%	24.3%	16.2%	13.5%	70.2%

Table 3. Results of statistical analyses

Variable pair		
Body weight-axillary infiltration	**Age-axillary infiltration**	**BMI-axillary infiltration**
Paired Student's t-test		
***p* <0.001**	***p* <0.001**	***p* <0.001**
Pearson's linear correlation		
R = +0.315 (p = 0.058)	R = −0.103 (p = 0.543)	**R = +0.329 (p = 0.046)**

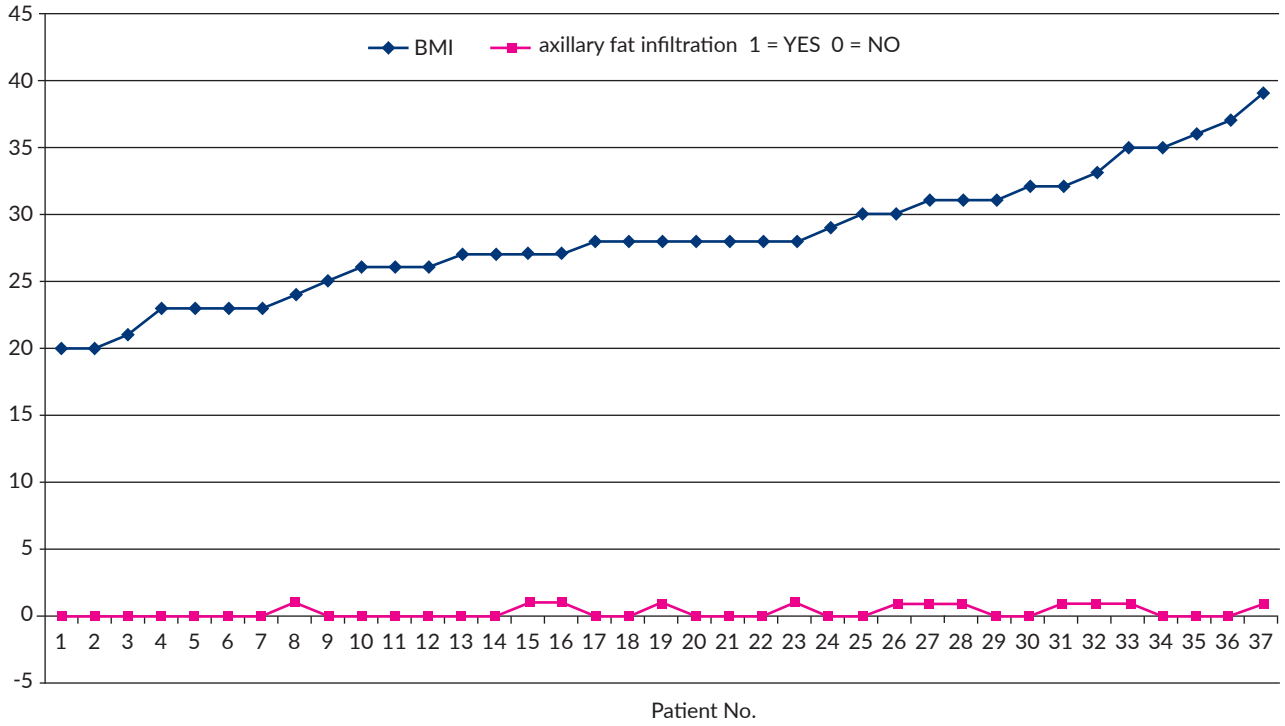

Figure 1. BMI-axillary fat infiltration

breast cancer, and axillary fat infiltration in a cohort of patients who underwent both procedures – SLNB and ALND – and were initially classified as cN0. A paired t-test (CI = 95%) was conducted for related variables (all features were measured across the same 37 patients). The test detected statistically significant relationships between body weight, BMI, age, and axillary fat infiltration ($p < 0.001$).

Linear Pearson correlations for the "weight-infiltration" and "age-infiltration" pairs were not statistically significant. However, for the "BMI-infiltration" pair, the Pearson linear correlation ($r = +0.329$) was statistically significant ($p = 0.046$), demonstrating a sufficient, positive relationship.

This means a higher likelihood of nodal metastases with axillary fat involvement along with increasing BMI.

The main limitation of the present analysis is the small sample (37 patients) derived from a single centre, and its retrospective design.

Prior scientific studies show that enlargement of the fatty hilum on MRI is associated with a high likelihood of nodal metastasis in obese women with breast cancer, regardless of BMI and tumour characteristics [12]. Whether this warrants broader utilisation of MRI in the routine staging of obese patients remains controversial. Other studies do not support this strategy. For example, a large (2,084 patients with invasive breast cancer) study shows that MRI prediction had lower accuracy in overweight women (65.1%) than in normal-weight (67.8%) and underweight women (76.1%) [13].

Furthermore, some studies on the value of ultrasound in detecting axillary lymph node metastases depending on BMI in breast cancer patients indicate that axillary ultrasound (AUS) is a valuable method in diagnosing the condition of axillary lymph nodes ($p < 0.0001$). However, the specificity ($p = 0.001$) and accuracy ($p = 0.008$) of AUS were better in overweight ($p = 0.007$) and obese ($p = 0.02$) patients than in individuals with normal BMI [14].

It can be concluded that AUS is a dependable method for detecting axillary metastases; however, it requires substantial experience on the part of the radiologist to avoid false-negative evaluations.

Conclusions

There is a statistically significant, sufficient, positive linear correlation between BMI and lymph node metastases with axillary fat involvement in women with breast cancer, initially diagnosed as cN0. The linear correlations between age, body weight, and axillary fat metastatic involvement were identified but did not reach statistical significance.

The primary limitation of this study was the small, retrospective sample from a single centre: 37 patients who underwent both procedures: SLNB followed by ALND as a separate procedure due to axillary node involvement (initially cN0 staging on AUS and mammography). It is necessary to verify these findings in a larger, prospective, multi-centre study.

