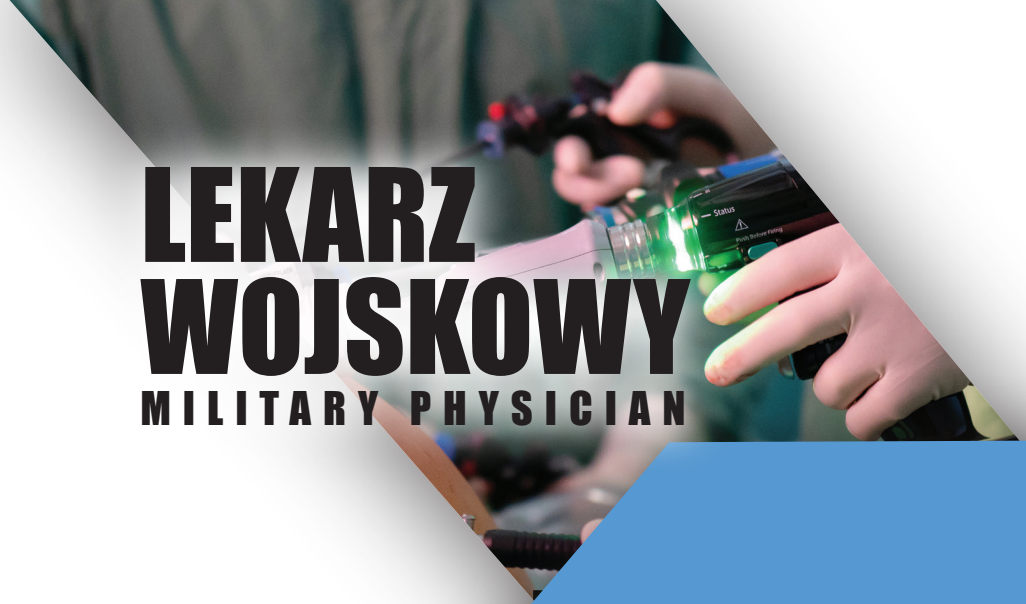

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   Calpin C, Macarthur C, Stephens D, et al. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systemic review of the literature. J Allergy Clin Immunol, 1997; 100: 452–457 . doi: 10.1016/s0091-6749(97)70134-9

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

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Dear Readers,

Modern medicine is evolving at a dynamic pace. We continue to witness the emergence of novel therapeutic approaches, new healthcare challenges, and increasingly complex scenarios that call for cross-disciplinary collaboration.

It is particularly gratifying to note that the papers published in this issue are the result of joint efforts by researchers and clinicians from diverse academic and medical centres. This diversity of perspectives remains one of the greatest strengths of contemporary science, enabling the development of solutions that address the real needs of both patients and the healthcare system.

The second issue of *Lekarz Wojskowy* (*Military Physician*) this year features papers exploring innovative therapeutic avenues, including the application of platelet-rich plasma in oral surgery and current trends in oncological treatment. Our contributors also address essential topics such as the paediatric microbiome, nosocomial infections, cardiovascular diseases, and the impact of physical activity on cognitive function in older adults.

Crucially, this issue also places a strong emphasis on military medicine and health security. It presents comprehensive studies on the impact of military service in extreme conditions on soldiers' health, civil-military cooperation during mass-casualty incidents, and the medical consequences of modern armed conflicts – themes that carry profound significance in today's world.

I would like to express my sincere gratitude to the Authors for their trust and for choosing our journal to share their research findings. My thanks also go to the Reviewers for their unwavering commitment, and to you, our Readers, for your continued engagement and for helping shape the professional community around *Lekarz Wojskowy*.

I wish you an inspiring read and a well-deserved respite from your daily responsibilities during the summer season.

With best regards

Prof. Bolesław Kalicki, MD, PhD

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Military Physician – 20 points Ministry of Science and Higher Education

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THE EFFECT OF VITAMIN C ON ALVEOLAR HEALING FOLLOWING TOOTH EXTRACTION

Wpływ witaminy C na gojenie zębodołu po ekstrakcji zęba

Patrycja Różak, Konstancja Nosowicz, Adrianna Gliszczyńska, Nina Szczepańska, Adam Łuczak, Agata Tuczyńska

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Abstract

Introduction: Over the past decades, significant advancements have been made in understanding oral wound healing mechanisms, which are increasingly being integrated into clinical practice. Tooth extraction remains one of the most common procedures in dental practice, underscoring the need for continued investigation into strategies that promote optimal regeneration of both soft and hard oral tissues. Ascorbic acid (vitamin C) is a water-soluble micronutrient essential for physiological functions, including collagen synthesis and immune modulation, both critical for efficient wound healing. Unlike most animals, humans are unable to endogenously synthesize vitamin C due to the absence of the enzyme L-gulonolactone oxidase, and therefore require its dietary intake. In post-extraction care, vitamin C supplementation may serve as a valuable adjunct to conventional dental management, offering a readily accessible means of enhancing tissue repair and improving clinical outcomes. **Aim:** This study aimed to assess the role of vitamin C in tissue regeneration, focusing on alveolar socket healing following tooth extraction. We performed a review of scientific literature addressing the impact of vitamin C on wound healing and bone regeneration processes to provide evidence-based recommendations for its application in dental practice. **Materials and methods:** The data presented in this study were derived from peer-reviewed scientific publications available in the PubMed database. The analysed studies spanned various countries and included populations diverse in age, geography, and socioeconomic status. **Conclusions:** Vitamin C promotes alveolus healing post-tooth extraction by accelerating tissue regeneration, reducing inflammation, and alleviating pain. Supplementation with doses of 600–2000 mg/day, as well as local application (including nanotechnology and submucosal injections), enhances healing and reduces the risk of alveolar osteitis. Vitamin C therapy can complement standard post-extraction care, especially in patients with impaired healing.

Streszczenie

Wprowadzenie: W ciągu ostatnich dziesięcioleci poczyniono znaczące postępy w zrozumieniu mechanizmów gojenia ran w jamie ustnej, które coraz częściej są wdrażane do praktyki klinicznej. Ekstrakcja zębów pozostaje jednym z najczęściej wykonywanych zabiegów w gabinetach dentystycznych, co podkreśla potrzebę dalszych badań nad strategiami wspomagającymi regenerację tkanek miękkich i twardych jamy ustnej. Kwas askorbinowy (witamina C) to rozpuszczalny w wodzie mikroskładnik odżywczy, niezbędny do wielu funkcji fizjologicznych, w tym syntezy kolagenu i modulacji układu odpornościowego, które są kluczowe dla efektywnego gojenia ran. W przeciwieństwie do większości zwierząt, ludzie nie mogą endogennie syntetyzować witaminy C z powodu braku enzymu oksydazy L-gulonolaktonowej, co wymaga jej dostarczania wraz z dietą. W opiece poekstrakcyjnej suplementacja witaminą C może stanowić cenny dodatek do tradycyjnego leczenia stomatologicznego, oferując łatwo dostępne narzędzie wspomagające naprawę tkanek i poprawiające wyniki kliniczne. **Cel pracy:** Celem niniejszego opracowania jest analiza roli witaminy C w procesach regeneracji tkanek, ze szczególnym uwzględnieniem gojenia zębodołu po ekstrakcji zęba. Badanie opiera się na przeglądzie literatury naukowej dotyczącej wpływu witaminy C na mechanizmy gojenia ran oraz procesy odbudowy kostnej i ma na celu opracowanie rekomendacji opartych na dowodach naukowych w zakresie jej zastosowania w praktyce stomatologicznej. **Materiały i metody:** Dane zaprezentowane w niniejszej pracy pochodzą z recenzowanych publikacji naukowych dostępnych w bazie PubMed. Analizowane badania zostały przeprowadzone w różnych krajach i obejmowały populacje zróżnicowane pod względem wieku, lokalizacji geograficznej oraz uwarunkowań społeczno-ekonomicznych. **Wnioski:** Witamina C wspomaga gojenie zębodołu po ekstrakcji, przyspieszając regenerację tkanek, redukując stan zapalny oraz łagodząc ból. Suplementacja w dawkach 600–2000 mg/dobę oraz miejscowa aplikacja (w tym z wykorzystaniem nanotechnologii i iniekcji) poprawiają gojenie i zmniejszają ryzyko zapalenia kości zębodołowej. Terapia witaminą C może stanowić uzupełnienie standardowego postępowania, zwłaszcza u pacjentów z trudnościami w gojeniu.

Keywords: tooth extraction; bone regeneration; vitamin C; alveolus

Słowa kluczowe: ekstrakcja zęba; regeneracja kości; witamina C; zębodół

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Introduction

The past few decades have witnessed a substantial expansion of knowledge of oral wound healing mechanisms, which are being increasingly introduced into modern clinical practice [1]. Tooth extraction remains one of the most common dental procedures, underscoring the need for ongoing research into regenerative potential of hard and soft oral tissues [2, 3].

Ascorbic acid (vitamin C) is essential for human life; it is water-soluble and obtained through the diet [4]. It can be synthesized from D-glucose by most animals, but not by humans, other primates, or some animal species such as guinea pigs, fruit bats, certain species of fish, insects, and birds. Vitamin C synthesis relies on the enzyme L-gulonolactone oxidase, which is absent in these animals [5], therefore it must be supplied exogenously. The recommended daily intake is 75 mg for women and 90 mg for men. Deficiency typically develops following long-term (several weeks) intake of less than 10 mg per day [6] (Tab. 1). Vitamin C deficiency can lead to scurvy, symptoms of which include gingival hyperplasia and bleeding, impaired wound healing, altered dentin structure, bone demineralisation, abnormal tooth mobility, and tooth loss [7].

In the context of tooth extraction, postoperative vitamin C supplementation may serve as an important adjunct to standard dental care. It is a readily available and potentially effective approach that supports tissue regeneration and enhances healing, which may translate into more favourable clinical outcomes [8].

The aim of this study was to assess the role of vitamin C in tissue regeneration, particularly in alveolar socket repair following tooth extraction, and to present evidence-based recommendations for its use in dental practice. The study was based on a review of scientific literature addressing the effects of vitamin C on wound healing and bone regeneration. It further evaluated the efficacy of vitamin C supplementation in improving clinical outcomes following tooth extraction, taking into account its potential role in accelerating tissue healing, reducing inflammation, and minimizing the risk of complications.

Materials and methods

The data presented were derived from peer-reviewed publications retrieved from the PubMed database. The studies analysed were conducted across multiple countries and encompassed populations diverse in terms of age, geographic location, and socioeconomic background. The literature search was conducted between January and May 2025. Only articles published in English or Polish and available full-text online were included. The following keywords were employed in the literature search: vitamin C, tooth socket, ascorbic acid, tooth extraction, and healing process. Only papers published in peer-reviewed journals directly related to the topic of the study were included in the analysis.

Physiological alveolar socket healing

The process of alveolar bone regeneration begins immediately after tooth extraction and can last up to six months [9]. Nevertheless, literature data indicate that alveolar modelling and remodelling are considerably longer, often extending beyond one year following the procedure [10, 11].

Following tooth extraction, the alveolar socket is immediately filled by a blood clot, initiating spontaneous healing. The clot subsequently undergoes progressive transformation into granulation tissue, typically within 2–7 days. Reepithelialisation is initiated within the first 24 hours following the procedure and is generally completed within 1–4 weeks [12]. Socket healing occurs in several stages, comprising four distinct yet temporally overlapping

Table 1. Daily vitamin C intake – RDA, deficiency, and excess (by sex)

Group	RDA (mg/day)	Deficiency (mg/day)	Symptoms of deficiency	Excess (mg/day)	Symptoms of excess
Female adults (≥18 years)	75	<10	Scurvy, gingival bleeding, impaired wound healing, fatigue	>2000	Diarrhoea, nausea, abdominal pain, risk of kidney stones
Male adults (≥18 years)	90	<10	As above	>2000	As above
RDA – recommended dietary allowance					

phases: haemostasis and coagulation, the inflammatory phase, the proliferative phase, and the remodelling phase. The development of lamellar bone and marrow facilitates the relatively rapid progression of the early stages of healing in humans; however, remodelling of the newly formed bone proceeds considerably more slowly and may continue for many years following tooth extraction [11, 13].

Haemostasis and coagulation

The socket healing process begins immediately after tooth extraction, with the first step being haemostasis, which aims to stop bleeding and stabilize the wound. Bleeding activates the coagulation cascade, leading to platelet aggregation on the exposed vascular surface. Platelets subsequently interact with the extracellular matrix and endothelial cells, giving rise to a fibrin clot [14].

In addition to its role in arresting bleeding, the clot serves as a biological scaffold, facilitating the attachment and migration of cells involved in the subsequent phases of tissue repair, including fibroblasts, mesenchymal cells, and leukocytes [15]. Platelets aggregate at the site of injury and release growth factors, including platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), as well as proinflammatory cytokines, collectively initiating inflammatory and regenerative processes [14, 15]. A fibrin clot is formed, serving as a temporary scaffold and protective barrier that prevents further bleeding and facilitates the migration of cells involved in tissue repair [16].

During the first 7 days after the procedure, the clot gradually degrades and is replaced by well-vascularized granulation tissue, consisting mainly of young connective tissue containing multiple blood vessels, mesenchymal cells and leukocytes [11, 13]. In a histological study by Trombelli et al. (2008) [11], biopsies retrieved from alveolar sockets 2–4 weeks following extraction contained predominantly mesenchymal cells and a small number of red blood cells, suggesting that the primary clot undergoes complete transformation within the first week of the healing process. This early clot transformation lays the foundation for the initiation of subsequent repair phases, including the inflammatory and proliferative phases, during which further tissue maturation and structural alveolar socket remodelling occur [11, 14].

Inflammation

The inflammatory phase begins almost simultaneously with haemostasis and typically lasts 24 to 72 hours. Neutrophils, followed by monocytes and macrophages, infiltrate the extraction site, clearing dead cells, tissue debris, and microorganisms. Macrophages also play a regulatory role, by secreting cytokines and growth factors (including TGF-β, IL-1, IL-6), which initiate further repair processes. Although inflammation represents a physiological response, excessive inflammation may disrupt or delay healing [17, 18].

Proliferation

The proliferative phase begins within a few days following tooth extraction and may persist from several days to several weeks, depending on local and systemic conditions. A key role in this phase is played by the intensive proliferation of fibroblasts, which synthesize collagen and other components of the extracellular matrix, thereby facilitating tissue reconstruction [18]. Simultaneously, angiogenesis occurs, ensuring an adequate supply of oxygen and nutrients to the regenerating tissues.

According to research, the proliferative process occurs in two stages. The first, fibroplasia, involves the formation of granulation connective tissue, which gradually replaces the blood clot and remnants of the periodontal ligament. The resulting provisional matrix consists primarily of densely distributed mesenchymal cells embedded in a collagenous extracellular matrix, which is abundant in blood vessels and contains a small number of mononuclear leukocytes [10, 11].

The second stage involves the formation of woven bone, which represents the primary form of bone tissue deposited around the newly formed blood vessels by osteoblasts residing within the matrix [10, 14].

Woven bone becomes detectable approximately two weeks following extraction and progressively displaces the granulation connective tissue. It is believed that a substantial portion of granulation tissue is replaced by woven bone during the 6–8 week healing process [14, 19].

Bone modelling and remodelling

The final phase, comprising modelling and remodelling, may persist from several months to over a year following tooth extraction. During this period, granulation tissue is resorbed and replaced by mature bone. Osteoblasts synthesize new bone, while osteoclasts are responsible for modelling and removing structural excess. Woven bone is replaced by mature bone tissue, including bone marrow and lamellar bone [10, 20]. Remodelling leads to the final development of the alveolar process architecture, while also being associated with a physiological loss of bone volume, both vertically and horizontally [14, 21]. Alveolar healing following tooth extraction is a complex, multiphase biological process. Each phase follows precisely regulated cellular and molecular mechanisms that lead to the reconstruction of both soft tissue and osseous structures. Mesenchymal cells, inflammatory mediators, growth factors, as well as the processes of angio- and osteogenesis play a key role in this process. Nevertheless, the progressive modelling and remodelling of alveolar bone frequently result in a physiological loss of bone volume, which carries significant clinical implications for prosthetic and implant treatment planning [20, 22].

The role of vitamin C in the wound healing

Ascorbic acid, the biologically active form of vitamin C, plays a key role in tissue regeneration, particularly in wound healing and connective tissue repair [23]. As a potent antioxidant, it neutralizes free radicals and reactive oxygen species generated during oxidative stress induced by tissue injury or host immune responses. This helps reduce cell damage arising from excessive oxidative activity within the affected area [24].

Vitamin C is essential for the proper immune function, particularly in patients with open wounds. Its mechanism of action further involves supporting the regeneration of other antioxidants, such as vitamin E, and supporting enzymatic activity in collagen biosynthesis [25]. Ascorbic acid participates in the hydroxylation of proline and lysine during collagen biosynthesis, acting as a cofactor for the enzyme prolyl hydroxylase in procollagen [26].

Collagen represents a fundamental structural component of bone, cartilage, teeth, ligaments, gingival tissue, and blood vessels. Owing to its tensile strength conferred by ascorbic acid, newly synthesized collagen is capable of withstanding mechanical deformation without disruption. Ultimately, the initial protective layer of type III collagen is replaced within the extracellular matrix by a fully functional layer of type I collagen. Without ascorbic acid, the collagen structure becomes unstable, resulting in the formation of defective protein during synthesis [27].

Furthermore, vitamin C influences the functioning of immune cells, particularly macrophages, which play a pivotal role in clearing cellular debris from affected areas and regulating inflammatory processes. Furthermore, ascorbic acid supports angiogenesis, the process of creating new blood vessels, thereby ensuring the delivery of essential nutrients to regenerating tissues [28].

Discussion

Evidence from studies conducted across multiple countries demonstrates that vitamin C, administered systemically and topically, significantly enhances bone and soft tissue regeneration, which are critical determinants of clinical success. A study conducted by the International Institute of Nutrition and Stress in Florida demonstrated that oral vitamin C administered at a dose of 500 mg three or four times daily (1,500 mg/day and 2,000 mg/day) accelerates the healing of post-extraction wounds [29]. Nusgens et al. noted several significant changes following topical administration of vitamin C, including an increased number of fibroblasts, leading to the formation of more prominent collagen fibres. Furthermore, the formation of several newly developed small capillaries was also observed [27]. These changes consistently occur as new connective tissue forms in the healing wound.

Vitamin C is essential for neutrophil apoptosis and subsequent clearance during the inflammatory phase. As a cofactor in the hydroxylation of proline and lysine during collagen synthesis, vitamin C plays a role in the biosynthesis, maturation, secretion, and degradation of collagen during the proliferative phase. It is further associated with fibroblast proliferation, which in turn influences angiogenesis and capillary integrity [26].

In 2018–2019, researchers from the Department of Oral and Maxillofacial Surgery at the Faculty of Dentistry, Chulalongkorn University, conducted a study in which placebo or vitamin C (600 mg or 1,500 mg) was administered to patients for 10 days following extraction. The intervention was randomly assigned to each patient in a blinded manner. The most significant improvements in wound healing parameters, including a reduction in mesiodistal socket length and probing depth, reduction of pain and inflammation, as well as enhanced bone regeneration, were observed following administration of the 600 mg preparation [30].

In contrast, other *in vitro* studies have shown that rinsing with a low doses of vitamin C (20 µg/mL) improves gingival wound healing, fibroblast migration, and proliferation compared to higher doses (50 µg/mL). In oral fibroblast cultures, elevated doses of vitamin C have also been observed to compromise the viability of these cells [8, 31].

Another study, conducted at the Department of Oral and Maxillofacial Surgery, Saveetha University in Tamil Nadu,

Table 2. Therapeutic vitamin C dosage and healing outcomes following tooth extraction

Study/source	Route of administration	Dose	Study duration	Primary clinical outcomes
International Institute of Nutrition and Stress, Florida (1993) [29]	Oral	1500–2000 mg/day (500 mg 3–4 × day)	21 days	Accelerated healing of post-extraction wounds
Chulalongkorn University, Bangkok (2019) [30]	Oral	600 mg/day (3 × 200 mg)	10 days	Reduced postoperative pain and accelerated mesiodistal wound closure
Chulalongkorn University, Bangkok (2020) [31]	Local (rinsing)	20 µg/ml vs 50 µg/mL	3 and 7 days	20 µg/ml improves fibroblast migration and proliferation; 50 µg/ml reduces fibroblast survival
Saveetha University, Tamil Nadu (2021) [32]	Submucosal injection	200 mg	3 and 7 days	Improved healing outcomes on day 7; no significant effect on pain reduction
Complutense University, Madrid (2021) [33]	Local (nanoemulsion)	Intra-socket gel 3 × day	7 days	Reduced incidence of alveolar osteitis and postoperative discomfort
Chulalongkorn University, Bangkok (2021) [34]	Oral	600 mg	21 days	Reduced postoperative pain, enhanced bone regeneration, and increased radiographic bone density
Army Medical College, Rawalpindi (2023) [35]	Oral	500 mg (2 × day)	7 days	Decreased C-reactive protein, indicating limited systemic inflammation

India, evaluated the effect of submucosal injection of vitamin C (L-ascorbic acid) on wound healing following tooth extraction. Patients were divided into two groups: a vitamin C group and a control group. Signs of healing were assessed in the extraction sockets on days 3 and 7 following surgery. No significant differences were observed on day 3. On post-operative day 7, healing rates in the vitamin C group were significantly superior to those observed in controls. No significant reduction in pain was noted on days 3 or 7. The study authors concluded that L-ascorbic acid injection promotes favourable post-operative healing but does not significantly reduce post-operative discomfort [32].

Other researchers evaluated topical application of propolis extract, nanovitamin C, and nanovitamin E for the prevention of alveolar osteitis following the extraction of an impacted mandibular third molar. The study demonstrated the efficacy of nanovitamin C in reducing the incidence of alveolar osteitis and the associated discomfort [33].

Other studies have demonstrated that vitamin C significantly enhances soft tissue healing and increases radiographic bone density 21 days following extraction compared to controls [34]. Patients receiving vitamin C were also found to have decreased C-reactive protein levels compared to controls [35]. Table 2 summarizes the reviewed studies, stratified by vitamin C dose and route of administration.

Conclusions

Available evidence indicates that vitamin C plays an important role in alveolar socket healing following tooth extraction, supporting all critical stages of tissue regeneration. Vitamin C supplementation, both systemically and topically, may accelerate fibroblast proliferation, collagen biosynthesis, and angiogenesis, while also reducing inflammation and postoperative pain.

Oral administration of vitamin C at doses of 600–2,000 mg/day has been shown to exert a beneficial effect on healing dynamics, reduce postoperative pain, and improve regenerative parameters such as socket depth and radiographic bone density. Local application of vitamin C, including nanotechnology-based preparations and submucosal injections, has also been shown to yield beneficial clinical outcomes, including a reduced risk of alveolar osteitis. Based on the available evidence, adjunctive vitamin C therapy should be considered as a complement to standard post-extraction care, particularly in patients with impaired healing, nutritional deficiencies, or an elevated risk of postoperative complications. Nevertheless, further randomized controlled trials are required to establish the optimal dosage, duration of therapy, and most efficacious route of vitamin C administration across different patient populations.

References

1. Sculean A, Gruber R, Bosshardt DD. Soft tissue wound healing around teeth and dental implants. J Clin Periodontol, 2014; 41 (Suppl 15): S6–S22. doi: 10.1111/jcpe.12206
2. Steiner GG, Francis W, Burrell R, et al. The healing socket and socket regeneration. Compend Contin Educ Dent, 2008; 29(2): 114–116
3. Van der Weijden F, Dell'Acqua F, Slot DE. Alveolar bone dimensional changes of post-extraction sockets in humans: a systematic review. J Clin Periodontol, 2009; 36(12): 1048–1058. doi: 10.1111/j.1600-051X.2009.01482.x
4. Bechara N, Flood VM, Gunton JE. A systematic review on the role of vitamin C in tissue healing. Antioxidants (Basel), 2022; 11(8): 1605. doi: 10.3390/antiox11081605
5. Nishikimi M, Fukuyama R, Minoshima S, et al. Cloning and chromosomal mapping of the human nonfunctional gene for L-gulono-gamma-lactone oxidase, the enzyme for L-ascorbic acid biosynthesis missing in man. J Biol Chem, 1994; 269(18): 13685–13688
6. Ruzijevaite G, Acaite E, Jagelaviciene E. Therapeutic impact of ascorbic acid on oral and periodontal tissues: a systematic literature review. Medicina (Kaunas), 2024; 60(12): 2041. doi: 10.3390/medicina60122041
7. Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington (DC): National Academies Press (US); 2000
8. Moores J. Vitamin C: a wound healing perspective. Br J Community Nurs, 2013; Suppl: S6–S11. doi: 10.12968/bjcn.2013.18.sup12.s6
9. Farina R, Trombelli L. Wound healing of extraction sockets. Endod Top, 2011; 25: 16–43. doi: 10.1111/etp.12016
10. Araújo MG, Silva CO, Misawa M, Sukekava F. Alveolar socket healing: what can we learn? Periodontol, 2000, 2015; 68(1): 122–134. doi: 10.1111/prd.12082
11. Trombelli L, Farina R, Marzola A, et al. Modeling and remodeling of human extraction sockets. J Clin Periodontol, 2008; 35(7): 630–639. doi: 10.1111/j.1600-051X.2008.01246.x
12. Amler MH. Disturbed healing of extraction wounds. J Oral Implantol, 1999; 25(3): 179–184. doi: 10.1563/1548-1336(1999)025<0179:DHOEW>2.3.CO;2
13. Schropp L, Wenzel A, Kostopoulos L, Karring T. Bone healing and soft tissue contour changes following single-tooth extraction: a clinical and radiographic 12-month prospective study. Int J Periodontics Restorative Dent, 2003; 23(4): 313–323
14. de Sousa Gomes P, Daugela P, Poskevicius L, et al. Molecular and cellular aspects of socket healing in the absence and presence of graft materials and autologous platelet concentrates: a focused review. J Oral Maxillofac Res, 2019; 10(3): e2. doi: 10.5037/jomr.2019.10302
15. Al Hezaimi K, Al-Askar M, Al-Rasheed A, et al. Tissue dynamics in the alveolar socket following tooth extraction. J Int Acad Periodontol, 2013; 15(2): 43–51
16. Rousselle P, Montmasson M, Garnier C. Extracellular matrix contribution to skin wound re-epithelialization. Matrix Biol, 2019; 75–76: 12–26. doi: 10.1016/j.matbio.2018.01.002
17. Pippi R. Post-surgical clinical monitoring of soft tissue wound healing in periodontal and implant surgery. Int J Med Sci, 2017; 14(8): 721–728. doi: 10.7150/ijms.19727
18. Amler MH. The time sequence of tissue regeneration in human extraction wounds. Oral Surg Oral Med Oral Pathol, 1969; 27(3): 309–318. doi: 10.1016/0030-4220(69)90357-0
19. Udeabor SE, Heselich A, Al-Maawi S, et al. Current knowledge on the healing of the extraction socket: a narrative review. Bioengineering (Basel), 2023; 10(10): 1145. doi: 10.3390/bioengineering10101145

20. Pagni G, Pellegrini G, Giannobile WV, Rasperini G. Postextraction alveolar ridge preservation: biological basis and treatments. Int J Dent, 2012; 2012: 151030. doi: 10.1155/2012/151030
21. Cardaropoli G, Araújo M, Hayacibara R, et al. Healing of extraction sockets and surgically produced – augmented and non-augmented – defects in the alveolar ridge. An experimental study in the dog. J Clin Periodontol, 2005; 32(5): 435–440. doi: 10.1111/j.1600-051X.2005.00692.x
22. Tan WL, Wong TL, Wong MC, Lang NP. A systematic review of post-extractional alveolar hard and soft tissue dimensional changes in humans. Clin Oral Implants Res, 2012; 23 (Suppl 5): 1–21. doi: 10.1111/j.1600-0501.2011.02375.x
23. Pullar JM, Vissers MCM. Role of vitamin C in chronic wound healing. In: Eggersdorfer M, ed. Vitamin C. Cham, Switzerland: Springer; 2020: 161–179
24. Jacob RA, Sotoudeh G. Vitamin C function and status in chronic disease. Nutr Clin Care, 2002; 5(2): 66–74. doi: 10.1046/j.1523-5408.2002.00005.x
25. Praskevicius A, Ivanoviene L, Stasiuniene N, et al. Biochemistry. In: Burneckiene J, ed. Vitamins. Kaunas, Lithuania: KMU Publisher; 2003: 161–197
26. Collins N. Nutrition 411: revisiting vitamin C and wound healing. Ostomy Wound Manage, 2013; 59(9): 12
27. Nusgens BV, Humbert P, Rougier A, et al. Topically applied vitamin C enhances the mRNA level of collagens I and III, their processing enzymes and tissue inhibitor of matrix metalloproteinase 1 in the human dermis. J Invest Dermatol, 2001; 116(6): 853–859. doi: 10.1046/j.0022-202x.2001.01362.x
28. Li X, Tang L, Lin YF, Xie GF. Role of vitamin C in wound healing after dental implant surgery in patients treated with bone grafts and patients with chronic periodontitis. Clin Implant Dent Relat Res, 2018; 20(5): 793–798. doi: 10.1111/cid.12647
29. Abrahmsohn GM, Halberstein RA, Fregeolle S. Vitamin C and dental healing: testing and placebo effect. Gen Dent, 1993; 41(6): 523–530
30. Pisalsitsakul N, Pinnoi C, Sutanthavibul N, Kamolratanakul P. Taking 200 mg vitamin C three times per day improved extraction socket wound healing parameters: a randomized clinical trial. Int J Dent, 2022; 2022: 6437200. doi: 10.1155/2022/6437200
31. Chaitrakoonthong T, Ampornaramveth R, Kamolratanakul P. Rinsing with L-ascorbic acid exhibits concentration-dependent effects on human gingival fibroblast in vitro wound healing behavior. Int J Dent, 2020; 2020: 4706418. doi: 10.1155/2020/4706418
32. Ramasubbu S, Gaur S, Wahab PU, Marimuthu M. Efficacy of L-ascorbic acid in the healing of extraction site after transalveolar extraction of third molar teeth. Int J Res Pharm Sci, 2020; 11(Suppl 4): 1179–1182
33. González-Serrano J, López-Pintor RM, Cecilia-Murga R, et al. Application of propolis extract, nanovitamin C and nanovitamin E to prevent alveolar osteitis after impacted lower third molar surgery. A randomized, double-blind, split-mouth, pilot study. Med Oral Patol Oral Cir Bucal, 2021; 26(2): e118–e125. doi: 10.4317/medoral.23915
34. Yingcharoenthana S, Ampornaramveth R, Subbalekha K, et al. A split-mouth randomized clinical trial to evaluate the effect of local and systemic administration of vitamin C on extraction wound healing. J Oral Sci, 2021; 63(2): 198–200. doi: 10.2334/josnusd.20-0515
35. Fatima M, Farhat K, Ali S, et al. Evaluation of anti-inflammatory efficacy of ascorbic acid after third molar surgery. J Ayub Med Coll Abbottabad, 2023; 35(3): 442–446. doi: 10.55519/JAMC-03-11901

WAR CRIMES AND RUSSIA'S ACCOUNTABILITY FOR MILITARY ACTIONS IN UKRAINE: CHALLENGES FOR INTERNATIONAL JUSTICE AND MEDICAL CONSEQUENCES FOR INJURED VICTIMS

Zbrodnie wojenne i odpowiedzialność Rosji w kontekście działań militarnych na Ukrainie: wyzwania dla międzynarodowego wymiaru sprawiedliwości oraz skutki medyczne dla ofiar urazów

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Abstract

The armed conflict in Ukraine, ongoing since 2014 and escalating in 2022, represents one of the most serious challenges to the international order since the end of the Cold War. Its protracted nature and intensity have led to severe geopolitical, economic, humanitarian, and health-related consequences. This paper analyses Russia's accountability for war crimes in the context of international humanitarian law, highlighting the challenges related to enforcing accountability before international tribunals. It also presents the differing approaches of European Union member states to the conflict, stemming from varying perceptions of their relations with Russia, the United States, and China, as well as the war's impact on European security and transatlantic cooperation. From a socio-economic perspective, the conflict has resulted in regional recession, an energy crisis, disruption of supply chains, and mass refugee migration, particularly to Poland. Special attention is also given to the long-term health consequences for victims of military operations, including physical injuries and the burden placed on healthcare systems. The article constitutes an attempt at a multifaceted assessment of the conflict and its implications for the future of the international order.

Streszczenie

Konflikt zbrojny na Ukrainie, trwający od 2014 roku i eskalujący w 2022 roku, stanowi jedno z najpoważniejszych wyzwań dla międzynarodowego ładu po zakończeniu zimnej wojny. Jego długotrwałość i intensywność prowadzą do poważnych konsekwencji o charakterze geopolitycznym, gospodarczym, humanitarnym i zdrowotnym. Niniejszy artykuł analizuje odpowiedzialność Rosji za zbrodnie wojenne w kontekście międzynarodowego prawa humanitarnego, wskazując na wyzwania związane z egzekwowaniem odpowiedzialności przed trybunałami międzynarodowymi. Przedstawiono również różnice w podejściu państw Unii Europejskiej do konfliktu, wynikające z odmiennego postrzegania relacji z Rosją, Stanami Zjednoczonymi i Chinami, a także skutki wojny dla europejskiego bezpieczeństwa i współpracy transatlantyckiej. W ujęciu społeczno-gospodarczym konflikt doprowadził do recesji w regionie, kryzysu energetycznego, załamania łańcuchów dostaw oraz masowej migracji uchodźców, zwłaszcza do Polski. Szczególną uwagę poświęcono również długofalowym skutkom zdrowotnym dla ofiar działań zbrojnych, w tym urazów i obciążeń systemów opieki medycznej. Artykuł stanowi próbę wieloaspektowej oceny konfliktu i jego implikacji dla przyszłości ładu międzynarodowego.