References

1. Whang JS, Baker SR, Patel R, et al. The causes of medical malpractice suits against radiologists in the United States. Radiology, 2013; 266(2): 548–554. doi: 10.1148/radiol.12111119

2. Jassem J, Krzakowski M, Bobek-Billewicz B, et al. Breast cancer. Oncol Clin Pract, 2020; 16. doi: 10.5603/OCP.2020.0038
3. Voutsadakis IA, Spadafora S. Axillary lymph node management in breast cancer with positive sentinel lymph node biopsy. World J Clin Oncol, 2015; 6(1): 1–6. doi: 10.5306/wjco.v6.i1.1
4. Bedi DG, Krishnamurthy R, Krishnamurthy S, et al. Cortical morphologic features of axillary lymph nodes as a predictor of metastasis in breast cancer: in vitro sonographic study. AJR Am J Roentgenol, 2008; 191(3): 646–652. doi: 10.2214/AJR.07.2460
5. Bonnema J, van Geel AN, van Ooijen B, et al. Ultrasound-guided aspiration biopsy for detection of nonpalpable axillary node metastases in breast cancer patients: new diagnostic method. World J Surg, 1997; 21(3): 270–274. doi: 10.1007/s002689900227
6. Tartare M, Comstock CE, Kipper MS. Diagnostyka obrazowa raka sutka. Wydanie I polskie. Wrocław: Elsevier Urban & Partner; 2010, Tom I: 110–111
7. Yang WT, Chang J, Metreweli C. Patients with breast cancer: differences in color Doppler flow and gray-scale US features of benign and malignant axillary lymph nodes. Radiology, 2000; 215(2): 568–573. doi: 10.1148/radiology.215.2.r00ap20568
8. Tartare M, Comstock CE, Kipper MS. Diagnostyka obrazowa raka sutka. Wydanie I polskie. Wrocław: Elsevier Urban & Partner; 2010, Tom I: 113
9. McCartan D, Stempel M, Eaton A, et al. Impact of body mass index on clinical axillary nodal assessment in breast cancer patients. Ann Surg Oncol, 2016; 23(10): 3324–3329. doi: 10.1245/s10434-016-5330-0
10. diFlorio Alexander RM, Haider SJ, MacKenzie T, et al. Correlation between obesity and fat-infiltrated axillary lymph nodes visualized on mammography. Br J Radiol, 2018; 91(1089): 20170110. doi: 10.1259/bjr.20170110
11. Tartare M, Comstock CE, Kipper MS. Diagnostyka obrazowa raka sutka. Wydanie I polskie. Wrocław: Elsevier Urban & Partner; 2010, Tom I: 81
12. diFlorio-Alexander RM, Song Q, Dwan D, et al. Fat-enlarged axillary lymph nodes are associated with node-positive breast cancer in obese patients. Breast Cancer Res Treat, 2021; 189(1): 257–267. doi: 10.1007/s10549-021-06262-z
13. Chen ST, Lai HW, Wu WP, et al. The impact of body mass index (BMI) on MRI diagnostic performance and surgical management for axillary lymph node in breast cancer. World J Surg Oncol, 2022; 20(1): 45. doi: 10.1186/s12957-022-02520-6
14. Shah AR, Glazebrook KN, Boughey JC, et al. Does BMI affect the accuracy of preoperative axillary ultrasound in breast cancer patients? Ann Surg Oncol, 2014; 21(10): 3278–3283. doi: 10.1245/s10434-014-3902-4

POST-TRAUMATIC ACUTE PANCREATITIS COMPLICATED BY WALLED-OFF PANCREATIC NECROSIS – A CASE REPORT

Pourazowe ostre zapalenie trzustki powikłane zbiornikami otorbionej martwicy – opis przypadku

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Abstract

Pancreatic injuries are rare but particularly insidious consequences of traffic accidents. Their clinical course can be unpredictable, with potential long-term complications arising long after the acute phase has been treated, falling outside the classic framework of acute pancreatitis. The aim of this study is to illustrate the complexity and dynamics of the several-year clinical course of post-traumatic pancreatic injury in a young man, with particular consideration of the role of possible interruption of the Wirsung duct and the underlying anatomical conditions. A 21-year-old man developed acute pancreatitis complicated by recurrent formation of peripancreatic fluid collections following abdominal trauma. Despite early intervention and intensive treatment, the disease became chronic, with periods of apparent stabilization and sudden exacerbations. During subsequent hospital stays, staged endoscopic procedures were performed, including drainage of the reservoirs and temporary pancreatic duct stenting. Radiological imaging suggested disconnected the Wirsung duct, and the clinical course of the disease was further complicated by suspected pancreas divisum. The lack of clear confirmation of this anomaly significantly hindered the permanent control of the patient's clinical condition. This case report highlights the fact that traumatic damage to the pancreas can contribute to a long-term destructive and recurrent disease process. Staged treatment using the latest endoscopic techniques can help protect the patient from extensive surgery, although it does not eliminate the need for long-term and careful observation. Effective management requires the involvement of an experienced team, individualized therapy, and treatment in specialized centres.

Streszczenie

Urazy trzustki są rzadkim, jednak szczególnie podstępnym następstwem urazów jamy brzusznej. Ich przebieg bywa nieprzewidywalny, a odległe powikłania mogą ujawnić się długo po zakończeniu leczenia ostrej fazy, wykraczając poza klasyczne ramy ostrego zapalenia trzustki. Celem pracy jest przedstawienie złożoności i dynamiki kilkuletniego przebiegu pourazowego uszkodzenia trzustki u młodego mężczyzny, z uwzględnieniem roli możliwego przerwania przewodu Wirsunga oraz uwarunkowań anatomicznych. U 21-letniego mężczyzny po urazie jamy brzusznej doszło do rozwoju ostrego zapalenia trzustki powikłanego nawracającym tworzeniem się zbiorników okołotrzustkowych. Mimo wczesnej interwencji i intensywnego leczenia choroba przyjęła postać przewlekłą, z okresami pozornej stabilizacji oraz gwałtownych zaostrzeń. W czasie kolejnych hospitalizacji wykonywano etapowe zabiegi endoskopowe, obejmujące drenaż prześcienny oraz czasowe protezowanie przewodu trzustkowego. Obraz radiologiczny sugerował przerwanie ciągłości przewodu Wirsunga, a przebieg choroby dodatkowo komplikowało podejrzenie występowania trzustki dwudzielnej. Brak jednoznacznego potwierdzenia tej anomalii istotnie utrudniał trwałe opanowanie stanu klinicznego pacjenta. Przypadek ten pokazuje, że pourazowe uszkodzenie trzustki może prowadzić do rozwoju wieloletniego procesu chorobowego o destrukcyjnym i nawrotowym charakterze. Leczenie etapowe z zastosowaniem najnowszych technik endoskopowych pozwala uchronić chorego przed rozległymi zabiegami operacyjnymi, jednak nie eliminuje konieczności długotrwałej i czujnej obserwacji. Skuteczne postępowanie wymaga udziału doświadczonego zespołu, indywidualizacji terapii oraz leczenia w wyspecjalizowanych ośrodkach.