Keywords: protection of civilians; war in Ukraine; international law; war injuries

Słowa kluczowe: ochrona ludności; wojna w Ukrainie; prawo międzynarodowe; urazy wojenne

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Introduction

The nature of the war in Ukraine, differing in many respects from previous armed conflicts, poses a significant challenge to the current *jus in bello*. It is also subject to assessment in the context of possible future conflicts, both conventional and unconventional (hybrid, cyber, and economic). International conventions and protocols governing the conduct of warfare are frequently ignored by the conflicting parties. The use of force disproportionate to the threat, resulting in widespread human suffering, including mass displacement of populations and the destruction of residential properties and civilian infrastructure, is one of the most prevalent violations. The conflict in Ukraine, as an example of violations of the laws of war, raises fundamental questions for the international community concerning the effectiveness and enforceability of these laws in contemporary conflicts, where competition extends beyond direct armed confrontation and encompasses the media and information space, including information operations (INFOOPS) and psychological operations (PSYOPS).

Conflict duration and its consequences

The war in Ukraine has far-reaching geopolitical, economic, and humanitarian consequences. The armed conflict has highlighted divergences in how Eastern and Western member states of the European Union (EU) perceive the strategic situation. These divergences pertain to the relations of the EU and its individual member states with the United States, the Russian Federation, and the People's Republic of China, and, more broadly, to the EU's strategic positioning within the international order at a supra-regional level [1].

At the outset of the 21st century, two principal geopolitical visions emerged within the European Union. France and Germany sought to establish a geostrategic centre independent of the United States, while simultaneously pursuing economic rapprochement with the Russian Federation. The second concept was represented primarily by the United Kingdom, certain Central European states, and the Baltic states. Its foundations rested upon strong transatlantic relations and US military presence in Europe, perceived as a key element guaranteeing security against the threat posed by the Russian Federation [1].

The policies of individual EU member states towards Ukraine, with respect to both aid and relations, varied considerably. Central European countries regarded the defence of Ukrainian independence as a crucial element in safeguarding their own sovereignty. Western European countries, by contrast, were predominantly concerned with the potential adverse consequences of a prolonged conflict, both for their national economies and for the growing geopolitical influence of the United States and its allies within EU structures [1]. This translated into a desire to end the hostilities in Ukraine as quickly as possible and to ease or lift sanctions against the Russian Federation.

The conflict in Ukraine highlighted the need to strengthen the defence capabilities of EU member states, but in close cooperation with the North Atlantic Treaty Organization (NATO) and the United States.

Beyond its political and military dimensions, the war in Ukraine has given rise to profound humanitarian and economic consequences. It has dramatically worsened living conditions and the economic situation in Ukraine and Russia, with its effects indirectly impacting Central Europe and other world regions. The war should further be seen as a contributing factor to inflation and the slowdown of economic growth, particularly in countries bordering Ukraine and Russia. Within Russia itself, the imposed financial sanctions have significantly compromised the stability of the banking sector and the state's capacity to meet its fiscal obligations. The massive influx of refugees represents a further significant factor affecting the economies of the region. According to data from the United Nations High Commissioner for Refugees (UNHCR), several million individuals have fled Ukraine, the majority of whom sought refuge in Poland [2]. Rapidly escalating inflation and rising prices, particularly in fuel and energy sectors, emerged as a key trigger for Europe's 2022 energy crisis. The armed conflict has also caused major disruptions to industrial production and significant impediments to global supply chain operations. The imposition of economic sanctions on Russia and its allied countries since March 2022 is yet another factor intensifying the scale of the aforementioned economic downturn [3].

War crimes in the context of the conflict in Ukraine

Ukrainian authorities and international observers have collected evidence showing that Russia is perpetrating numerous war crimes on Ukrainian territory, including assaults on civilian populations and the intentional de-

struction of civilian infrastructure. Even when considering collateral damage typical of armed conflict, from operational errors or military technology limitations, some of these attacks clearly reflect the aggressor's frustration and represent a deliberate effort to break Ukrainian society's will to resist.

Violations of the core principles of international humanitarian law, such as targeting civilian infrastructure (including telecommunications, water, heating, gas, electricity, and even agricultural infrastructure), medical personnel, and humanitarian aid workers, as well as launching indiscriminate attacks on both military and civilian targets (e.g., residential buildings, hospitals, religious sites, educational and cultural institutions, commercial establishments, and other public utilities), represent a blatant violation of international law and may qualify as war crimes. Russian forces have also been documented perpetrating acts of murder, rape, looting, abduction, including forcible removal of children, torture, and the use of civilians as human shields. Evidence of these acts is being collected by Ukrainian law enforcement agencies and, internationally, by the United Nations (UN), the International Committee of the Red Cross (ICRC), the United Nations High Commissioner for Refugees (UNHCR), Amnesty International, as well as by accredited war correspondents [4]. Ongoing Ukrainian and international investigations continue, with verdicts and arrest warrants being issued. However, enforcing these warrants poses a major challenge [4].

Russia's responsibility for war crimes

Currently, the International Criminal Court (ICC) remains the sole body with universal jurisdiction over international criminal matters, functioning complementarily to national criminal justice systems. This indicates that international criminal law does not aim to replace national justice systems, but can only be effected when a given case falls within the jurisdiction of a state that unwilling or unable to carry out effective criminal proceedings. The ICC's jurisdiction covers four core aspects: substantive, territorial, subjective, and temporal [5].

The ICC's subject-matter jurisdiction covers the heaviest international crimes listed in the Rome Statute of the International Criminal Court dated 17 July 1998 (hereinafter the Statute), namely genocide, crimes against humanity, war crimes, and the crime of aggression (Article 5) [6].

Following the principle of territorial jurisdiction, the ICC holds authority over international crimes committed on the territory of States Parties to the Statute (Article 14).

State Party to the Statute or the Security Council acting under Chapter VII of the United Nations Charter (Article 13) is an entity authorized to refer a situation indicating one or more international crimes to the ICC Prosecutor [6].

The ICC has jurisdiction over crimes committed by nationals of states that are parties to the Statute. The principle that no individual shall be exempt from criminal liability under the Statute, a concept known as the principle of irrelevance of official capacity, is of fundamental importance. The position held by the accused, or any immunity they may enjoy, is irrelevant to the proceedings (Articles 25 and 26) [6].

Temporal jurisdiction means the ICC has jurisdiction solely over crimes committed after the Statute's entry into force, specifically after 1 July 2002. Nevertheless, if a state accedes to the Statute after its entry into force, the Court's jurisdiction will generally be limited to crimes committed after the Statute's entry into force for that state (Article 11) [6].

When considering the jurisdiction of the ICC with regard to crimes committed during the Russo-Ukrainian war, the starting point is to note that the Russian Federation is not a State Party to the Rome Statute, whereas Ukraine, after having previously accepted the jurisdiction of the ICC by declaration, became a State Party to the Rome Statute on 1 January 2025. This does not mean, however, that the earlier criminal jurisdiction of the ICC over crimes committed on the territory of Ukraine was entirely excluded. The Statute provides for the possibility for a state that is not a party to the Statute to accept the jurisdiction of the Court by means of a declaration lodged with the Registrar, thereby recognizing the jurisdiction of the ICC with respect to a given crime (Article 12) [6].

Ukraine's first declaration referred to crimes committed during the Maidan protests, which occurred between 21 November 2013 and 22 February 2014 [7]. The second declaration, submitted in September 2015, addressed all crimes committed since 15 February 2015. Through this declaration, Ukraine provided its forward-looking consent to the investigation, prosecution, and judgment of all crimes committed on Ukrainian territory [8]. Following the declarations, the ICC conducted a preliminary examination of its jurisdiction and the factual occurrence of the crimes identified by Ukraine. After completing this examination, the statutory criteria for launching a formal investigation on the Ukraine situation were found to be met [9].

Following the outbreak of war in February 2022, the ICC issued a statement confirming a reasonable basis to launch an investigation, including suspicions that alleged war crimes and crimes against humanity had been committed in Ukraine. At the same time, given the expansion of the conflict, the investigation was set to encompass all crimes committed by any party to the conflict across Ukraine's entire territory [10]. Granting the Court's jurisdiction over a specific state means that, irrespective of nationality, any person who committed an ICC jurisdictional crime on that state's territory may be held criminally accountable under the Statute [11].

Challenges for international justice

Under customary international law, the highest-ranking representatives of a state enjoy absolute immunity from jurisdiction of other states' domestic courts, even when accused of international crimes. Nevertheless, Article 27 of the Rome Statute explicitly states that immunities and other privileges stemming from official functions, regardless of their domestic or in-

ternational origin, do not prevent the International Criminal Court from exercising jurisdiction over such an individual. Obligations to prevent, investigate, and punish crimes under ICC jurisdiction apply *erga omnes*. Accordingly, the Court may require any State Party to the Statute to execute an arrest warrant, including one issued against a sitting Head of State who is not a Party to the Statute. This provision guarantees that individuals responsible for the most serious international crimes cannot escape accountability merely due to their position [11].

On 17 March 2023, the ICC issued arrest warrants against Russian President Vladimir Putin and the Commissioner for Children's Rights, Maria Lvova-Belova. The charges concern the alleged unlawful deportation of Ukrainian children from occupied territories to the Russian Federation. These acts are alleged to have taken place on Ukrainian territory under Russian occupation, starting no later than the date the invasion began (24 February 2022) [12]. States Parties are obligated to detain Vladimir Putin and Maria Lvova-Belova if they enter their jurisdiction and subsequently surrender them to ICC. However, it should be noted that States Parties to the Statute may exploit legal uncertainties about detaining Vladimir Putin to avoid fulfilling their international obligations.

Beyond the legal implications of the ICC arrest warrants against Vladimir Putin and Maria Lvova-Belova, it is worth noting their considerable political dimension. These warrants help internationally isolate the Russian president, carrying major implications for potential diplomatic efforts concerning the Ukraine situation and other Russian Federation actions [13].

Medical consequences of war injuries for victims and health protection in the context of violations of international humanitarian law

The war in Ukraine has caused widespread destruction of civilian infrastructure, including medical facilities, representing a blatant violation of international humanitarian law, particularly the Geneva Conventions. According to current international humanitarian law, attacks on hospitals, ambulances, and medical personnel are explicitly prohibited [14]. Despite this, numerous reports from international organizations, including the World Health Organization (WHO), UNHCR, and Amnesty International, document cases of deliberate attacks on healthcare infrastructure in Ukraine. The missile struck on Kyiv's Okhmatdyt Children's Hospital, along with recorded cases of blocking access to injured civilians, is a particularly dramatic case [4, 15, 16].

These actions have two primary consequences. They involve direct physical injuries such as craniocerebral trauma, limb amputations, burns, and internal organ damage [17]. They have also triggered an escalating public health crisis. With the severely overburdened healthcare system, critically limited access to medications and medical equipment, and substantially reduced capacity to evacuate patients from combat zones, thousands of injured individuals, both civilians and combatants, remain without adequate medical care.

Deliberate attacks on medical facilities and the obstruction of humanitarian aid represent a clear violation of international law, including the core provisions of the Geneva Conventions, which protect civilians, medical personnel, and civilian infrastructure during armed conflict. Victims of these actions suffer not only physical injuries, but also severe psychological trauma stemming from war's brutality and the blatant disregard of core international humanitarian law principles.

There has been a marked rise in mental health disorders, especially post-traumatic stress disorder (PTSD), depression, and acute anxiety. Children, the elderly, and individuals with prior war experiences are particularly vulnerable [18–20].

The rising number of refugees and internally displaced persons (IDPs), putting significant strain on Ukraine's neighbouring countries, especially Poland, which hosts the largest number of refugees and thus bears primary responsibility for providing medical care to those affected, is yet another consequence of this conflict [19, 21, 22].

In this context, it is essential not only to enhance health protection mechanisms in conflict zones, but also to consistently enforce accountability for attacks on medical personnel and facilities as war crimes. Throughout the ongoing conflict, serious violations of international law, particularly those concerning the protection of healthcare workers, have been occurring with increasing frequency. Physicians, nurses, and paramedics, all granted full protection under the Fourth Geneva Convention and its Additional Protocols, are increasingly becoming targets of direct armed attacks [14, 23]. Cases of medical personnel being detained, intimidated, and subjected to physical violence while performing their professional duties have been documented. Particularly concerning are the documented attacks on ambulances and medical convoys displaying the Red Cross emblem – a symbol explicitly protected under international law. One example is the tragic incident on September 12, 2024, in Viroliubivka (Donetsk Oblast), when an International Committee of the Red Cross convoy was attacked by Russian artillery fire and Lancet drones. Three humanitarian workers were killed and two others were seriously injured. On April 10, 2025, a drone strike was reported in Donbas on an evacuation convoy whose vehicles were clearly marked with the Red Cross symbol; the attack damaged an ambulance and injured two medical workers [24, 25].

Such actions, targeting medical personnel, blatantly violate international humanitarian law norms and may constitute war crimes. While the international community has repeatedly condemned such acts of violence, their persistence and scale raise serious concerns and necessitate a decisive, coordinated response.

Violation of the laws of war with weapons of mass destruction: humanitarian consequences and implications for healthcare systems

Modern armed conflicts, such as the war in Ukraine, are increasingly characterized not only by the use of conventional weapons, but also by the escalation of threats as-

sociated with weapons of mass destruction (WMD): chemical, biological, radiological, and nuclear (CBRN) [26]. The use of such weapons represents a blatant violation of the core international humanitarian law norms, including the Geneva Conventions and the Chemical Weapons Convention (CWC) [14, 27]. Reports of the potential use or preparations for such weapons by the Russian Federation, including possible attacks on nuclear power plant infrastructure, as in the case of the Zaporizhzhia facility [28], nuclear weapon threats [26], and possible radiological attacks in combat zones [26, 29] raise serious concerns within the international community and may be classified as war crimes or state terrorism. CBRN weapons used in civilian environments not only result in immediate deaths among many victims, but also carry long-term health, environmental, and social consequences. This results in extreme strain on local healthcare systems, the shutdown of hospital operations, the inability to deliver proper care to victims, and, over time, the exhaustion of human and infrastructural resources of healthcare services [26]. The use of such agents in populated areas not only directly violates the ban on inhumane treatment, but also undermines the principle of distinction between military and civilian targets – a cornerstone of the law of armed conflict [30]. Given this risk, healthcare systems must urgently prepare for swift, coordinated responses to potential CBRN incidents. Critical priorities include readiness to identify and manage radiation sickness, chemical poisoning, and biological infections affecting both combatants and civilians.

One of the most serious aspects of radiological weapons threat is their capacity to trigger mass panic alongside long-term somatic and psychological health effects [26]. Therefore, properly trained medical personnel play a key role not only in delivering first aid, but also in mitigating psychological effects, including combat stress and PTSD [26]. In response to these challenges, the Military Institute of Medicine — National Research Institute has launched a collaborative project with Ukrainian medical services to exchange expertise, improve medical procedures, and conduct joint training. The current programme focuses on the rehabilitation of wounded individuals, as well as diagnosing and treating patients with war-related trauma [26]. Such initiatives are vital for ensuring comprehensive care, encompassing both surgical and psychological support, for individuals injured during armed conflicts. The concurrently developing medical component within the Armed Forces aims to ensure a mobile, swift, and professional medical response under battlefield conditions, including in the event of CBRN weapon deployment. These initiatives not only strengthen the defence capabilities of states supporting Ukraine, but also contribute to protecting the lives and health of civilians and combatants affected by the armed conflict.

Conclusions

The armed conflict in Ukraine, ongoing since 2014 and markedly escalating after Russia's full-scale invasion in 2022, exemplifies the challenges facing modern international law, particularly international humanitarian law and the Geneva Conventions. The choice of Ukraine as the subject of analysis is justified by the scale and nature of violations by Russian forces, including attacks on civilian infrastructure and violence against civilian populations.

This conflict highlights deep geopolitical divisions within the EU, with Central and Eastern European countries strongly supporting Ukraine, and Western European countries taking a more cautious approach due to economic and energy concerns. The conflict has further emphasized the need to reinforce the EU's defence capabilities through close cooperation with NATO and the United States.

The consequences of the conflict are multifaceted, encompassing political, military, humanitarian, and economic aspects. These include a refugee crisis, rising inflation, disruptions to global supply chains and industrial production, and an intensifying energy crisis in Europe. The sanctions against Russia have further deepened economic instability throughout the region.

Legally, particular focus falls on war crimes by Russian forces, including murder, rape, looting, attacks on civilians and their use as human shields. Many international organizations are documenting evidence of these acts. Delivering comprehensive medical care, including adequate supplies and psychological support, to victims of armed conflict is critically important. Brutal hostilities, often involving breaches of international conventions, require not only immediate surgical intervention but also sustained care for trauma victims. Effective psychological support plays a crucial role in reducing the long-term effects of armed conflict and aiding recovery for both combatants and civilians. The Military Institute of Medicine — National Research Institute partners with Ukrainian medical services, conducting joint training and victim rehabilitation, thereby enhancing medical response capabilities both at the front lines and within civilian healthcare systems.

The International Criminal Court, operating under the Rome Statute, is responsible for the prosecution of the most serious international crimes. The ICC has jurisdiction over, among other things, war crimes and crimes against humanity committed after July 1, 2002. The Court may hold individual perpetrators accountable regardless of their official position, and may exercise jurisdiction over nationals of States Parties or via UN Security Council referral.