Keywords: acute pancreatitis; walled-off pancreatic necrosis; pancreatic trauma; Wirsung duct; pancreas divisum

Słowa kluczowe: ostre zapalenie trzustki; zbiornik otorbionej martwicy; uraz trzustki; przewód Wirsunga; trzustka dwudzielna

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Introduction

Road traffic accidents and the resulting injuries represent a major global public health burden and are among the leading causes of hospital stays in the working-age population. Most abdominal injuries involve the liver or spleen, whereas pancreatic injuries are exceedingly rare. Epidemiological data indicate that pancreatic injuries occur in 0.2%–1.1% of all trauma patients, depending on the source [1].

The most common complications include acute pancreatitis, pseudocysts, pancreatic cysts, and pancreatic abscesses. These complications may not manifest immediately after the injury but can develop several weeks later. Such cases often require multi-stage, specialised treatment.

Case report

We present a case of a 21-year-old man with no significant medical history, who was initially hospitalised at another centre following abdominal trauma sustained in a road traffic accident in mid-2023.

Given the clinical presentation, mechanism of injury, and diagnostic findings, the patient underwent exploratory laparotomy with drainage of the peripancreatic space. A computed tomography (CT) scan of the abdomen performed on 26 October 2023 found an evolving collection within the oedematous pancreatic head, measuring 23 × 25 × 36 mm, located within an area of necrosis. Infiltrative lesions were also identified in the paraduodenal groove, around the duodenal loop, and in the retroperitoneum surrounding the visceral vessels. Magnetic resonance imaging (MRI) performed the following day showed an enlarged collection measuring 30 × 35 × 69 mm and an additional collection measuring 48 × 35 × 69 mm located superior to the pancreatic head in the hepatic hilum. The collection contained several solid components.

A subsequent abdominal CT scan (31 October 2023) demonstrated further enlargement of thin-walled collections: up to 70 × 43 × 80 mm in the hepatic hilum and 56 × 54 × 67 mm in the pancreatic head.

On 6 November 2023, the patient was urgently admitted to the Department of Gastrointestinal Surgery at the University Clinical Center in Katowice due to acute pancreatitis. Physical examination found significant upper abdominal pain and tenderness, without peritoneal signs. Biochemistry showed elevated pancreatic enzymes: alpha-amylase 669 U/L and lipase 1956 U/L. A CT scan performed on 7 November 2023 showed further progression in the size of collections. The collection in the hepatic hilum measured 85 × 70 × 94 mm and exhibited homogeneous contents, consistent with a pseudocyst. The collection in the pancreatic head measured 68 × 60 × 70 mm, displayed heterogeneous contents, and was consistent with an encapsulated necrotic collection complicated by haemorrhage. The Wirsung duct was dilated proximally to 6 mm by the dense collection and extended toward it, while its distal course could not be seen, raising a suspicion of disconnected duct syndrome (DDS).

On 13 November 2023, cystogastrostomy was performed, with a double-pigtail plastic stent inserted into each collection. Turbid, brown fluid (30 mL) was aspirated from the larger collection for microbiological and biochemical analysis. Aspirate analysis found amylase 14,316 U/L, glucose 46.7 mg/dL, CA 19.9 697 U/mL, CEA 2.67 ng/mL, and negative aerobic and anaerobic cultures.

On 21 November 2023, endoscopic retrograde cholangiopancreatography (ERCP) was performed. Fluoroscopy demonstrated two plastic stents placed during the previously described procedure. Following catheterisation of the ampulla of Vater, access to the pancreatic ducts could not be achieved, even despite the use of cannulotomy. A large minor papilla was identified adjacent to the major papilla and was catheterised; the pancreatic ducts were contrasted. A distal ductal segment, approximately 2.5 cm in length and 3 mm in diameter, was visualised. At this level, contrast extravasation was observed, without a clearly defined site of injury, filling a triangular space containing the tip of the double-pigtail stent inserted during cystogastrostomy. The distal course of the pancreatic duct was visible, with a diameter of up to 5.5 mm within the pancreatic body, but its trajectory toward the major papilla was not delineated. The appearance was consistent with a dorsal duct in a bifid pancreas. The procedure was completed by placing a single-pigtail stent in the pancreatic duct, and thereby achieving effective drainage.

During hospital stay, the patient received antibiotic therapy, intravenous fluid therapy, and parenteral nutrition. Abdominal ultrasonography (US) performed on 27 November 2023 demonstrated reduction in the size of one collection with effective drainage, whereas the second collection was could not be seen due to overlying intestinal gas. Laboratory workup showed a marked decrease in alpha-amylase, lipase, and inflammatory markers, leading to the decision to discharge the patient.

During a follow-up visit at the hospital clinic, an abdominal CT scan was ordered and performed on 10 January

2024, showing complete resolution of the collection in the hepatic hilum and near-complete resolution of the collection in the pancreatic head.

In April 2024, the patient was readmitted to the surgical ward for removal of the pancreatic duct stent. On 10 April 2024, ERCP was performed, during which one of the stents placed during the cystogastrostomy and the pancreatic stent were removed. Unfortunately, contrast extravasation persisted following stent removal; consequently, a straight stent was placed in the pancreatic duct, with its proximal end positioned at the junction of the pancreatic body and tail. A CT scan performed on 11 April 2024 showed further reduction of the post-inflammatory collections, including one that had completely collapsed and another with a maximum dimension of up to 18 mm. Inflammatory parameters were unremarkable, and the patient's good general condition along with absence of pain permitted discharge.

In June 2024, the patient returned to the surgical clinic for a follow-up visit, during which a referral was issued to the Department of Gastroenterology for pancreatic duct stent removal or replacement. He was admitted on 17 October 2024, and ERCP was performed the following day. During the procedure, the remaining cystogastrostomy stent and the pancreatic duct stent were removed. Following contrast administration into the pancreatic ducts, no extravasation was observed. As recommended by the endoscopist, an abdominal CT scan was taken, revealing further reduction of the collection in the pancreatic head and complete resolution of the second collection. Reduction of lymph nodes and peripancreatic reactive changes was also noted. The patient was discharged home in good condition.

At that time, the patient's condition appeared to have stabilised; however, on 26 August 2025, he presented to the Emergency Department with severe, stabbing right upper quadrant pain, rated 8/10 on the numeric rating scale (NRS), radiating to the back, persisting for one week and progressively worsening. Laboratory workup on admission showed alpha-amylase 128 U/L, lipase 553 U/L, and total bilirubin 1.57 mg/dL. A CT scan performed on admission revealed a 26 × 26 × 27 mm collection in the pancreatic head, as well as a new adjacent collection measuring approximately 5.5 mm in diameter. To further assess pancreatic ductal dilatation, magnetic resonance cholangiography (MRC) was performed and showed dilatation of the Wirsung duct at the level of the pancreatic body and tail (up to 4 mm). However, it had a filiform course from the level of the cyst to the orifice, making visualization of the orifice impossible. The presence of an additional duct draining into the minor papilla could not be excluded.

During hospital stay, the patient was managed with a nil-per-os diet, parenteral fluid therapy, analgesia, and anticoagulant prophylaxis. An endoscopic consultation was obtained, but endoscopic treatment was not recommended. Owing to improvement in his clinical condition and normalization of laboratory parameters, the patient was discharged home with appropriate recommendations.

The patient's condition again deteriorated in October 2025, when he was transferred from another facility to the Department of Gastrointestinal Surgery at the University Clinical Center in Katowice due to enlargement of the aforementioned collection to 5 cm and markedly elevated inflammatory markers (CRP 427 mg/L). On 3 October 2025, a repeat cystogastrostomy was performed. Following insertion of an echoendoscope, a thick-walled collection measuring at least 60 × 50 mm was visualized. The collection was punctured through the duodenal wall, followed by insertion of a plastic double-pigtail stent (7F in diameter and 8 cm in length).

Broad-spectrum antibiotic therapy was administered over the subsequent days, allowing for gradual improvement in his general condition and reduced inflammatory parameters, with CRP decreasing to 55 mg/L. Despite suboptimal imaging conditions, ultrasound (US) demonstrated a reduced size of the pancreatic head collection to 22 × 19 mm. On 9 October 2025, the patient was discharged home in good general condition.

Following another visit to the surgical clinic, a follow-up abdominal CT scan was performed on 13 November 2025, confirming further reduction of the pancreatic head collection to 16 × 16 × 24 mm. Proximal to the collection, the pancreatic duct was irregularly dilated, measuring up to 4 mm at the level of the pancreatic tail. From the level of collection, the duct remained non-visualized, precluding exclusion of communication between the duct and the described collection.

On 9 December 2025, the patient was admitted for removal of the double-pigtail cystoduodenostomy stent, which was successfully performed on 10 December 2025, with no complications. Our case report concludes with the patient being discharged in good general condition and pain-free, with a recommendation for follow-up at the surgical clinic in February 2026.

Discussion

The history of the presented case indicates that early diagnosis of pancreatic injury and prompt initiation of treatment do not necessarily prevent long-term, recurrent complications, whose clinical course may extend well beyond the framework of classical acute pancreatitis. Of particular importance is the multi-year disease course, characterized by periods of apparent stability followed by recurrent exacerbations requiring hospital stay and endoscopic intervention. This pattern is consistent with literature data indicating that post-traumatic acute pancreatitis, although rare, is more likely to follow a chronic and recurrent course, particularly when associated with Wirsung duct injury, compared to alcoholic or biliary pancreatitis [2, 3].

Notably, the appearance of the pancreatic duct in serial imaging and endoscopic follow-up suggested disruption or an abnormal course, potentially related to the anatomical variant of pancreas divisum, the most common developmental anomaly of the pancreas, affecting up to 15% of the population. It results from failure of fusion of the pancreatic buds during foetal development, leading to drainage of most of the glandular tissue via the dorsal duct into the minor papilla, while the ventral duct

drains the head and uncinate process through the major papilla. Coexisting pancreatic duct injury and anatomical anomalies can substantially complicate both diagnosis and treatment. The coexistence of these factors may promote persistent pancreatic juice leakage and recurrent formation of peripancreatic collection [4].

During the diagnostic process, disconnected duct syndrome (DDS), a known complication of severe necrotizing pancreatitis and pancreatic injury, was also considered. Disruption of the main pancreatic duct results in functional separation of the secretory pancreatic parenchyma and persistent impairment of pancreatic juice outflow. This condition leads to recurrent peripancreatic collections, fistula formation, and subsequent inflammatory episodes. This pattern is reflected in the clinical course of our patient, in whom, despite periodic improvement following conservative and endoscopic treatment, recurrent collections were observed, consistent with the typical presentation of DDS [5, 6].

The use of endoscopic transmural drainage of the collections and pancreatic duct stenting were key elements of the treatment, allowing to avoid extensive surgery and aligning with current trends in minimally invasive management, particularly given the patient's young age. Contemporary studies have shown that this step-up approach, when implemented in specialized centres, is associated with better long-term outcomes than conventional surgical treatment [7, 8].

This case underscores the need for long-term follow-up of patients with pancreatic injuries, even after radiological regression of lesions. Recurrent inflammatory episodes occurring months or even years later should prompt more thorough diagnostic evaluation and reassessment of the therapeutic strategy, considering not only functional but also, as in the present case, anatomical factors.