References

1. Grosse GT. Geopolityczne skutki wojny na Ukrainie dla Unii Europejskiej. Studia Polityczne, 2023; 51(3): 207–235. doi: 10.35757/STP.2023.51.3.08
2. Wojciechowicz JJ. Konsekwencje wojny na Ukrainie. Towarzystwo Ekonomistów Polskich. Available from: https://tep.org.pl/konsekwencje-wojny-na-ukrainie/ (access: 10.04.2025)
3. Prokopowicz D. Gospodarcze skutki wojny w Ukrainie. In: Soroka P, Pająk K, ed. Wybrane aspekty rosyjskiej agresji na Ukrainę w obszarze politycznym, militarnym i gospodarczym. Warszawa, Dom Wydawniczy i Handlowy Elipsa, 2023; 284–333

4. Olchowski J. Rosyjskie zbrodnie wojenne – kolejna odsłona starej taktyki. Instytut Europy Środkowej; 2022. Available from: https://ies.lublin.pl/komentarze/rosyjskie-zbrodnie-wojenne-kolejna-odslona-starej-taktyki/ (access: 10.04.2025)
5. Czeszejko-Sochacka K. Zbrojna napaść Rosji na Ukrainę a kwestia odpowiedzialności karnej jednostki. Roczniki Nauk Społecznych, 2023; 15(2): 147–167. doi: 10.18290/rns23511.1
6. Rzymski Statut Międzynarodowego Trybunału Karnego z 17 lipca 1998 r. Dz.U. 2003 nr 78, poz. 708 ze zm.
7. Kuczyńska H. Odpowiedzialność przed Międzynarodowym Trybunałem Karnym za zbrodnie prawa międzynarodowego popełnione w czasie konfliktu na Ukrainie. Palestra, 2022; 4: 7–30
8. International Criminal Court. Ukraine accepts ICC jurisdiction over alleged crimes committed since 20.02.2014. The Hague: ICC; 08.09.2015. Available from: https://www.icc-cpi.int/news/ukraine-accepts-icc-jurisdiction-over-alleged-crimes-committed-20-february-2014 (access: 12.04.2025)
9. International Criminal Court. Statement of the Prosecutor, Fatou Bensouda, on the conclusion of the preliminary examination in the situation in Ukraine. The Hague: ICC; 11.12.2020. Available from: https://www.icc-cpi.int/news/statement-prosecutor-fatou-bensouda-conclusion-preliminary-examination-situation-ukraine (access: 12.04.2025)
10. International Criminal Court. Statement of the ICC Prosecutor, Karim A.A. Khan QC: "I have decided to proceed with opening an investigation" on the situation in Ukraine. The Hague: ICC; 28.02.2022. Available from: https://www.icc-cpi.int/news/statement-icc-prosecutor-karim-aa-khan-qc-situation-ukraine-i-have-decided-proceed-opening (access: 12.04.2025)
11. Lachowski T. Odpowiedzialność Władimira Putina przed Międzynarodowym Trybunałem Karnym za zbrodnie popełnione na terytorium Ukrainy. Od zbrodni wojennych do ludobójstwa. Sprawy Międzynarodowe, 2023; 76(2): 38–66. doi: 10.35757/sm.2023.76.2.01
12. International Criminal Court. Situation in Ukraine: ICC judges issue arrest warrants against Vladimir Vladimirovich Putin and Maria Alekseyevna Lvova-Belova. The Hague: ICC; 17.03.2023. Available from: https://www.icc-cpi.int/news/situation-ukraine-icc-judges-issue-arrest-warrants-against-vladimir-vladimirovich-putin-and (access: 11.04.2025)
13. Lachowski T. Czy Władimir Putin trafi do Hagi? O prawno-politycznych konsekwencjach nakazów aresztowania wydanych przez Międzynarodowy Trybunał Karny. Instytut Europy Środkowej; 2023. Available from: https://ies.lublin.pl/komentarze/czy--wladimir-putin-trafi-do-hagi-o-prawno-politycznych-konsekwencjach-nakazow--aresztowania-wydanych-przez-miedzynarodowy-trybunal-karny/ (access: 13.04.2025)
14. Łubiński P. Ochrona rannych, chorych. Personel Medyczny i duchowny. In: Falkowski Z, Marcinko M, ed. Międzynarodowe prawo humanitarne konfliktów zbrojnych. Warszawa, Wojskowe Centrum Edukacji Obywatelskiej, 2014; 169–183
15. Médecins Sans Frontières. Ukraine: MSF condemns shelling of two hospitals by Russian military. 14.02.2024. Available from: https://www.doctorswithoutborders.org/latest/ukraine-msf-condemns-shelling-two-hospitals-russian-military (access: 17.06.2025)
16. Médecins Sans Frontières. Ukraine: Attack on Okhmatdyt Children's Hospital in Kyiv. 08.07.2024. Available from: https://msfsouthasia.org/ukraine-attack-on-okhmatdyt-childrens-hospital-in-kyiv/ (access: 17.06.2025)
17. Lawry LL, Mani V, Hamm TE, et al. Qualitative assessment of combat-related injury patterns and injury prevention in Ukraine since the Russian invasion. BMJ Mil Health, 2026; 172(2): 154–159. doi: 10.1136/military-2024-002863
18. Zasiekina L, Zasiekin S, Kuperman V. Post-traumatic stress disorder and moral injury among Ukrainian civilians during the ongoing war. J Community Health, 2023; 48(5): 784–792. doi: 10.1007/s10900-023-01225-5
19. Długosz P. War trauma and strategies for coping with stress among Ukrainian refugees staying in Poland. J Migr Health, 2023; 8: 100196. doi: 10.1016/j.jmh.2023.100196
20. Lushchak O, Velykodna M, Bolman S, et al. Prevalence of stress, anxiety, and symptoms of post-traumatic stress disorder among Ukrainians after the first year of Russian invasion: a nationwide cross-sectional study. Lancet Reg Health Eur, 2023; 36: 100773. doi: 10.1016/j.lanepe.2023.100773
21. Rzecznik Praw Obywatelskich. Problemy opieki zdrowotnej uchodźców z Ukrainy – RPO pisze do Ministra Zdrowia, odpowiedź. Warszawa: Biuro RPO; 13.04.2022. Available from: https://bip.brpo.gov.pl/pl/content/problemy-opieki-zdrowotnej-uchodzcow-z-ukrainy-rpo-pisze-do-ministra-zdrowia-odpowiedz (access: 20.06.2025)
22. European Commission. Fleeing Ukraine: healthcare. Brussels: European Commission; 2024. Available from: https://commission.europa.eu/topics/eu-solidarity-ukraine/eu-assistance-ukraine/information-people-fleeing-war-ukraine/fleeing-ukraine-healthcare_pl (access: 20.06.2025)
23. United Nations in Ukraine. Attacks on health care in Ukraine are a grave violation of international humanitarian law. Kyiv: United Nations; 01.08.2023. Available from: https://ukraine.un.org/en/240605-attacks-health-care-ukraine-are-grave-violation-international-humanitarian-law (access: 20.06.2025)
24. Reuters. Russian shelling kills three Red Cross workers in eastern Ukraine. 12.09.2024. Available from: https://www.reuters.com/world/europe/three-killed-two-injured-russian-shelling-eastern-ukrainian-village-2024-09-12/ (access: 20.06.2025)
25. Centre for Information Resilience. Footage reveals Russian drone strike on marked medical convoy. London: CIR; 17.04.2025. Available from: https://www.info-res.org/reports/footage-reveals-russian-drone-strike-on-marked-medical-convoy/ (access: 20.06.2025)
26. Grębowski J, Skalski M, Bijak M. Zagrożenie bronią masowego rażenia w kontekście konfliktu na Ukrainie i jego wpływ na medycynę pola walki. Lekarz Wojskowy, 2025; 103(2): 99–103. doi: 10.53301/lw/195580

27. Konwencja o zakazie prowadzenia badań, produkcji, składowania i użycia broni chemicznej oraz o zniszczeniu jej zapasów. Dz.U. 1999 nr 63 poz. 703. Available from: https://sip.lex.pl/akty-prawne/dzu-dziennik-ustaw/konwencja-o-zakazie-prowadzenia-badan-produkcji-skladowania-i-uzycia-16838264 (access: 20.06.2025)
28. Polska Agencja Prasowa. Elektrownia jądrowa w Ukrainie bez prądu. Komunikat Państwowej Agencji Atomistyki. 09.03.2023. Available from: https://www.pap.pl/aktualnosci/news%2C1546500%2Celektrownia-jadrowa-w-ukrainie-bez-pradu-komunikat-panstwowej-agencji (access: 27.08.2025)
29. Grębowski J. Skutki użycia broni radiologicznej. Przegląd Sił Zbrojnych, 2017; 5: 68–70
30. Protokoły dodatkowe do Konwencji genewskich z dnia 12 sierpnia 1949 r. dotyczące ochrony ofiar międzynarodowych konfliktów zbrojnych (Protokół I) oraz dotyczący ochrony ofiar niemiędzynarodowych konfliktów zbrojnych (Protokół II). Warszawa: Dz.U. 1992 nr 41 poz. 175. Available from: https://sip.lex.pl/akty-prawne/dzu-dziennik-ustaw/protokoly-dodatkowe-do-konwencji-genewskich-z-12-sierpnia-1949-r-16794697 (access: 23.06.2025)

REVIEW ARTICLE

THE USE OF PLATELET-RICH PLASMA IN ORAL SURGERY

Zastosowanie osocza bogatopłytkowego w chirurgii stomatologicznej

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Abstract

Introduction: Contemporary oral surgery focuses on minimally invasive techniques and methods that support tissue healing and regeneration. One of the modern approaches involves the use of platelet-rich plasma (PRP), a concentrated plasma fraction containing platelets and growth factors such as PDGF, TGF-β, and VEGF, which play key roles in regenerative processes and angiogenesis. PRP has wide applications in oral surgery, including procedures such as tooth extractions, implant placements, bone augmentations, and soft tissue regeneration. Due to its pro-regenerative and anti-inflammatory properties, PRP contributes to shorter recovery times, reduced pain, and improved quality of newly formed tissue. **Materials and methods:** A systematic review of the literature from the PubMed database was conducted to analyse publications on the use of PRP in dental surgery. **Conclusions:** PRP is a promising tool supporting tissue regeneration in dental surgery due to the presence of multiple growth factors that play an essential role in angiogenesis, cellular proliferation, and extracellular matrix remodeling. In the context of tooth extraction, PRP helps reduce pain, swelling, and the risk of complications, while also accelerating soft tissue regeneration. For bone augmentation procedures, it supports osteogenesis, particularly when combined with bone substitute materials, although its effectiveness depends on several factors, such as the quality of the biomaterial and surgical technique. PRP used in sinus lift and implantology has shown moderate outcomes, and its efficacy in promoting peri-implant tissue regeneration remains a subject of debate. In periodontology, PRP supports soft tissue and periodontal regeneration, accelerating wound healing and the restoration of connective tissue attachment. PRP represents a valuable adjunct in oral surgery; however, given the lack of clear evidence on its efficacy in bone regeneration, further clinical studies and standardization of PRP preparation and application methods are needed.

Streszczenie

Wprowadzenie: Współczesna chirurgia stomatologiczna koncentruje się na technikach minimalnie inwazyjnych oraz metodach wspomagających procesy gojenia i regeneracji tkanek. Jednym z nowoczesnych podejść jest zastosowanie osocza bogatopłytkowego, które stanowi skoncentrowaną frakcję osocza zawierającą płytki krwi i czynniki wzrostu, takie jak PDGF, TGF-β i VEGF, odpowiedzialne za procesy regeneracyjne i angiogenezę. Osocze bogatopłytkowe znajduje szerokie zastosowanie w chirurgii stomatologicznej, w tym w procedurach takich jak ekstrakcje zębów, zabiegi implantologiczne, leczenie ubytków kostnych oraz regeneracja tkanek miękkich. Dzięki swoim właściwościom proregeneracyjnym i przeciwzapalnym przyczynia się do skrócenia czasu rekonwalescencji, zmniejszenia dolegliwości bólowych oraz poprawy jakości nowo tworzonej tkanki. **Materiał i metody:** W badaniu przeprowadzono systematyczny przegląd literatury dostępnej w bazie PubMed, analizując publikacje dotyczące zastosowania osocza bogatopłytkowego w chirurgii stomatologicznej. **Wnioski:** Osocze bogatopłytkowe jest obiecującym narzędziem wspomagającym regenerację tkanek w chirurgii stomatologicznej dzięki obecności licznych czynników wzrostu, które odgrywają istotną rolę w angiogenezie, proliferacji komórkowej oraz przebudowie macierzy pozakomórkowej. W przypadku ekstrakcji zębów pomaga w redukcji bólu, obrzęku i ryzyka powikłań, a także przyspiesza regenerację tkanek miękkich. W zabiegach augmentacyjnych wspiera osteogenezę, szczególnie w połączeniu z materiałami kościozastępczymi, jednak zależy to od wielu czynników, takich jak jakość biomateriału i technika chirurgiczna. Wyniki zastosowania PRP w zabiegach podniesienia dna zatoki szczękowej oraz implantologii są umiarkowane, a jego skuteczność w regeneracji tkanek otaczających implanty jest wciąż przedmiotem debat. W periodontologii wspomaga regenerację tkanek miękkich i przyzębia, przyspieszając gojenie ran i odbudowę przyczepu łącznotkankowego. Osocze bogatopłytkowe stanowi wartościowe wsparcie w chirurgii stomatologicznej, ale ze względu na brak jednoznacznych dowodów na skuteczność w regeneracji kostnej, konieczne są dalsze badania kliniczne i standaryzacja metod jego przygotowania i aplikacji.

Keywords: oral surgery; platelet-rich plasma; PRP

Słowa kluczowe: chirurgia stomatologiczna; osocze bogatopłytkowe; PRP

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Introduction

Modern dental surgery is rapidly evolving toward minimally invasive techniques and approaches that promote tissue healing and regeneration. One such approach involves the use of autologous blood concentrates, particularly platelet-rich plasma (PRP). PRP is a plasma fraction enriched in platelets, which serve as a source of many growth factors, including platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), and vascular endothelial growth factor (VEGF). These agents play a key role in regenerative processes and angiogenesis [1, 2].

PRP is used in dental surgery across a wide range of procedures, including tooth extractions, implantology, bone defect treatment, and the promotion of healing following soft tissue procedures [3]. Owing to its pro-regenerative and anti-inflammatory properties, PRP may shorten recovery time, reduce postoperative pain, and improve the quality of newly formed tissue [4].

The aim of this paper was to review the available scientific evidence regarding the mechanism of action of PRP and its clinical efficacy in dental surgery. Both *in vitro* findings and clinical reports were analysed to evaluate the therapeutic potential of this approach in dental practice.

Materials and methods

Data were sourced from scientific publications indexed in the PubMed database. A systematic literature review was conducted encompassing studies on the use of PRP across various domains of dentistry, with particular emphasis on oral surgery. The literature search was conducted between February and May 2025. Only scientific articles published in English or Polish and available as full-text online publications were included. Systemic diseases affecting the healing process or platelet count, smoking, and pregnancy were the exclusion criteria. The following keywords were used for literature search: PRP, healing process, tooth extraction, dental implants, bone augmentation, periodontology, and soft tissue. Studies published in peer-reviewed scientific journals with direct relevance to the topic of the present review were included in the analysis.

Characteristics of PRP – mechanism of action, impact on the wound healing process and methods of preparation

The regenerative properties of PRP are primarily attributable to the high concentration of platelets, which constitute the principal mediators of this preparation's biological activity. The standard normal platelet count in healthy adults is 150 to 300 × 10^9/L. Their average lifespan is 8–10 days. Beyond their haemostatic function, platelets play a critical and indispensable role in tissue regeneration and wound healing, particularly during the initial inflammatory phase. Wound healing typically occurs in a pro-inflammatory environment, where elevated proteolytic enzyme activity restricts the availability of endogenous growth factors essential for tissue regeneration. To counteract these unfavourable conditions, PRP provides a concentrated exogenous source of growth factors, supporting tissue regeneration through its mitogenic, angiogenic, and chemotactic properties [5]. Platelets contain three main types of granules: alpha granules, dense (delta) granules, and lysosomes, with each group harbouring a distinct set of mediators that coordinate the repair process. Alpha granules are of particular relevance in the regenerative context, serving as a principal source of numerous growth factors, cytokines, adhesion molecules, and signalling proteins. These include, among others, PDGF (αα, ββ, and αβ isoforms), VEGF, insulin-like growth factor (IGF), TGF-β1, TGF-β2, epidermal growth factor (EGF), interleukin-1, osteocalcin, osteonectin, as well as structural proteins such as fibrinogen, vitronectin, fibronectin, and thrombospondin [2, 6, 7]. In addition to platelets, PRP also contains leukocytes, plasma, and erythrocyte remnants [2]. The effects of PRP derive in part from the activity of PDGF, which has been identified as a key mediator in the healing of both hard and soft tissues. PDGF has been shown to stimulate chemotaxis, mitogenesis, and stem cell replication at sites of wound and tissue damage. This induces bone matrix formation and angiogenesis through the upregulation of VEGF, which may consequently accelerate soft tissue healing via neovascularization. PDGF additionally stimulates the synthesis of fibronectin, a cell adhesion molecule involved in cell proliferation and migration during the healing process, including osteoconduction of hyaluronic acid, and contributes to wound contraction and remodelling [8].