Conclusions

The aim of this study was to present the complexity of the diagnostic and therapeutic process in cases of post-traumatic pancreatic injury. Despite multi-stage treatment following current guidelines, the young patient developed a long-term, recurrent disease. This case demonstrates that the sequelae of pancreatic injury may be significantly delayed and include complications extending beyond typical acute pancreatitis.

The suspicion of disconnected pancreatic duct syndrome and the coexistence of pancreas divisum were of particular importance in this case. The inability to definitively confirm these abnormalities substantially complicated both imaging assessment and the selection of an optimal therapeutic strategy. The use of endoscopic techniques allowed to avoid extensive surgical procedures and resulted in satisfactory clinical outcomes. These findings underscore the need for long-term follow-up of patients with pancreatic injuries and individualized treatment in specialized centres with appropriate diagnostic and therapeutic resources.

References

1. Dave S, Toy FK, London S. Pancreatic trauma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
2. Bradley EL 3rd, Young PR Jr, Chang MC, et al. Diagnosis and initial management of blunt pancreatic trauma: guidelines from a multiinstitutional review. Ann Surg, 1998; 227(6): 861–869. doi: 10.1097/00000658-199806000-00009
3. Debi U, Kaur R, Prasad KK, et al. Pancreatic trauma: a concise review. World J Gastroenterol, 2013; 19(47): 9003–9011. doi: 10.3748/wjg.v19.i47.9003
4. Kushnir VM, Wani SB, Fowler K, et al. Sensitivity of endoscopic ultrasound, multidetector computed tomography, and magnetic resonance cholangiopancreatography in the diagnosis of pancreas divisum: a tertiary center experience. Pancreas, 2013; 42(3): 436–441. doi: 10.1097/MPA.0b013e31826c711a
5. Verma S, Rana SS. Disconnected pancreatic duct syndrome: updated review on clinical implications and management. Pancreatology, 2020; 20(6): 1035–1044. doi: 10.1016/j.pan.2020.07.402
6. Satyam S, Singh S, Sah PK. Disconnected pancreatic duct syndrome: a case series. Euroasian J Hepatogastroenterol, 2022; 12(1): 60–63. doi: 10.5005/jp-journals-10018-1357
7. van Santvoort HC, Besselink MG, Bakker OJ, et al.; Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med, 2010; 362(16): 1491–1502. doi: 10.1056/NEJMoa0908821
8. Bang JY, Arnoletti JP, Holt BA, et al. An endoscopic transluminal approach, compared with minimally invasive surgery, reduces complications and costs for patients with necrotizing pancreatitis. Gastroenterology, 2019; 156(4): 1027–1040.e3. doi: 10.1053/j.gastro.2018.11.031

PROFESSOR STANISŁAW ILNICKI (1942–2025) – MEDICAL DOCTOR, SCIENTIST, HUMANIST

Profesor Stanisław Ilnicki (1942–2025) – lekarz, naukowiec, humanista

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Abstract

This article presents the profile of Professor Stanisław Ilnicki, an eminent specialist in military psychiatry who is widely regarded as a pioneer and leading authority in this field in Poland. He was the initiator of national research on combat stress and one of the architects of the psychological support system for military personnel, encompassing both participants of overseas missions and military veterans. Professor Ilnicki's scholarly output includes hundreds of publications and conference presentations, documenting his research interests as well as his practical commitment to the development of military psychiatry, particularly in its clinical and educational dimensions. The aim of this paper is to present Professor Stanisław Ilnicki's scientific and implementation achievements across all areas of his professional activity. Owing to the breadth and diversity of these accomplishments, this constitutes a significant scholarly challenge. Therefore, given the nature of this paper, a selective approach was adopted, limiting the analysis to several representative works reflecting the principal directions of his scholarly interests. Consequently, the study focuses on highlighting the Professor's most significant scientific achievements, emphasizing his contribution to the development of the psychiatric care system within the Polish Armed Forces, and underscoring his role as a mentor and authority for many generations of physicians.

Streszczenie

Artykuł przedstawia sylwetkę profesora Stanisława Ilnickiego, wybitnego specjalisty w dziedzinie psychiatrii wojskowej, uznawanego za jej nestora w Polsce. Był on inicjatorem krajowych badań nad stresem bojowym oraz jednym z twórców systemu pomocy psychologicznej dla żołnierzy, obejmującego zarówno uczestników misji zagranicznych, jak i weteranów służby wojskowej. Dorobek naukowy Profesora obejmuje setki publikacji i wystąpień, dokumentujących jego zainteresowania badawcze oraz praktyczne zaangażowanie w rozwój psychiatrii wojskowej, przede wszystkim w wymiarze klinicznym i dydaktycznym. Celem niniejszego opracowania jest przedstawienie dorobku naukowego i wdrożeniowego Stanisława Ilnickiego we wszystkich obszarach jego działalności. Zadanie to, ze względu na rozległość i różnorodność osiągnięć, stanowi jednak istotne wyzwanie badawcze, dlatego z uwagi na charakter artykułu dokonano selekcji materiału, ograniczając analizę do kilkunastu prac reprezentatywnych dla głównych nurtów jego zainteresowań. W konsekwencji opracowanie koncentruje się na ukazaniu najważniejszych osiągnięć naukowych Profesora, podkreśleniu jego wkładu w rozwój systemu opieki psychiatrycznej w Polskich Siłach Zbrojnych oraz wskazaniu jego roli jako mentora i autorytetu dla wielu pokoleń lekarzy.

Keywords: Polish psychiatrist; Stanisław Ilnicki; military psychiatry; combat stress

Słowa kluczowe: polscy psychiatrzy; Stanisław Ilnicki; psychiatria wojskowa; stres bojowy

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It was with profound sadness that we received the news of the passing of Dr. Stanisław Ilnicki, MD, PhD, professor at the Military Institute of Medicine - National Research Institute and an outstanding military psychiatrist, valued scientist, dedicated educator, and humanist. Dr. Stanisław Ilnicki was a physician by vocation and a man of extraordinary sensitivity. He devoted his life to serving others, particularly those affected by trauma and suffering. His professional and scientific work left a lasting mark on Polish psychiatry, particularly in military care. He is regarded as the founder of Polish military psychiatry in the field of combat stress and post-traumatic stress disorder (PTSD), a pioneer of combat stress research in Poland, and a co-creator of the mental health support system within the Polish Armed Forces (Fig. 1).

Stanisław Ilnicki was born on May 8, 1942, in Klesów, Volhynia. After the war, his family settled on the coast. He began his schooling in Lębork and, in 1959, passed his A-levels at King Jan III Sobieski High School in Wejherowo, to which he remained emotionally attached throughout his life. He started his studies at the Jagiellonian University but, after one year, transferred to the Military Medical Academy in Łódź, graduating with distinction in 1966 as the top student in his class. His need for a deeper understanding of human nature is further evidenced by his completion of philosophy studies at the University of Warsaw in 1972. Philosophy became an important foundation for his understanding of humanity and his work as a physician. In 1978, he defended his doctoral dissertation on predicting adaptation to military service, and in 2000, he obtained a postdoctoral degree.

Figure 1. Stanisław Ilnicki (from the WIM–PIB archives)

He began his professional career at the Military Institute of Medicine–National Research Institute (WIM–PIB) in Warsaw, the successor to and continuation of the former Central Clinical Hospital of the Military Medical Academy (CSK WAM) [1]. After obtaining specialization in psychiatry between 1971 and 1973, he worked at the Mental Health Clinic (PZP) for many years, where he earned the respect of both patients and colleagues. In 1980, he became head of the Clinic and later took over the management of the Day Psychiatric Ward.

As a physician, he distinguished himself by an approach based on empathy and respect. Rather focusing on the symptoms alone, he sought to understand people in the full complexity of their experiences. Managing the clinic provided the foundation for establishing a specialized PTSD treatment centre. After nearly four decades of dedicated work, in 2005 he led the establishment of the Clinic of Psychiatry, Combat Stress and Psychotraumatology at the Military Institute of Medicine–National Research Institute [2], which he subsequently headed. It was one of the first centres in Poland to provide comprehensive PTSD therapy, particularly for veterans of foreign missions and their families. For many patients, the Clinic became a place of support and understanding. The centre also provided psychiatric and psychological care for Polish Army soldiers experiencing symptoms of PTSD, as well as to their close ones and other victims, including victims of terrorist attacks.

He became known within the military community as “the doctor who patched up soldiers’ souls”, a nickname that best reflected both the nature of his work and his relationships with patients.

In parallel, he conducted scientific research, also in the field of forensic psychiatry, collaborating with institutions involved in the investigation and prevention of crime.

The Professor’s scientific achievements, encompassing hundreds of publications and scientific presentations documenting both his research interests and his practical contributions to the development of military psychiatry, were primarily clinical and educational in nature. The establishment of the Clinic of Psychiatry and Combat Stress at the Military Institute of Medicine, as well as the development of a model for the diagnosis and treatment of PTSD in soldiers, the prevention of combat stress, and the provision of care to veterans were his most important scientific contributions.

The Professor’s research interests focused on key areas of psychiatry, particularly those related to contemporary experiences, stress, and the psychological consequences of military service.

His key contribution to the development of military psychiatry included research on the epidemiology of mental disorders in the military environment, particularly the mental health of soldiers returning from foreign deployments.

A significant achievement was his scientific editorship of the Polish edition of the monograph Combat Stress Injury: Theory, Research, and Management, the first comprehensive Polish-language publication devoted to the psychological effects of combat exposure. The publication was intended for specialists providing mental care to soldiers and veterans of the Polish Military Contingents (PMC) as well as their family members.

The results of research conducted within the project "The Impact of Individual Characteristics and Family Structure on the Adaptability of Polish Military Contingent (PMC) Veterans to Socio-Professional Functioning After Mission Completion" also found practical application. They were used in war trauma psychotherapy, including PTSD in PMC veterans. The study was the first attempt in Poland to assess the impact of deployment and combat exposure on family relationships and marital communication among PMC veterans [4–6].

Another study evaluating the efficacy of psychotherapy in PMC veterans with PTSD demonstrated, among other findings, that no single universal therapeutic approach exists and that treatment strategies used in NATO armies cannot be directly transferred to Poland. The clinical picture of PTSD is complex, requiring individualized diagnosis, a prolonged diagnostic process, and the management of specific barriers to effective therapy. Effective treatment often requires family involvement, combining various psychotherapeutic strategies with pharmacotherapy, and consideration of co-occurring physical injuries and somatic symptoms that may mask PTSD [7, 8].

The professor also initiated systematic research for the Ministry of National Defence, focusing on the psychological effects of military service. The epidemiological significance of this research primarily lay in determining the prevalence of mental disorders in a specific professional group, identifying risk factors associated with military deployment, and highlighting the underestimation of the problem arising from the stigmatization of individuals struggling with mental health issues [9–11].

He presented the results of his scientific research and experience gained in clinical practice in professional journals and at numerous national and international conferences, including NATO workshops on PTSD.

The professor's earlier research interests focused largely on medical examinations and qualifications for military service, including the assessment of military fitness among conscripts and soldiers, military medical examinations, and forensic psychiatric expertise. His theoretical work in this field included, among other topics, the assessment of suicide in military compensation proceedings, the analysis of the causal relationship between neurosis, schizophrenia, and encephalopathy and military service, as well as the issue of disability among professional soldiers deemed unfit for service [12–18].

The Professor's interests further included issues related to the diagnosis and psychiatric care of soldiers, with a focus on ongoing medical care and psychological support. The need for psychological support for soldiers was overlooked by state and military authorities for many post-war years. Until 1994, Poland lacked a comprehensive legal framework for mental healthcare; these matters were addressed only fragmentarily through scattered regulations. Only the Mental Health Protection Act [19] comprehensively regulated the rights of psychiatric patients, the principles of compulsory treatment, and the organization of care. It also became a reference point for psychiatric reforms in the military health service [20]. These issues constituted a significant part of the professor's clinical and scientific work. The conclusions from the research, including those concerning the prevention of adjustment disorders in soldiers and the analysis of the Act in terms of organizational changes in mental health care, were submitted to the Ministry of National Defence and provided a basis for creating a military psychologist position. The professor's work became the starting point for developing military implementing regulations [21–25]. He also participated in the team responsible for preparing materials for the Minister of National Defence. This work contributed to the decision to organize psychoprophylactic activities within the Armed Forces. The practical outcome was the employment of approximately 120 psychologists in the military, serving as consultants to unit commanders on psychoprophylactic matters.