PRP represents an autologous product as it is prepared from the patient's own venous blood. The preparation procedure involves isolating plasma fractions and concentrating platelets to levels substantially exceeding those observed in peripheral circulation under physiological conditions. This is typically achieved through centrifugation of the collected venous blood. Evidence suggests that a platelet concentration approximately 2.5–5 times higher than baseline levels is optimal for maximiz-

ing regenerative effects [9, 10]. In clinical practice, PRP is obtained through centrifugation of peripheral blood. Following centrifugation of anticoagulant-treated blood, the sample separates into three distinct layers: a dense bottom layer of red blood cells, an intermediate "buffy coat" containing platelets and leukocytes, and an upper plasma layer [11]. Further processing of the plasma and buffy coat layer through additional centrifugation allows for the isolation of PRP. Commercially available PRP preparation kits are also widely used, incorporating separation gels that facilitate platelet isolation during centrifugation and enabling standardized, reproducible outcomes. PRP gel is produced by combining platelet-rich plasma with thrombin or calcium chloride, typically at a concentration of 10%. The addition of thrombin and calcium chloride induces automatic activation of alpha granules, triggering the release of biologically active growth factors [7]. Numerous protocols and techniques for PRP preparation have been described in the literature, alongside a wide range of therapeutic applications. However, methodological variability and inconsistent nomenclature across studies complicate the interpretation and comparison of results, often introducing ambiguity and limiting the generalizability of conclusions [11, 12].

PRP derived from the patient's own venous blood eliminates the risk of viral pathogen transmission associated with allogeneic blood products. The autologous origin of PRP likewise precludes the risk of prion contamination and virtually eliminates the possibility of allergic or other immune-mediated adverse reactions. It should be noted, however, that the use of bovine thrombin as an exogenous activator in PRP preparation may be associated with acquired coagulopathies due to cross-reactivity of antibodies directed against bovine factor V with its human counterpart [13]. To date, no evidence of carcinogenic effects associated with the clinical use of PRP has been reported [14, 15].

Results

During the selection process, 305 publications were initially identified, of which 142 were excluded at the preliminary stage. The remaining 163 papers underwent abstract review, following which a further 121 were excluded. Forty-three papers were considered for further analysis, of which three were excluded upon verification of detailed exclusion criteria. Ultimately, 40 papers were included in the systematic review, comprising seven comparative studies, five clinical trials, and nine randomized controlled trials.

Discussion

Autologous PRP concentrates represent a valuable adjunct that supports regenerative processes in dental surgery, demonstrating the potential to modulate tissue repair through the activity of multiple bioactive growth factors. The mechanism of action of PRP is based on the induction of angiogenesis, stimulation of mesenchymal cell proliferation, promotion of extracellular matrix component synthesis, and enhancement of bone mineralization. These preparations are employed across a broad range of dental procedures, including the management of extraction sockets, augmentation procedures, implant therapies, sinus lift procedures, and soft tissue regeneration. Despite numerous reports documenting beneficial clinical effects of PRP, its therapeutic efficacy remains under ongoing investigation. Outcomes may be substantially influenced by variations in preparation protocols, platelet concentrations, and individual patient clinical characteristics.

PRP preparation protocols varied across the analysed studies. The results and a summary of the parameters employed for PRP preparation are presented in Tables 1–4.

Extraction sockets

Tooth extraction is among the most frequently performed surgical procedures in dentistry. Despite its routine nature, it may give rise to numerous complications that can substantially impair the healing process. The most common complications include pain, oedema, trismus, infection, and dry socket. In some cases, tissue regeneration may be delayed, adversely affecting treatment outcomes and patient comfort [16, 17].

Table 1. Platelet-rich plasma (PRP) preparation protocols and research findings regarding its effect on post-extraction sockets

Study	Parameters		Activator used	Outcomes
	First centrifugation	Second centrifugation		
Biomet, Indiana, USA [16]	1000 rpm for 10 minutes	1000 rpm for 10 minutes	10% $CaCl_2$	More rapid soft tissue healing, reduced rates of local complications such as dry socket, diminished postoperative pain, and improved trabecular bone structure on radiographic imaging in PRP-treated areas
Haydarpaşa Training Hospital, Istanbul [19]	1200 rpm for 10 minutes	1000 rpm for 10 minutes	-	No significant differences in new bone formation between PRP-treated and control groups
Dental Services Department, Nigeria [20]	1200 rpm for 10 minutes	1000 rpm for 10 minutes	10% $CaCl_2$ and 1000 U of bovine thrombin	Reduced pain and oedema, improved range of mouth opening
Duquesne University [21]	1150 rpm for 10 minutes	-	-	Increased radiographic bone density in PRP-treated areas; no significant observations regarding postoperative pain or bleeding severity

Table 2. Platelet-rich plasma (PRP) preparation protocols and research findings regarding its effect on bone augmentation

Study	Parameters		Activator used	Outcomes
	First centrifugation	Second centrifugation		
Maharishi Markandeshwar College of Dental Sciences and Research, Mullana [26]	200 × g for 20 minutes	400 × g for 10 minutes	-	No significant differences were identified for osseointegration or the quality of newly formed bone tissue
Yeditepe University, Istanbul [27]	2,400 rpm for 10 minutes	3,600 rpm for 15 minutes	10% $CaCl_2$	Superior efficacy of PRP combined with xenograft material relative to standard augmentation procedures has not been confirmed
Kenia Dental College, Nepal [28]	2000 rpm for 15 minutes	3000 rpm for 10 minutes	10% $CaCl_2$	Autologous PRP is biocompatible and significantly improves soft tissue healing, bone regeneration, and bone density in extraction sockets
King Saud University, Saudi Arabia [29]	200 × g for 20 minutes	400 × g for 10 minutes	10% $CaCl_2$	Improved healing of soft tissues, faster bone regeneration in the socket with the use of PRP

Table 3. Platelet-rich plasma (PRP) preparation protocols and research findings regarding its effect on implants

Study	Parameters		Activator used	Outcomes
	First centrifugation	Second centrifugation		
King Saud University, Saudi Arabia [29]	200 × g for 20 minutes	400 × g for 10 minutes	10% $CaCl_2$	Improved healing of soft tissues, faster bone regeneration in the socket with the use of PRP
Biotechnology Institute, Vitoria [30]	460 × g for 8 minutes	-	10% $CaCl_2$	Coating of the implant surface elicits a more dynamic tissue response and promotes accelerated bone mineralization
University of Rome Tor Vergata, Italy [31]	1100 rpm for 10 minutes	-	10% $CaCl_2$	Faster regeneration of soft and hard tissues
Bapuji Dental College and Hospital, India [32]	3000 rpm for 10 minutes	-	-	Minimizing delayed integration of implants into hard and soft tissues
School of Dentistry Sao Paulo, Brazil [34]	1200 rpm for 10 minutes	1200 rpm for 15 minutes	-	The use of PRP in the treatment of peri-implant bone defects does not yield significant improvement in bone tissue regeneration

Table 4. Platelet-rich plasma (PRP) preparation protocols and research findings regrading its effect on sinus lift

Study	Parameters		Activator used	Outcomes
	First centrifugation	Second centrifugation		
Cairo University, Egypt [36]	160 × g for 16 minutes	-	10% $CaCl_2$	No significant differences were observed in the quality of newly formed bone or the efficiency of osseointegration
Medical University of Vienna, Austria [37]	1800 rpm for 10 minutes	3000 rpm for 10 minutes	10% $CaCl_2$ and bovine thrombin	Potential synergistic effects of PRP and synthetic bone substitutes

In response to these challenges, research into methods for accelerating post-extraction regeneration has focused on the use of autologous platelet concentrates, which, by virtue of their high concentration of growth factors such as PDGF, TGF-β, and VEGF, have the potential to favourably modulate the healing environment [18]. PRP preparations are capable of stimulating angiogenesis, fibroblast and osteoblast proliferation, and extracellular matrix reconstruction, thereby potentially contributing to accelerated regeneration of both soft and hard tissues. PRP is therefore regarded as a promising therapeutic tool with the potential to prevent complications

and optimize the healing process following tooth extraction [19].

A 2010 study by Alissa et al. found that PRP significantly accelerated soft tissue healing in extraction sockets compared to controls. Patients who did not receive PRP exhibited a higher incidence of local complications, including dry socket and acute alveolitis. Although these differences were of borderline statistical significance, they suggest a preventive potential for PRP. Radiographic evaluation of healed sockets additionally revealed a marked improvement in trabecular bone structure in PRP-treated areas, although statistically significant differences were observed only in sockets exhibiting dense and homogeneous bone structure. Furthermore, patients treated with PRP reported lower levels of postoperative pain, particularly during the first three days following surgery [16].

Similar observations were reported by researchers assessing the effect of PRP on the healing process following surgical extraction of impacted third molars. The PRP-treated group demonstrated a significant reduction in pain and oedema, as well as improved mouth opening. Differences in radiological parameters, including bone density and trabecular bone structure, were observable, yet did not reach statistical significance [20].

Clinicians from Duquesne University employed digital radiography and computed tomography (CT) to assess changes in bone density within the extraction socket. Their analysis revealed a statistically significant increase in radiographic density in PRP-treated areas, suggesting a beneficial effect on early mineralisation. However, no significant effect of PRP on postoperative pain or bleeding was observed [21].

Despite numerous positive reports demonstrating the efficacy of PRP in improving soft tissue healing and reducing post-extraction complications, evidence regarding its effect on bone regeneration remains more ambiguous. Some studies have failed to confirm significant differences in new bone formation between PRP-treated and control groups, underscoring the need for further well-designed clinical trials and standardized PRP preparation protocols. Given the available evidence, PRP may be assumed to exert a beneficial effect primarily during the initial phase of post-extraction wound healing, supporting early osteogenesis. However, the magnitude of this effect may diminish in later stages of tissue remodelling [22].

Bone augmentation

Augmentation procedures intended to restore mandibular bone may utilize PRP to provide biological support to enhance osteogenesis. Used alone or in combination with bone substitutes, PRP can modulate the local healing environment by activating progenitor cells and initiating bone remodelling. Consequently, PRP may contribute to increased volume and improved quality of newly formed bone tissue. Its mechanisms of action have been confirmed at the cellular level: as early as day 3 post application, increased osteoblast and fibroblast proliferation, enhanced neovascularization, and accelerated bone mineralisation have been observed [23]. These processes form the basis for the application of PRP in implantology and guided bone regeneration (GBR), particularly in cases of significant alveolar process atrophy requiring augmentation prior to planned implant treatment [24].

The osteogenic potential of PRP is supported by both experimental and clinical evidence. For example, Daif (2012) demonstrated that direct application of PRP along mandibular fracture lines may support the healing process by accelerating bone tissue regeneration [25]. A 2007 study comparing bone marrow mononuclear cell transplants containing the CD34+ population with PRP preparations demonstrated that PRP stimulated new alveolar bone formation more effectively than stem cells alone. These findings suggest that the growth factors contained in PRP may positively modulate the osteogenic microenvironment [26].

Although numerous studies indicate a beneficial effect of PRP on bone regeneration, the available evidence remains inconclusive. Some comparative studies comparing platelet concentrates against synthetic alloplasts (such as PerioGlass) and bioresorbable xenografts (e.g., Bio-Oss) failed to demonstrate significant differences in osseointegration or the quality of newly formed bone tissue [27]. Similarly, Cabbara et al. did not confirm superior efficacy of combining PRP with xenograft material compared to standard augmentation procedures [28]. At the same time, other clinical reports demonstrate a statistically significant increase in bone density in areas treated with PRP, particularly at longer follow-up intervals of 1, 4, and 12 months, suggesting a positive effect of PRP on the rate and quality of long-term bone regeneration [29, 30].

Discrepancies in the reported results may be attributable to numerous confounding factors, including the absence of standardized protocols for PRP preparation and application, the heterogeneous physicochemical properties of biomaterials used as carriers, and variability in surgical techniques. These factors substantially complicate the definitive assessment of PRP efficacy relative to conventional bone augmentation approaches.

Implantology

Modern implantology seeks to optimize the early stages of osseointegration with the aim of achieving predictable and durable treatment outcomes. One promising approach involves the use of autologous PRP as a biological adjunct supporting regenerative peri-implant processes [18]. PRP contains high concentrations of growth factors capable of supporting the differentiation of osteoprogenitor cell differentiation, stimulating angiogenesis, and initiating extracellular matrix remodelling [18, 30]. The application of PRP, both to implant surfaces and within the bone bed, may accelerate healing, enhance primary and secondary implant stability, and reduce the risk of postoperative inflammatory complications. Given its biologically active properties, PRP may positively modulate the microenvironment at the implant site, creating conditions that promote effective and durable implant-bone integration [24].

Experimental studies have demonstrated that PRP-coated implants exhibit a higher degree of bone integration.

Anitua confirmed that biological implant coating elicits a more dynamic tissue response and promotes more rapid mineralisation [31]. Similar observations were reported by researchers from the University of Rome Tor Vergata, who, in the context of maxillary reconstruction and post-extraction tissue regeneration, documented a beneficial effect of PRP on the healing process as well as high patient tolerability of this intervention [32]. Furthermore, innovative techniques proposed by Anand et al., involving the application of PRP to the implant surface within immediate loading protocols, suggest the potential for improved treatment outcomes through biological tissue stimulation while minimising delays in the integration of hard and soft tissue structures [33].

Available evidence also suggests that PRP may improve bone density indices and reduce marginal bone loss, parameters that are critical for long-term implant stability and functionality. Taschieri et al. observed that implants placed in fresh extraction sockets demonstrated improved soft tissue integration with PRP, potentially attributable to its angiogenic properties and its impact on collagen expression and extracellular matrix remodelling [34].

It should be noted, however, that the results of clinical trials remain ambiguous. Casati et al. reported that PRP alone failed to yield significant improvement in bone tissue regeneration in the management of peri-implant bone defects [35]. Discrepancies in research findings may be partially explained by the absence of standardized PRP harvesting and activation procedures, biological variability among patients, and heterogeneity in study designs.

Sinus lift

Sinus lift surgery is an important preparatory step for implant placement in the posterior maxilla with insufficient alveolar ridge height. The use of PRP in this procedure aims to enhance angiogenesis and osteogenesis at the graft site. As a biologically active carrier of growth factors, PRP may support bone remodelling and improve treatment outcomes with respect to both the quality of newly formed bone and implant survival.

The use of PRP in combination with bone substitutes, particularly β-tricalcium phosphate (β-TCP), has been assessed as moderately beneficial [36]. Some studies have demonstrated that combining PRP with β-TCP may yield approximately 8–10% greater new bone formation compared to β-TCP monotherapy, without affecting the rate of biomaterial resorption. These findings suggest a potential synergistic effect of PRP and synthetic bone substitutes; however, the efficacy of this approach depends on multiple variables, including the composition and preparation method of the concentrate, the quality of the biomaterial, and the surgical technique employed [37, 38].

It is also noteworthy that not all comparisons of PRP with other graft materials have yielded favourable results. Several studies comparing PRP with alloplastic materials (e.g., PerioGlass) or bioresorbable xenografts (e.g., Bio-Oss) have failed to demonstrate significant differences in the quality of newly formed bone or the efficacy of osseointegration. Such discrepancies may be attributable to inconsistent methodologies, differences in the materials employed, and the absence of standardized PRP preparation protocols [37, 38].

Periodontology and oral soft tissues

Autologous PRP represents a valuable adjunct supporting regenerative processes, with particular relevance to the treatment of periodontal disease and the reconstruction of oral soft tissues. Its therapeutic potential stems from its high concentration of growth factors and bioactive molecules that modulate the local inflammatory response, initiate angiogenesis, and stimulate the proliferation of cells integral to the healing process, including fibroblasts and keratinocytes [29, 37]. These mechanisms promote accelerated epithelial and mucosal regeneration, enhancing the predictability of clinical outcomes in interventions such as gingival recession management, autogenous grafting, and postoperative tissue regeneration.

In periodontology, PRP is employed as an adjunctive biological agent in procedures aimed at reconstructing periodontal structures, including root cementum, the periodontal ligament, and alveolar bone [29]. PRP has the capacity to stimulate progenitor cell migration and differentiation as well as extracellular matrix remodelling, supporting graft integration and the restoration of lost attachment. It has further been documented to promote fibrin clot formation, which translates into increased collagen production and fibroblast proliferation within the wound [21].

Systematic reviews indicate that PRP may improve the healing of periodontal defects, particularly when used in combination with graft materials. Del Fabbro et al. demonstrated a potentially beneficial effect of PRP in the management of intraosseous defects, although no clear benefit was identified in the treatment of gingival recession [3]. Two controlled clinical trials demonstrated that combining PRP with bone graft material yielded superior clinical outcomes compared to graft material alone [39, 40].

Regarding soft tissue healing, three of the four analysed studies reported a statistically significant acceleration of the regeneration process ($p < 0.05$), as confirmed by wound assessments performed at 7–14 day intervals following the procedure [29, 30, 37, 39]. Similar findings were reported by Gawai et al., who demonstrated significantly superior healing outcomes in patients receiving PRP compared to controls [41].

Conclusions

Platelet-rich plasma (PRP) represents a promising adjunct for supporting tissue regeneration in dental surgery, owing to its high platelet concentration and the presence of growth factors such as PDGF, TGF-β, VEGF, and EGF, which play a central role in angiogenesis, cell proliferation, and extracellular matrix remodelling. PRP is employed across a broad range of clinical interventions, including extraction socket management, bone augmentation, sinus lift, implantology, and periodontal surgery.

In the context of tooth extraction, PRP has the potential to reduce pain, oedema, and the risk of complications such as dry socket. Clinical studies indicate accelerated soft tissue regeneration and improved radiographic parameters, although evidence regarding bone regeneration remains inconclusive. In augmentation procedures, PRP may support osteogenesis, particularly when used in combination with bone substitutes, although the efficacy of this approach depends on many factors, including biomaterial quality, surgical technique, and the lack of standardized PRP preparation protocols. PRP demonstrates moderate potential for improving regenerative parameters in sinus lift, although research findings remain inconsistent. In implantology, PRP may accelerate osseointegration and enhance implant stability, primarily through its angiogenic properties and stimulation of peri-implant tissue regeneration. Despite encouraging experimental data, clinical trials remain inconsistent. In periodontology, PRP is employed as an adjunct supporting the regeneration of soft tissues and periodontal structures. PRP has demonstrated a beneficial effect on wound healing, progenitor cell migration, and connective tissue attachment restoration, particularly when used in combination with graft materials.

In summary, PRP represents a valuable adjunct to surgical procedures in dentistry, particularly during the initial stages of healing. However, given the insufficient evidence regarding its efficacy in bone regeneration and the considerable variability in reported outcomes, further well-designed clinical trials and standardisation of preparation and application protocols are warranted.

References

1. Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? Implant Dent, 2001; 10(4): 225–228. doi: 10.1097/00008505-200110000-00002
2. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol, 2009; 27(3): 158–167. doi: 10.1016/j.tibtech.2008.11.009
3. Del Fabbro M, Bortolin M, Taschieri S, Weinstein R. Is platelet concentrate advantageous for the surgical treatment of periodontal diseases? A systematic review and meta-analysis. J Periodontol, 2011; 82(8): 1100–1111. doi: 10.1902/jop.2010.100605
4. Anitua E, Andia I, Ardanza B, et al. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost, 2004; 91(1): 4–15. doi: 10.1160/TH03-07-0440
5. Koltai K, Kesmarky G, Feher G, et al. Platelet aggregometry testing: molecular mechanisms, techniques and clinical implications. Int J Mol Sci, 2017; 18(8): 1803. doi: 10.3390/ijms18081803
6. Barrientos S, Stojadinovic O, Golinko MS, et al. Growth factors and cytokines in wound healing. Wound Repair Regen, 2008; 16(5): 585–601. doi: 10.1111/j.1524-475X.2008.00410.x
7. Alissa R, Esposito M, Horner K, Oliver R. The influence of platelet-rich plasma on the healing of extraction sockets: an explorative randomised clinical trial. Eur J Oral Implantol, 2010; 3(2): 121–134
8. Yang D, Cheng J, Jing Z, Jin D. Platelet-derived growth factor (PDGF)-AA: a self-imposed cytokine in the proliferation of human fetal osteoblasts. Cytokine, 2000; 12(8): 1271–1274. doi: 10.1006/cyto.2000.0707
9. Cole BJ, Seroyer ST, Filardo G, et al. Platelet-rich plasma: where are we now and where are we going? Sports Health, 2010; 2(3): 203–210. doi: 10.1177/1941738110366385
10. Graziani F, Ivanovski S, Cei S, et al. The in vitro effect of different PRP concentrations on osteoblasts and fibroblasts. Clin Oral Implants Res, 2006; 17(2): 212–219. doi: 10.1111/j.1600-0501.2005.01203.x
11. Sánchez-González DJ, Méndez-Bolaina E, Trejo-Bahena NI. Platelet-rich plasma peptides: key for regeneration. Int J Pept, 2012; 2012: 532519. doi: 10.1155/2012/532519
12. Landesberg R, Moses M, Karpatkin M. Risks of using platelet rich plasma gel. J Oral Maxillofac Surg, 1998; 56(9): 1116–1117. doi: 10.1016/s0278-2391(98)90286-5
13. Andia I, Abate M. Platelet-rich plasma: underlying biology and clinical correlates. Regen Med, 2013; 8(5): 645–658. doi: 10.2217/rme.13.59
14. Alves R, Grimalt R. A review of platelet-rich plasma: history, biology, mechanism of action, and classification. Skin Appendage Disord, 2018; 4(1): 18–24. doi: 10.1159/000477353
15. Croisé B, Paré A, Joly A, et al. Optimized centrifugation preparation of the platelet rich plasma: literature review. J Stomatol Oral Maxillofac Surg, 2020; 121(2): 150–154. doi: 10.1016/j.jormas.2019.07.001
16. Woodell-May JE, Ridderman DN, Swift MJ, Higgins J. Producing accurate platelet counts for platelet rich plasma: validation of a hematology analyzer and preparation techniques for counting. J Craniofac Surg, 2005; 16(5): 749–756. doi: 10.1097/01.scs.0000180007.30115.fa
17. Antonello Gde M, Torres do Couto R, Giongo CC, et al. Evaluation of the effects of the use of platelet-rich plasma (PRP) on alveolar bone repair following extraction of impacted third molars: prospective study. J Craniomaxillofac Surg, 2013; 41(4): e70–e75. doi: 10.1016/j.jcms.2012.11.003
18. Arenaz-Búa J, Luaces-Rey R, Sironvalle-Soliva S, et al. A comparative study of platelet-rich plasma, hydroxyapatite, demineralized bone matrix and autologous bone to promote bone regeneration after mandibular impacted third molar extraction. Med Oral Patol Oral Cir Bucal, 2010; 15(3): e483–e489. doi: 10.4317/medoral.15.e483
19. Gürbüzer B, Pikdöken L, Urhan M, et al. Scintigraphic evaluation of early osteoblastic activity in extraction sockets treated with platelet-rich plasma. J Oral Maxillofac Surg, 2008; 66(12): 2454–2460. doi: 10.1016/j.joms.2008.03.006
20. Ogundipe OK, Ugboko VI, Owotade FJ. Can autologous platelet-rich plasma gel enhance healing after surgical extraction of mandibular third molars? J Oral Maxillofac Surg, 2011; 69(9): 2305–2310. doi: 10.1016/j.joms.2011.02.014
21. Rutkowski JL, Johnson DA, Radio NM, Fennell JW. Platelet rich plasma to facilitate wound healing following tooth extraction. J Oral Implantol, 2010; 36(1): 11–23. doi: 10.1563/AAID-JOI-09-00063
22. Albanese A, Licata ME, Polizzi B, Campisi G. Platelet-rich plasma (PRP) in dental and oral surgery: from the wound healing to bone regeneration. Immun Ageing, 2013; 10(1): 23. doi: 10.1186/1742-4933-10-23
23. Grassi FR, Ciccolella F, D'Apolito G, et al. Effect of low-level laser irradiation on osteoblast proliferation and bone formation. J Biol Regul Homeost Agents, 2011; 25(4): 603–614. Erratum in: J Biol Regul Homeost Agents, 2012; 26(1): 3 p following 163. Dipalma, M [corrected to Dipalma, G]

24. Carlson NE, Roach RB Jr. Platelet-rich plasma: clinical applications in dentistry. J Am Dent Assoc, 2002; 133(10): 1383–1386. doi: 10.14219/jada.archive.2002.0054
25. Daif ET. Effect of autologous platelet-rich plasma on bone regeneration in mandibular fractures. Dent Traumatol. 2013; 29(5): 399–403. doi: 10.1111/edt.12021
26. Wojtowicz A, Chaberek S, Urbanowska E, Ostrowski K. Comparison of efficiency of platelet rich plasma, hematopoieic stem cells and bone marrow in augmentation of mandibular bone defects. N Y State Dent J, 2007; 73(2): 41–45
27. Tomar N, Dahiya S, Sharma PK, et al. A Comparative clinical evaluation of effectiveness of platelet-rich plasma, synthetic allograft, and bioresorbable xenograft during immediate implant placement. Cureus, 2022; 14(12): e32121. doi: 10.7759/cureus.32121
28. Cabbar F, Güler N, Kürkcü M, et al. The effect of bovine bone graft with or without platelet-rich plasma on maxillary sinus floor augmentation. J Oral Maxillofac Surg, 2011; 69(10): 2537–2547. doi: 10.1016/j.joms.2011.03.040
29. Dutta SR, Singh P, Passi D, Patter P. Mandibular third molar extraction wound healing with and without platelet rich plasma: a comparative prospective study. J Maxillofac Oral Surg, 2015; 14(3): 808–815. doi: 10.1007/s12663-014-0738-1
30. ArRejaie A, Al-Harbi F, Alagl AS, Hassan KS. Platelet-rich plasma gel combined with bovine-derived xenograft for the treatment of dehiscence around immediately placed conventionally loaded dental implants in humans: cone beam computed tomography and three-dimensional image evaluation. Int J Oral Maxillofac Implants, 2016; 31(2): 431–438. doi: 10.11607/jomi.3859
31. Anitua EA. Enhancement of osseointegration by generating a dynamic implant surface. J Oral Implantol, 2006; 32(2): 72–76. doi: 10.1563/736.1
32. Gentile P, Bottini DJ, Spallone D, et al. Application of platelet-rich plasma in maxillofacial surgery: clinical evaluation. J Craniofac Surg, 2010; 21(3): 900–904. doi: 10.1097/SCS.0b013e3181d878e9
33. Anand U, Mehta DS. Evaluation of immediately loaded dental implants bioactivated with platelet-rich plasma placed in the mandibular posterior region: A clinico-radiographic study. J Indian Soc Periodontol, 2012; 16(1): 89–95. doi: 10.4103/0972-124X.94612
34. Taschieri S, Lolato A, Ofer M, et al. Immediate post-extraction implants with or without pure platelet-rich plasma: a 5-year follow-up study. Oral Maxillofac Surg, 2017; 21(2): 147–157. doi: 10.1007/s10006-017-0609-2
35. Casati MZ, de Vasconcelos Gurgel BC, Gonçalves PF, et al. Platelet-rich plasma does not improve bone regeneration around peri-implant bone defects – a pilot study in dogs. Int J Oral Maxillofac Surg, 2007; 36(2): 132–136. doi: 10.1016/j.ijom.2006.06.004
36. Wiltfang J, Schlegel KA, Schultze-Mosgau S, et al. Sinus floor augmentation with beta-tricalcium phosphate (beta-TCP): does platelet-rich plasma promote its osseous integration and degradation? Clin Oral Implants Res, 2003; 14(2): 213–218. doi: 10.1034/j.1600-0501.2003.140212.x
37. Khairy NM, Shendy EE, Askar NA, El-Rouby DH. Effect of platelet rich plasma on bone regeneration in maxillary sinus augmentation (randomized clinical trial). Int J Oral Maxillofac Surg, 2013; 42(2): 249–255. doi: 10.1016/j.ijom.2012.09.009
38. Poeschl PW, Ziya-Ghazvini F, Schicho K, et al. Application of platelet-rich plasma for enhanced bone regeneration in grafted sinus. J Oral Maxillofac Surg, 2012; 70(3): 657–664. doi: 10.1016/j.joms.2011.04.027
39. Menezes LM, Rao J. Long-term clinical evaluation of platelet-rich plasma in the treatment of human periodontal intraosseous defects: a comparative clinical trial. Quintessence Int, 2012; 43(7): 571–582
40. Saini N, Sikri P, Gupta H. Evaluation of the relative efficacy of autologous platelet-rich plasma in combination with β-tricalcium phosphate alloplast versus an alloplast alone in the treatment of human periodontal infrabony defects: a clinical and radiological study. Indian J Dent Res, 2011; 22(1): 107–115. doi: 10.4103/0970-9290.80008
41. Gawai KT, Sobhana CR. Clinical evaluation of use of platelet rich plasma in bone healing. J Maxillofac Oral Surg, 2015; 14(1): 67–80. doi: 10.1007/s12663-013-0605-5

REVIEW ARTICLE

CIVIL-MILITARY COOPERATION DURING MASS CASUALTY EVENTS

Współpraca cywilno-wojskowa w trakcie zdarzeń masowych

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Abstract

The paper discusses the importance of civil-military cooperation during mass events between 2013 and 2024. We analysed the COVID-19 pandemic, the 2024 Olympic Games in Paris, and the Boston Marathon bombing, highlighting various forms of armed force involvement in supporting civil institutions. We found that the effectiveness of civil-military cooperation depends on a clear division of responsibilities, mutual trust, training, and coordinated procedures. The paper further underscores the need to formalize this cooperation as an inherent component of the national security system.

Streszczenie

Praca omawia znaczenie współpracy cywilno-wojskowej podczas zdarzeń masowych w latach 2013–2024. Analizuje przypadki, takie jak pandemia COVID-19, igrzyska olimpijskie w Paryżu (2024) oraz zamach podczas Maratonu Bostońskiego (2013), ukazując różnorodne formy zaangażowania sił zbrojnych we wsparcie instytucji cywilnych. Wskazuje, że efektywność współpracy cywilno-wojskowej zależy od jasnego podziału kompetencji, wzajemnego zaufania, szkoleń oraz wspólnych procedur. Praca podkreśla również potrzebę formalizacji tej współpracy jako stałego elementu systemu bezpieczeństwa narodowego.

Keywords: mass events; crisis management; terrorist attack; COVID-19 pandemic; civil-military cooperation

Słowa kluczowe: zdarzenia masowe; zarządzanie kryzysowe; zamach terrorystyczny; pandemia COVID-19; współpraca cywilno-wojskowa

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Introduction

Civil-military cooperation (CIMIC) has become an integral part of successful crisis management in the current geopolitical context. Given the growing frequency and scale of mass incidents, including pandemics, natural and anthropogenic disasters (including chemical, industrial, ecological, and construction emergencies, terrorism, armed conflicts, biological or chemical threats, and cyberattacks), close coordination between civilian sector and the armed forces is essential.

The boundaries between military and civilian operational domains are becoming increasingly blurred. The armed forces no longer exist merely for defence purposes intended to protect state sovereignty and territorial integrity, but they are also expected to support public administration and relief efforts during emergencies.

The role of CIMIC has considerably expanded over the past decade, particularly where security-related activities like handling disasters, terrorism, and search-and-rescue missions are concerned. The COVID-19 pandemic exposed significant deficiencies in civilian systems while simultaneously underscoring the value of military resources and capabilities, including logistics, organizational capacity, rapid mobilization, and the ability to operate under crisis conditions. Similarly, organisation

of large-scale international events such as the Olympic Games, as well as addressing natural disasters, including fires and floods, have demonstrated that effective crisis management without military involvement is often challenging and, sometimes, impossible. Our paper attempts to analyse civil-military cooperation in the context of selected mass events held in the past decade, with particular focus on practical and legal aspects, as well as developmental barriers and opportunities in this domain. We also assessed cross-national differences in approaches to CIMIC and lessons learned from past experiences.

Legal framework for CIMIC

Civil-military cooperation is governed by certain legal regulations that defining the extent to which military activity can be conducted during crises within particular countries. Depending on the national context, this framework may be statutory, constitutional, or executive (acts, regulations, or bylaws). A state of natural disaster or emergency, or decisions made by executive authorities in relation to an emergency, serve as a legal basis for engaging military forces in operations supporting civilian administration in most European countries, including Poland [1].

Poland

In Poland, the legal framework for civil-military cooperation is defined, among others, by:

- **The Act of 21 November 1967 on universal obligation to defend the Republic of Poland**, which allows for directing the armed forces to actions other than defence tasks, including support in crisis situations (Articles 3 and 11);
- **The Act of 26 April 2007 on Crisis Management**, which establishes a crisis management system in Poland and designates the armed forces as one of the institutions responding to crisis;
- **Act of 18 April 2002 on the state of natural disaster**, regulating circumstances under which the armed forces may be deployed to provide assistance during natural disasters and threats to the life and health of the population;
- **Regulations of the Minister of National Defence and internal regulations of the Polish Armed Forces**, including the *Operational Doctrine of the Polish Armed Forces* [2, 3].

Furthermore, specialized units and cells responsible for CIMIC have been established within Polish Armed Forces, most notably the Territorial Defense Forces Component Command, which plays a key role in aid operations, particularly at the local level.

NATO and the European Union

The following international frameworks are also of relevance:

- **NATO documents**, including Allied Joint Publication 3.4.9 (AJP-3.4.9) "Civil-Military Cooperation (CIMIC)", which outline the principles for planning and implementing civil-military cooperation in Allied operations [1];
- **The Treaty of Lisbon (2007)**, which introduced the "solidarity clause" (TFEU Article 222), obliging EU Member States to collaborate in the event of disasters and terrorist attacks, including the use of military resources [4].