Prevention and management of alcohol-related problems in the military population, which he encountered daily while working at the Mental Health Clinic, was equally important area of the Professor's work. While conducting research on alcohol dependence among soldiers, he focused on the effectiveness of outpatient therapy, particularly in settings with limited access to inpatient treatment. His work also focused on adapting established international therapeutic models to the realities of the Polish healthcare system. Of particular importance was the evaluation of the efficacy of outpatient treatment for alcohol dependence based on the Minnesota Model, which combines psychotherapy, the Twelve-Step Program [26], and group therapy. Analyses conducted in a sample of patients at the Mental Health Clinic demonstrated that this model can be used in an outpatient setting, which had significant practical implications given the limited resources of the healthcare system [26, 27].

As a distinguished specialist in his field, he also provided numerous psychiatric and psychological consultations to patients in other clinics at the Military Institute of Medicine. In the 1990s, he initiated collaboration with the Haematology Clinic and the Center of Bone Marrow Transplant at the Central Clinical Hospital of the Military Medical Academy. This collaboration resulted in publications and conference presentations highlighting the importance of psychological and psychiatric support during bone marrow transplantation and chemotherapy for haematological malignancies.

Works on the history of psychiatry and military psychology in Poland and other countries constitute a significant part of his scientific output [28]. These papers addressed:

- the history of military health service,
- the development of military psychiatry in Poland,
- biographies of important military doctors,
- editing and translation of old medical texts.

Figure 2. Stanisław Ilnicki, winner of the Director's Award for organizational achievements, 2016 (from the WIM–PIB archives)

Figure 3. Stanisław Ilnicki, scientific presentation at the conference on September 30, 2025, Warsaw (from the WIM–PIB archives)

Among the Professor's achievements, the Polish translation of Antoni Schneeberger's *De bona militum valetudine conservanda liber*, *the oldest modern military hygiene manual*, a book on maintaining good health for soldiers, deserves particular mention [29]. He worked on this publication for approximately 15 years. The introduction, translation, footnotes, and indexes were prepared by Professor Ilnicki. The Latin text and translation were edited by Dr. Robert A. Sucharski, MD, PhD.

His passion for the history of psychiatry is also evidenced by the extensive work he devoted to the development and publication of the *Bibliography of Scientific Works in the Field of Military Psychiatry and Related Fields of Psychology for the Years 1940–1970* [30]. In addition to his professional work and numerous responsibilities, the Professor continually upgraded his qualifications by completing internships in Sweden, Germany, the Netherlands, the United States, and other countries. He also served as a consultant in psychiatry for the Military Health Service and was also a member and activist of the Polish Society of Forensic Psychiatry and the Polish Society for Traumatic Stress Research.

Teaching was an important part of his work. He sought to impart to young physicians not only knowledge and experience but also a strong work ethic grounded in responsibility, commitment, and service to others.

In 2011, the Professor received the "Buzdygan" award for his lifetime achievement, presented by the editorial staff of the magazine "Polska Zbrojna," and in 2020, he received the prestigious Pro Publico Bono award. His work was also recognized on numerous occasions by the Director of the Military Institute of Medicine for his organizational, scientific, and implementation achievements. The laudations emphasized his passion for psychiatry, military service, and the history of military healthcare (Fig. 2).

He worked actively almost until the end of his life, despite being retired for many years. His last scientific presentation was devoted to the contemporary mental health crises in the Polish Army at a conference held on September 30, 2025 (Fig. 3). He passed away on October 24, 2025.

Professor Stanisław Ilnicki will be remembered as a physician who combined concern for patients' mental health with respect for their dignity.

References

1. Rozporządzenie Ministra Obrony Narodowej z dnia 27 listopada 2002 r. w sprawie utworzenia Wojskowego Instytutu Medycznego (Dz. U. Nr 201, poz. 1699 z późn. zm.)
2. Zarządzenie nr 12 Dyrektora Wojskowego Instytutu Medycznego z dnia 28 listopada 2005 r. w sprawie ustanowienia Regulaminu Organizacyjnego Wojskowego Instytutu Medycznego
3. Figley CR, Nash WP, red. Stres bojowy: teorie, badania, profilaktyka i terapia. Ilnicki S, red. nauk. wyd. pol.; Dragan-Polak M, Höffner M, Radzicki J, tłum. Warszawa: Wydawnictwo Naukowe PWN; Wojskowy Instytut Medyczny; 2010