Limitations and controversies

Finding a proper balance between civilian supremacy over the armed forces and their effective performance remains one of the major legal challenges. Excessively rigid regulations may impede the timely response in an emergency, whereas overly broad regulations can give rise to misuse of power and, in extreme cases, overstepping the boundaries of competences. Some states, like Germany, have strict constitutional limitations on the domestic use of armed forces, while other, such as France or Poland, allow for a more flexible participation of the military in crisis operations.

Examples of civil-military cooperation

COVID-19 pandemic

The COVID-19 pandemic prompted armed forces to undertake unprecedented public health protection efforts. The Polish Armed Forces supported the state's logistical and organizational activities, including:

- Coordination of hospital logistics and delivery of personal protective equipment, respirators, beds, full hospital room equipment, etc.;
- Supporting civilian facilities through screening and testing done by military paramedics and Military Centers of Preventive Medicine (WOMP);
- Establishing and running swab testing sites and field hospitals (for instance at the National Stadium);
- Providing support to organise and operate the vaccination stations, especially in smaller communities;
- Involvement in transportation services to enable the elderly and disabled individuals access to the vaccination stations;
- Delivering masks, disinfectants and medical equipment to residents and public institutions;
- Organising convoys and providing support for the Material Reserves Agency;
- Cooperation with Border Guard and Police in carrying out border and sanitary epidemiological control activities;
- Monitoring of individuals under quarantine conditions conducted by Military Police officers;
- Conducting educational campaigns and providing telephone aid for isolated individuals and those experiencing crisis situations (the so-called WOT Support Telephone) by the Territorial Defence Forces.

In response to the COVID-19 pandemic, the United Kingdom launched Operation Rescript in March 2020, representing the largest peacetime military operation in the country's history, which gave rise to the COVID Support Force (CSF), comprising up to 23,000 soldiers and reservists. The CSF provided support to the National Health Service (NHS) and local authorities across many dimensions of the pandemic response.

Some of the CSF activities included:

- constructing temporary NHS Nightingale hospitals;
- distribution of personal protective equipment (PPE), with over 1.18 billion items delivered to NHS facilities;

- aiding the transport of patients and medical personnel;
- participation in the vaccination programme, including planning and logistics.

Operation Rescript was carried out according to the Military Aid to the Civil Authorities (MACA) procedure, which enables the armed forces to support civilian authorities in crisis situations [5–7]. These actions demonstrated the flexibility and adaptability of military structures when facing non-traditional threats.

Paris 2024 Olympic Games – International Mobilization of Security Forces

Preparing for the 2024 Olympic Games in Paris, France undertook extensive measures to ensure the safety of both participants and spectators. Approximately 15,000 soldiers, 45,000 police officers, and 20,000 private security personnel were deployed daily to support security operations. Additionally, support from 46 countries was requested, seeking military and police assistance for specialized operations.

These activities included, among others:

- night patrols using night vision and drones;
- patrols with sniffer dogs;
- securing the port of Ivry by combat divers;
- deployment of troops near the Olympic venues at a scale similar to Operation Sentinelle.

Operation Sentinelle was launched in France in January 2015 following the attacks against the Charlie Hebdo editorial office. Its objective was to prevent terrorist attacks and protect civilian population from these attacks through a permanent military presence across the country. As part of the operation, several thousand to over ten thousand soldiers are deployed to support police forces in patrolling public spaces, critical infrastructure, and symbolic objects.

Operation Sentinelle is an example of civil-military cooperation where:

- the armed forces support civil services (police, prefectures, civil protection);
- rapid deployment of armed patrols is possible;
- soldiers fulfil preventive and deterrent functions, protecting key locations.

This extensive mobilization of security forces was aimed at counteracting potential terrorist threats and ensuring an unimpeded conduct of sporting events [8, 9].

2013 Boston Marathon Bombing – Limited Military Involvement

Following the 2013 Boston Marathon bombing, the primary rescue and investigative efforts were run by civilian agencies, including local police and emergency medical services. Military involvement was limited and included:

- approximately 1,000 members of the Massachusetts National Guard who had already been deployed to secure the event;
- three Navy explosive ordnance disposal teams, who provided support in neutralizing potential explosives.

The response to the attack showed that effective crisis management can be achieved primarily with the use of civilian services, with minimal military support [5, 6].

Benefits of civil-military cooperation

Enhancement of crisis response capabilities

The armed forces have access to unique logistical and organizational resources, including transportation, communication, medical facilities, and personnel trained to operate under extreme conditions. Their involvement significantly enhances the capacity to respond to mass events such as natural disasters, pandemics, and terrorist attacks [10–12].

Example: During the COVID-19 pandemic, the armed forces across many countries assumed responsibility for transport, organized vaccination sites, and supported field hospitals, the scale of which exceeded the capabilities of the civilian system.

Increasing social trust

In crisis situations, the presence of the armed forces can positively impact citizens' sense of security, particularly when operations are coordinated and transparent. Military personnel are often perceived as neutral and effective, which helps legitimize state actions.

Example: In Poland, the activities of the Territorial Defence Forces during the pandemic (e.g. assisting elderly citizens and supporting hospital operations) were met with wide public recognition.

Synergy of experience and structures

The military and civilian administration operate under different principles and procedures. The integration of their experiences allows for developing more effective crisis management and scenario planning frameworks.

Increasing interoperability and combat readiness

CIMIC exercises and real-world operations are also beneficial from a military perspective; they allow for hands-on improvement of operational capabilities in a civilian setting, which is also important in foreign deployments, including stabilization, as well as humanitarian and peacekeeping missions.

Barriers and challenges in civil-military cooperation

Cultural and structural differences

Civilian and military administrations differ in their organizational cultures: civilians operate according to the logic of consensus and public administration, while the military relies on hierarchy, discipline, and rapid decision-making. These differences can give rise to misunderstandings, reduced efficiency, and competence conflicts [11].

Example: In some EU countries (e.g. Germany), constitutional constraints and cultural differences hinder the

effective integration of the armed forces into crisis management [10, 11].

Legislative deficiencies and inconsistent regulations

The lack of a coherent legal framework (e.g. clear delimitation of competencies, procedures for activating armed forces, command responsibility) may cause delays or prevent smooth cooperation.

Example: The need for prior parliamentary approval for military involvement significantly increases the response times in some NATO countries (e.g. Germany, Denmark, Italy, the Netherlands, Poland, Great Britain, the United States, France).

Many NATO countries have developed carefully designed mechanisms to ensure parliamentary oversight of military involvement in civilian operations during crisis situations. The scope of this oversight varies from country to country, ranging from mandatory parliamentary consent to the requirement to notify parliament after the decision has already been made. The common goal of these mechanisms is to ensure democratic oversight of military actions in crisis and emergency situations [13].

Fear of militarization of civilian space

Democratic societies show a natural distrust of excessive military presence in public life. There may be a risk that a prolonged military presence will be interpreted as a violation of civilian autonomy or even a pretext for authoritarianism [11].

Logistical and communication challenges

The lack of interoperable communication systems, differences in documentation, and unsynchronized information management protocols are frequently reported barriers during joint civil-military operations.

Suggestions for improvement:
- establishment of permanent civil-military coordination centres at the national and regional levels;
- regular exercises involving civil services and armed forces;
- integration of databases and IT systems;
- introduction of a civilian cooperation component into military education and, conversely, incorporation of CIMIC and disaster medicine training into public administration curricula [10, 11].

Theoretical analysis of civil-military cooperation

The concept and theoretical assumptions of CIMIC

Civil-military cooperation is defined by NATO as "a military joint function that integrates the understanding of the civil factors of the operating environment and that enables, facilitates and conducts civil-military interaction to support the accomplishment of missions and military strategic objectives in peacetime, crisis and conflict" [1].

From a theoretical perspective, CIMIC lies at the intersection of three research areas:
- security and defence studies;
- theory of public management and administration;
- sociology of organizations and intersectoral management.

This cooperation requires an integrated approach among military, civilian, local, and international structures. Reconciling the often conflicting logics of these systems poses particular challenge.

Conflict of roles and organizational culture

In her article, "NATO Civil-Military Cooperation: Expectations and Role Conflict," Agata Mazurkiewicz identifies a key problem stemming from the dual role of soldiers engaged in CIMIC. On the one hand, they remain part of the armed forces; on the other hand, they perform quasi-diplomatic, administrative, and civilian assistance functions [14].

The role conflict manifests, among others, in:
- the need to reconcile the orders of superiors with the expectations of local authorities and the civilian population;
- limited decision-making autonomy of CIMIC soldiers in unstable settings;
- ambiguity of status – being both "soldiers" and "civilian helpers", which creates ethical and practical tensions.

Mazurkiewicz notes that contemporary operations require soldiers to possess soft skills (empathy, intercultural communication), which were not traditionally part of the military professional identity [14].

CIMIC as a stabilization tool

In his extensive work on CIMIC, Dariusz Kozerawski investigates, among other topics, the activities of the Polish Military Contingent in Iraq (2003–2008). He argues that the success of stabilization operations depends not solely on military superiority, but also on:
- the ability to build trust with the local community;
- understanding the cultural and religious context;
- implementing infrastructure and educational projects in cooperation with local authorities.

Kozerawski stresses that in the case of Iraq, the CIMIC concept is seen as a "soft power" tool intended to minimize social opposition and generate civilian approval for the military presence [15].

It was a key challenge to maintain consistency of messaging between CIMIC soldiers and operational command to ensure that actions are seen as supportive rather than a tool of domination [15].

CIMIC models: classical versus integrated approach

Cottey and Forster identify two principal models of civil-military cooperation:

- **The classical model** – separation of military and civilian structures, cooperation restricted to what is necessary for mission accomplishment;
- **The integrated model** – full coordination of tasks, e.g. joint planning, implementation of operations and evaluation of outcomes.

NATO and the EU are striving for an integrated model, as evidenced, among others, by operations in the Balkans and EU missions (e.g. European Union Force (EUFOR), European Union Monitoring Mission (EUMM)) [16].

CIMIC as a concept of "humanitarian intervention"?

Some researchers (e.g. Duffield [17], Barnett [18]) criticize CIMIC as a tool for military expansion of Western influence in unstable states. In their opinion, CIMIC activities may, despite their intentions, serve as a "civilian wrapper" for occupation, ultimately undermining local sovereignty.

This theory brings the focus on the asymmetry of power between the armed forces and local populations, as well as to the risk of humanitarian aid being instrumentalized for geopolitical reasons [17, 18].

Summary of the theoretical analysis

CIMIC is not merely a technical instrument, but a complex social process in which the interests, values, and operational logics of various aspects of cooperation between civilian and military communities intersect. It requires continuous adaptation of military structures to the dynamic civilian environment and reflection on the military role in modern democracies.

Conclusions

The past decade has shown that civil-military cooperation is becoming increasingly relevant in dealing with large crises, both natural and man-made. Cases of the coronavirus epidemic, massive global events such as the Olympics, and acts of terrorism highlight the need for a dynamic, integrated, and flexible state response, of which the participation of armed forces is an integral part.

CIMIC as a component of contemporary crisis management

Contemporary crises are complex and multidimensional, often exceeding the capabilities of a single institution or sector. In this context, CIMIC emerges not only as a support tool, but also as an indispensable element of the state's crisis response structure [19]. The effectiveness of such cooperation depends on pre-defined procedures, competencies, and mutual trust between civilian and military partners [19].

As pointed out by NATO experts (AJP-3.4.9), the implementation of CIMIC should be based on the principles of reciprocity, coordination and synergy of actions rather than on hierarchical subordination of one of the parties [1].

The importance of flexibility and interoperability

Flexibility of structures and the ability to cross traditional institutional boundaries are key to the success of CIMIC operations.

During the COVID-19 pandemic, many countries were forced to improvise – the United Kingdom, for instance, stood up NHS support structures within a matter of weeks [7]. This experience shows that effective response requires:

- prior preparation of armed forces for non-kinetic operations (logistics, transport, evacuation, engineering);
- cross-sectoral training and CIMIC scenario exercises, e.g. "DEFENDER-Europe" [7].

Building trust and soft skills

Civil-military cooperation is not based solely on equipment, command structures and military capability – soft skills such as communication, negotiation, understanding the cultural and social context are crucial [14].

Especially in foreign environments (e.g. Iraq, Afghanistan), where local communities may be distrustful of the armed forces, the ability to build dialogue and relationships proves more important than combat capabilities [14].

The need to develop a common doctrine and legal framework

Cultural, institutional, and operational differences between civilians and the military lead to friction and misunderstandings. It is necessary to create a common doctrine for civil-military cooperation that:

- will account for the characteristics of 21st century threats (epidemics, migrations, terrorism);
- precisely defines competences, responsibilities and coordination mechanisms;
- will ensure compatibility between local, national and international levels (e.g. NATO, EU, UN).

Reports from the European Centre of Excellence for Civilian Crisis Management (CoE) show that there is still a lack of harmonised CIMIC procedures in the EU, which limits the effectiveness of joint operations [20].

Strategic conclusions and the future of CIMIC

- A modern army must be able to operate in the social, informational and humanitarian dimensions rather than only kinetic ones.
- CIMIC should become an integral part of internal security policy rather than merely a tool for expeditionary missions abroad.
- Civilian training for soldiers and military training for civilian crisis management structures should be the norm rather than an exception.
- It is necessary to implement early response systems and cross-sectoral planning, including digitalization and common information platforms.

References

1. NATO. AJP-3.4.9 Allied Joint Doctrine for CIMIC. NATO Standardization Office; 2013
2. Ustawa z dnia 26 kwietnia 2007 r. o zarządzaniu kryzysowym. Dz.U. 2007 nr 89 poz. 590
3. Ustawa z dnia 18 kwietnia 2002 r. o stanie klęski żywiołowej. Dz.U. 2002 nr 62 poz. 558
4. Traktat z Lizbony. Dz.U. UE C 306/1 z 17.12.2007
5. McKinley J. Boston bombing and the role of national guard. The New York Times. 2013 Apr 16
6. US Army. National Guard response to Boston marathon bombing. Army Times. 2013
7. UK Ministry of Defence. Operation Rescript. Defence News [Internet]. 2021 (access: 11.06.2025). Available from: https://www.gov.uk/government/news/operation-rescript
8. France24. Paris Olympics 2024 security plans [Internet]. 2023 (access: 11.06.2025). Available from: https://www.france24.com/en/live-news/20230718-paris-olympics-2024-security-plans
9. NATO. Support for Olympic Games. Brussels: NATO; 2024
10. Jabłoński M. Bariery CIMIC. Zarządzanie Kryzysowe, 2019; 2: 41–49
11. Król Z. Kompetencje służb cywilnych w CIMIC. Przegląd Administracji Publicznej, 2022; 3: 15–26
12. MON. Strategia bezpieczeństwa narodowego RP 2020. Warszawa: MON; 2020
13. Freyburg T, Richter T. Military deployments and parliamentary consent: a cross-national comparison. European Security, 2021; 30(2): 186–205
14. Mazurkiewicz A. Współpraca cywilno-wojskowa NATO: oczekiwania i konflikt ról. Przegląd Bezpieczeństwa Wewnętrznego, 2020; 12(3): 45–62
15. Kozerawski D. CIMIC as soft power: Polish Military efforts in Iraq 2003–2008. Security and Defence Quarterly, 2013; 4(14): 68–83
16. Cottey A, Forster A. The civil-military relationship in peace operations: The case for a unified approach. International Peacekeeping, 2005; 12(3): 364–382
17. Duffield M. Global Governance and the New Wars: The Merging of Development and Security. London: Zed Books; 2001
18. Barnett M. Empire of humanity: A history of humanitarianism. Ithaca: Cornell University Press; 2011
19. Kozerawski D. Współpraca cywilno-wojskowa w operacjach reagowania kryzysowego. Warszawa: Akademia Obrony Narodowej; 2012
20. European Centre of Excellence for Civilian Crisis Management (CoE). Civil-Military Cooperation (CIMIC) in EU Civilian CSDP Missions: State of Play and Ways Forward, [Internet]. 2021 (access: 11.06.2025). Available from: https://www.coe-civ.eu

REVIEW ARTICLE

CATHETER-ASSOCIATED URINARY TRACT INFECTIONS AMONG INTENSIVE CARE PATIENTS

Odcewnikowe zakażenia układu moczowego u pacjentów oddziału intensywnej terapii

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Abstract

Catheter-associated urinary tract infections are a major healthcare concern, particularly in hospitals and intensive care units (ICUs), despite significant educational and preventive efforts. They remain a significant concern in intensive care units settings due to factors such as prolonged catheterization, compromised immunity, and underlying medical conditions. Symptoms of catheter-associated urinary tract infections in intensive care unit patients can vary and may include fever, dysuria, haematuria and lower abdominal discomfort. *Escherichia coli*, *Klebsiella pneumoniae*, and *Candida albicans* are the primary pathogens responsible for catheter-associated urinary tract infections. Catheterized intensive care unit patients are at increased risk of developing catheter-associated urinary tract infections, which contribute to higher morbidity, mortality, and extended hospital stays. Early diagnosis and appropriate treatment are crucial to prevent complications associated with untreated urinary tract infections.