4. Szymańska S, red. Tułaczka Odyseusza: powrót z wojny do domu: praca zbiorowa. Warszawa: Wojskowy Instytut Medyczny; 2017.
5. Szymańska S. Nadal razem czy osobno? Wpływ zdarzeń wojennych o charakterze traumatycznym i objawów zespołu stresu pourazowego na relację małżeńską polskich weteranów. W: 45. Zjazd Psychiatrów Polskich PTP 2016: Człowiek i rodzina a zdrowie psychiczne. Katowice, 16–18 czerwca 2016: s. 106–107
6. Szyszko-Ginalska S, Szymańska S. Czy mnie słyszysz? Ekspozycja na stres bojowy a komunikacja w rodzinach polskich weteranów. W: 45. Zjazd Psychiatrów Polskich PTP 2016: Człowiek i rodzina a zdrowie psychiczne. Katowice, 16–18 czerwca 2016: s. 107
7. Ilnicki S. System oceny zdolności psychicznej do służby wojskowej poborowych w Polsce. W: Florkowski A, Gruszczyński W, red. Zdrowie psychiczne żołnierzy. Łódź: Wojskowa Akademia Medyczna; 2000: s. 2–12
8. Ilnicki S. System oceny zdolności psychicznej do służby wojskowej poborowych w wybranych państwach europejskich. W: Florkowski A, Gruszczyński W, red. Zdrowie psychiczne żołnierzy. Łódź: Wojskowa Akademia Medyczna; 2000: s. 13–23
9. Filarowska M, Ilnicki S, Młożniak E, et al. Problemy adaptacyjne żon polskich weteranów poszkodowanych w misjach w Iraku i Afganistanie. Lek Wojsk, 2013; 92(2): 138–144
10. Kosińska L, Ilnicki S, Petrović A, et al. Zaburzenia snu u weteranów Polskich Kontyngentów Wojskowych. Lek Wojsk, 2014; 92(1): 14–18
11. Zbyszewski M, Ilnicki S, Wiederhold B, et al. Personality and stress-coping factors in VR computer-assisted stress inoculation training of Polish ISAF soldiers. W: Wiederhold BK, red. New Tools to Enhance Posttraumatic Stress Disorder Diagnosis and Treatment: Invisible Wounds of War. Amsterdam: IOS Press; 2013, s. 172–180. doi: 10.3233/978-1-61499-189-2-172
12. Ilnicki S. Ekspertyza sądowo-psychiatryczna w wojsku w świetle teorii i praktyki orzeczniczej. Wojsk Przegl Prawn, 1992; 65(3–4): 45–53
13. Ilnicki S. Nerwice u żołnierzy zawodowych jako problem orzeczniczy [Neuroses in the professional military staff as a problem for military medical certification]. Biul WAM, 1986; 29(3): 219–221
14. Ilnicki S, Gajerska A. Zmiany struktury rozpoznań i decyzji orzeczniczych u żołnierzy badanych w latach 1967–1976 w Poradni Zdrowia Psychicznego CKP WAM. Lek Wojsk, 1979; (2 jawny): 68–74
15. Ilnicki S. Prognozowanie adaptacji do zasadniczej służby wojskowej na podstawie krótkiego, standaryzowanego wywiadu psychiatrycznego [praca doktorska]. Warszawa: Wojskowa Akademia Medyczna; 1977
16. Ilnicki S. Rozbieżności w ocenie zdolności do służby wojskowej w przypadkach nerwic i zaburzeń osobowości. Lek Wojsk, 1976; 52(2): 81–85
17. Ilnicki S, Bukowski S. Samobójstwo jako przedmiot ekspertyzy psychiatryczno-psychologicznej w wojskowym postępowaniu odszkodowawczym. Lek Wojsk, 1993: 69(9–10): 450–456
18. Ilnicki S. Nieprawidłowa osobowość (psychopatia) a inwalidztwo żołnierzy zawodowych. Lek Wojsk, 1990; 66(1–2): 1–4
19. Ustawa z dnia 19 sierpnia 1994 r. o ochronie zdrowia psychicznego (Dz. U. Nr 111, poz. 535). [dostęp 27.04.2026] https://isap.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=wdu19941110535
20. Ilnicki S. Zadania wojska wynikające z ustawy o ochronie zdrowia psychicznego. W: Psychologia a żołnierska służba: zbiór materiałów z dyskusji zorganizowanej przez Wojskową Akademię Medyczną i redakcję miesięcznika „Wojsko i Wychowanie". Seweryn F, Tomiło J, red. Warszawa: Wydawnictwo Czasopisma Wojskowe; 1995, s. 47–49
21. Ilnicki S. Dwa modele zapobiegania zaburzeniom adaptacyjnym u żołnierzy. W: Misztal Z, red. Ekologia i wychowanie. Środowisko, zdrowie, wychowanie. Warszawa: Wydawnictwo MON; 1989, s. 173–178
22. Ilnicki S, Bukowski S. Rola psychologa w zapobieganiu zaburzeniom adaptacyjnym żołnierzy. Wojsko i Wychow, 1991; 11: 32–34
23. Ilnicki S, Dziewulski H. Opinie żołnierzy służby zasadniczej na temat poradnictwa psychiatryczno-psychologicznego w wojsku. Lek Wojsk, 1996; 72 (1–2): 3–9
24. Ilnicki S. Psychoprofilaktyka elementem humanizacji życia wojskowego. W: Oficer, dowódca, wychowawca: z zagadnień współczesnej myśli pedagogicznej w wojsku; Materiały z konferencji na temat: „Edukacja humanistyczna w wykształceniu dowódcy", 13–14 czerwca 1996 roku, Toruń-WSO im. gen. J. Bema. Warszawa: Ministerstwo Obrony Narodowej, Departament Stosunków Społecznych, Biuro Edukacji Obywatelskiej; 1996, s. 223–230
25. Brown S. Leczenie alkoholików. Rozwojowy model powrotu do zdrowia. Warszawa: Państwowy Zakład Wydawnictw Lekarskich; 1990
26. Bukowski S, Bukowska B, Ilnicki S. Leczenie alkoholików według „Modelu Minnesota" w wojskowej Poradni Zdrowia Psychicznego. Lek Wojsk, 1996; 72(5–6): 288–292
27. Bukowski S, Bukowska B, Ilnicki S. Ocena efektywności ambulatoryjnej terapii alkoholików wzorowanej na modelu Minnesota. Alkoholizm i Narkomania, 1999; 35(2): 237–245
28. Augustynowicz D, Połeć D, Witkowska L. Pułkownik dr hab. n. med. Stanisław Ilnicki – prof. WIM-PIB (1942–2025). Lekarz – badacz historii medycyny wojskowej. Biuletyn GBL – Historia, 2026; 3: 195–216
29. Schneeberger A. De bona militum valetudine conservanda liber: Księga o zachowaniu dobrego zdrowia żołnierzy. Ed. tekstu łac. i przekł. Sucharski RA; przypisy Ilnicki S, Sucharski RA; wstęp, indeksy i red. całości dzieła Ilnicki S; nota wydawnicza Nowak TM. Warszawa: Wydawnictwo DiG, 2008.
30. Ilnicki S, oprac. Bibliografia prac naukowych z zakresu psychiatrii wojskowej i pokrewnych dziedzin psychologii za lata 1940–1970. Warszawa: Rada Nauk Społecznych MON, Rada Naukowa MON ds. Medycyny i Farmacji Wojskowej; 1973.