Streszczenie

Odcewnikowe zakażenia układu moczowego stanowią istotny problem zdrowotny, szczególnie w szpitalach i na oddziałach intensywnej terapii. Pomimo wdrażania działań profilaktycznych i edukacyjnych, ich częstość pozostaje wysoka, co wiąże się m.in. z długotrwałym cewnikowaniem, osłabieniem układu odpornościowego oraz współistniejącymi chorobami. Objawy odcewnikowych zakażeń układu moczowego mogą być zróżnicowane i obejmować gorączkę, dyzurię, krwiomocz oraz dyskomfort czy ucisk w podbrzuszu. Do głównych patogenów odpowiedzialnych za te zakażenia należą *Escherichia coli*, *Klebsiella pneumoniae* oraz *Candida albicans*. Pacjenci cewnikowani na oddziałach intensywnej terapii są obarczeni zwiększonym ryzykiem rozwoju tych zakażeń, co prowadzi do wyższej zachorowalności, śmiertelności oraz wydłużonego czasu hospitalizacji. Wczesna diagnostyka i odpowiednie leczenie mają kluczowe znaczenie w zapobieganiu powikłaniom związanym z nieleczonymi zakażeniami układu moczowego.

Keywords: intensive care unit; uropathogens; catheter-associated urinary tract infection; urinary catheter

Słowa kluczowe: oddział intensywnej terapii; uropatogeny; odcewnikowe zakażenie układu moczowego; cewnik moczowy

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Introduction

Catheter-associated urinary tract infections (CAUTIs) represent the most commonly reported nosocomial infections among intensive care unit patients. They typically develop as a consequence of indwelling urinary catheters, which play an instrumental role in monitoring patients' fluid balance [1]. It is estimated that these infections account for approximately 9% of all hospital-acquired infections, impacting an estimated 150 million individuals annually worldwide [2, 3]. According to the latest report from the European Centre for Disease Prevention and Control (ECDC), urinary tract infection (UTI) developed in 2% of patients remaining in the Intensive Care Unit (ICU) for more than 48 hours. A noteworthy finding is that 98% of these infections were associated with urinary catheters, underscoring their pivotal role in the occurrence of UTIs in intensive care settings [4]. Healthcare-associated infections (HAIs), including CAUTIs, are more prevalent in ICU patients compared to other wards, which is due to various factors, such as prolonged catheterization, diabetes, frailty, increased age, malnutrition and antimicrobial therapy [5]. The risk of infection increases with the duration of ICU stay [1]. A study conducted in the ICU at one of the Medical University Teaching Hospital (Poland) demonstrated a strong correlation between hospital-acquired infections and prolonged length of stay (LOS). The findings indicated that patients who developed at least one hospital-acquired infection had a median LOS three times longer compared to those who did not acquire any infections. Furthermore, the impact of multiple infections was found to be even more pronounced, with patients who experienced more than one infection exhibiting a sixfold increase in their median ICU stay. These results underscore the considerable impact of nosocomial infections on critically ill patients, highlighting the need for rigorous infection prevention and control measures to mitigate their effects on patient outcomes and healthcare resource utilisation [6].

This review focuses on the causes, most common pathogens, symptoms, risk factors, diagnostic approaches and current treatment options for ICU patients with CAUTIs.

Definition

Catheter-associated urinary tract infection is defined as a UTI occurring in a patient with an indwelling urinary catheter that has been in place for at least 48 hours prior to the onset of symptoms, with no other identifiable cause of infection [7, 8].

The classification of UTIs is refined based on their anatomical location. Lower UTIs, commonly known as cystitis, primarily affect the bladder and are characterised by symptoms such as frequent urination, painful urination (dysuria), and lower abdominal discomfort, which are seldom expressed in the ICU population due to the specific characteristics of these patients stemming from many factors, such as limited ability to communicate as a result of critical illness. Upper UTIs, medically termed pyelonephritis, involve the kidneys and often present with more severe symptoms, including fever, flank pain, and systemic signs of infection. Accurate diagnosis, effective treatment and prevention of recurrent infections depend on recognising this distinction [9].

Pathogens

UTIs can be caused by a variety of microorganisms, including Gram-negative and Gram-positive bacteria, as well as certain fungal species. Their development is typically associated with the formation of biofilms on the internal (intraluminal) or external (extraluminal) surfaces of urinary catheters, creating an environment that promotes bacterial adhesion and proliferation [7, 9]. The primary uropathogens responsible for these infections often originate from faecal contamination or skin-residing populations, which are part of the patient's natural or transient microflora. These microorganisms colonize the periurethral region and, over time, can ascend into the urinary tract, giving rise to infection. According to scientific evidence, *Escherichia coli* and *Klebsiella pneumoniae* were the most frequently isolated pathogens. Other microbes included *Candida* spp., *Proteus mirabilis*, *Enterococcus faecalis*, *Staphylococcus saprophyticus*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The presence of a pathogen in a urine sample, in the absence of additional signs of infection, should not be considered sufficient for diagnosis or used as a basis for initiating antibiotic therapy, given the high likelihood that the organism reflects catheter colonization rather than true infection [7, 9, 10].

Symptoms

Urinary tract infections can present with a range of non-specific symptoms in patients with indwelling urinary catheters, posing a diagnostic challenge. Common clinical manifestations include lower abdominal and pelvic discomfort or pain, as well as systemic symptoms such as fever, chills, nausea, and vomiting. In cases with upper urinary tract involvement, flank pain and tenderness in the costovertebral angle may be experienced, indicating kidney involvement. Critically ill individuals often have limited ability to communicate due to the severity of their condition, impaired or fluctuating levels of consciousness, endotracheal intubation, or complete loss of verbal contact. As a result the symptoms may not be clearly expressed by these patients, which can pose a diagnostic challenge. In such cases, medical personnel should rely on indirect indicators. These include changes in urine appearance, such as discoloration or turbidity, reduced urine output in the catheter bag, and a general decline in clinical status. In intubated patients, worsening of mechanical ventilation parameters may also serve as an early warning sign. The presentation of symptoms in catheterised patients can be subtle or atypical, underscoring the importance of thorough clinical assessment and timely symptom recognition to enable prompt diagnosis and appropriate treatment, thereby preventing further complications [3, 7].

Risk factors

ICU patients are at increased risk of developing CAUTIs due to a combination of patient- and treatment-related factors, including corticosteroid therapy, immunosuppression, antibiotic exposure, and baseline immune impairment resulting from critical illness. Additional risk factors include prolonged catheterization, diabetes, a history of prior catheterization, as well as extended hospital and ICU stays [11, 12].

Diagnostic methods

The U.S. Centers for Disease Control and Prevention (CDC) has established a set of diagnostic criteria for CAUTIs. In order to meet these criteria, a patient must have had an indwelling urinary catheter in place for a period of more than two consecutive days in an inpatient setting. Furthermore, the catheter must either remain in situ on the day the infection is identified or have been removed no more than one day prior. In addition to the catheterization requirements, the patient must exhibit at least one clinical symptom indicative of infection, such as fever exceeding 38.0°C, suprapubic tenderness, costovertebral angle pain or tenderness, urinary urgency, increased urinary frequency, or dysuria. Microbiological confirmation is also required, with urine culture identifying no more than two microbial species, at least one of which must be a bacterial strain present at a concentration of ≥105 colony-forming units (CFU) per millilitre. To confirm the presence of CAUTI, all diagnostic criteria must be fulfilled within a defined timeframe known as the Infection Window Period (IWP).

Accurate identification of CAUTI is essential for ensuring appropriate antimicrobial therapy, implementing infection control measures, and minimising the burden of catheter-related infections in hospitalized patients [8].

Urine collection for microbiological analysis should be performed via a newly inserted catheter. The sample must be obtained into a sterile container, adhering to strict aseptic technique, and the catheter port membrane should be disinfected prior to puncture. Disconnecting the catheter from the collection bag or obtaining urine directly from the bag is not recommended. In clinical practice, closed drainage systems are preferred, as they minimize the risk of infection. To ensure a representative sample, approximately 30 mL of urine should be collected immediately after catheter replacement [13].

Various diagnostic methods are employed to identify UTIs, including traditional techniques such as phenotypic biochemistry or culture-based identification. However, the latter modality can be time-consuming due to the time required for bacterial growth. Alternatively, PCR or immunoassay techniques offer rapid results; however, PCR may be affected by background contamination from external sources of DNA. Quantitative urine culture is considered the gold standard, yet results typically require approximately 24 hours, with antibiotic susceptibility testing requiring an additional 24 hours. Surface-enhanced Raman spectroscopy (SERS) is a promising tool for pathogen detection and identification. However, its current application is limited by restricted availability and insufficient number of reference Raman spectra of known bacterial species. Further research of a more extensive spectral library is needed before SERS can be routinely implemented in the clinical diagnosis of UTIs [14].

Treatment

In the treatment of CAUTI, the initial step involves removal of the urinary catheter alongside the initiation of antibiotic therapy. Catheter use should be minimized and discontinued as soon as it is no longer clinically necessary. For patients who continue to require a catheter, intermittent catheterization is recommended to help reduce microbial colonization prior to commencing antibiotic therapy. It is essential to obtain a urine culture before initiating antibiotics, particularly if the catheter has been in place for over two weeks [3, 7]. The initial empirical treatment of CAUTI should include broad-spectrum antibiotics selected on the basis of local antimicrobial susceptibility patterns. This approach is crucial for addressing a wide range of potential pathogens while awaiting definitive culture results. Once urine culture findings are available, it is essential for clinicians to promptly adjust the antibiotic regimen to target the identified microorganism and its resistance profile, thereby ensuring treatment efficacy.

It is well-established that the commencement of therapy with inappropriate broad-spectrum antibiotics can lead to an increased risk of adverse outcomes, including higher rates of complications and mortality. It is therefore important to carefully consider local resistance patterns and make timely therapy modifications based on culture results to ensure effective clinical management of this patient population [15].

For first-line treatment of complicated UTIs, fluoroquinolones such as ciprofloxacin or levofloxacin (IV), as well as ceftriaxone (IM or IV) or cefotaxime (IV), are recommended. Once antibiogram becomes available, the therapy should be adjusted according to the susceptibility profile of the isolated pathogen. In cases of clinical non-response or if antibiogram results are unavailable, second-line therapy includes piperacillin-tazobactam (IV) or aminoglycosides, such as gentamicin or amikacin (IV). Third-line treatment, reserved for severe or multidrug-resistant infections, involves the administration of carbapenems [16, 17].

References

1. Alqarni MS. Catheter-associated urinary tract infection (CAUTI) in ICU patients. Middle East J Adv Nurs, 2021; 15(1): 25–33. doi: 10.5742/MEJN2021.93799
2. Van Decker SG, Bosch N, Murphy J. Catheter-associated urinary tract infection reduction in critical care units: a bundled care model. BMJ Open Qual, 2021; 10(4): e001534. doi: 10.1136/bmjoq-2021-001534
3. Werneburg GT. Catheter-associated urinary tract infections: current challenges and future prospects. Res Rep Urol, 2022; 14: 109–133. doi: 10.2147/RRU.S273663
4. Maugeri A, Barchitta M, Agodi A. Catheter-associated urinary tract infections in the 'intensive care unit': Why we still should care. Intensive Crit Care Nurs, 2023; 75: 103360. doi: 10.1016/j.iccn.2022.103360
5. Parida S, Mishra SK. Urinary tract infections in the critical care unit: A brief review. Indian J Crit Care Med, 2013; 17: 370–374. doi: 10.4103/0972-5229.123451
6. Duszynska W, Rosenthal VD, Szczesny A, et al. Device associated – health care associated infections monitoring, prevention and cost assessment at intensive care unit of University Hospital in Poland (2015–2017). BMC Infect Dis, 2020; 20: 761. doi: 10.1186/s12879-020-05482-w
7. Firoozeh N, Agah E, Bauer ZA, et al. Catheter-associated urinary tract infection in neurological intensive care units: A narrative review. Neurohospitalist, 2022; 12(3): 484–497. doi: 10.1177/19418744221075888

8. Centers for Disease Control and Prevention. Urinary tract infection (catheter-associated urinary tract infection [CAUTI] and non-catheter-associated urinary tract infection [UTI]) events. [Internet]. Atlanta (GA): CDC; [access 06.2025]. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/7psccauticurrent.pdf
9. Flores-Mireles A, Walker J, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol, 2015; 13: 269–284. doi: 10.1038/nrmicro3432
10. Peng D, Li X, Liu P, et al. Epidemiology of pathogens and antimicrobial resistance of catheter-associated urinary tract infections in intensive care units: A systematic review and meta-analysis. Am J Infect Control, 2018; 46(12): e81–e90. doi: 10.1016/j.ajic.2018.07.012
11. Li F, Song M, Xu L, et al. Risk factors for catheter-associated urinary tract infection among hospitalized patients: A systematic review and meta-analysis of observational studies. J Adv Nurs, 2018; 74(5): 1072–1083. doi: 10.1111/jan.13863
12. Lalitha AV, Paul M, Nagraj S, Ghosh S. Risk factors for catheter-associated urinary tract infections (CA-UTI) in the pediatric intensive care unit. Indian Pediatr, 2022; 59(8): 613–616
13. Szpital Uniwersytecki w Krakowie. I-P-ZM-02/03. Pobieranie i przechowywanie moczu do mikrobiologicznych badań laboratoryjnych. Wydanie V. Kraków: Szpital Uniwersytecki w Krakowie; 23.07.2024. p. 1–5
14. Ni T, Lin TH, Hung ZC, et al. Diagnosis of bacterial pathogens in the urine of urinary-tract-infection patients using surface-enhanced Raman spectroscopy. Molecules, 2018; 23(12): 3374. doi: 10.3390/molecules23123374
15. Tenke P, Mezei T, Bőde I, Köves B. Catheter-associated urinary tract infections. European Urology Supplements, 2016; 16(4): 138–143
16. Dzierżanowska-Fangrat K. Przewodnik antybiotykoterapii 2025. Warszawa: Alfa Medica Press; 2025: p. 64
17. Hryniewicz W, Holecki M, eds. Rekomendacje diagnostyki, terapii i profilaktyki zakażeń układu moczowego u dorosłych. Warszawa; 2015

REVIEW ARTICLE

THE IMPACT OF VARIOUS FORMS OF PHYSICAL EXERCISE ON COGNITIVE FUNCTIONS IN OLDER ADULTS

Wpływ wysiłku fizycznego na funkcje poznawcze osób starszych z uwzględnieniem różnych form aktywności

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Abstract

Background: Population aging poses significant challenges in the context of cognitive function maintenance. This review aims to compare the effectiveness of various forms of physical activity, including aerobic, resistance, and mind–body exercise, in improving key cognitive domains, with a particular focus on the older adult population. **Methods:** A systematic review of recent scientific literature was conducted, focusing on meta-analyses and systematic reviews available in Google Scholar and PubMed, using keywords related to physical exercise, cognitive functions, aging, and forms of physical activity. **Results:** The analysis revealed that each training modality has a specific benefit profile. Mind–body exercises (e.g., Tai Chi) showed the greatest positive impact on global cognitive function in healthy seniors (Cohen's Effect Size d = 0.48), surpassing both purely aerobic or resistance forms. Aerobic exercises strongly correlated with improved executive functions (planning, attention), while resistance training effectively supported memory and showed the potential to attenuate cognitive decline in clinical populations. Recent evidence indicates that combined (multimodal) training, especially a combination of aerobic and resistance exercises, leads to synergistic and superior benefits for executive functions, which are further enhanced by the integration of cognitive training elements. **Conclusions:** Physical activity represents a critical non-pharmacological intervention. Combined training, which promotes both physical endurance and cognitive coordination, appears to be the most optimal strategy for maximizing and expanding cognitive benefits. Given the persistent knowledge gaps regarding optimal protocols (dose-response relationships) and underlying mechanisms, further high-quality research investigating the synergistic effects of multimodal interventions is needed.

Streszczenie

Wprowadzenie: Proces starzenia się populacji stwarza istotne wyzwania w zakresie utrzymania funkcji poznawczych. Niniejszy przegląd ma na celu porównanie skuteczności różnych form aktywności fizycznej – aerobowej, oporowej (siłowej) oraz integrującej ciało i umysł – w poprawie kluczowych domen poznawczych, ze szczególnym uwzględnieniem populacji osób starszych. **Metody:** Przeprowadzono systematyczny przegląd literatury naukowej z ostatnich lat, koncentrując się na metaanalizach i przeglądach systematycznych dostępnych w bazach danych takich jak Google Scholar i PubMed, z wykorzystaniem słów kluczowych związanych z ćwiczeniami fizycznymi, funkcjami poznawczymi, starzeniem się i rodzajami aktywności fizycznej. **Wyniki:** Analiza ujawniła, że każda modalność treningowa ma specyficzny profil korzyści. Ćwiczenia typu mind–body (np. Tai Chi) wykazały największy pozytywny wpływ na globalne funkcje poznawcze u zdrowych seniorów (wielkość efektu Cohena d = 0,48), przewyższając formy wyłącznie aerobowe lub oporowe. Ćwiczenia aerobowe były silnie związane z poprawą funkcji wykonawczych (planowanie, uwaga), podczas gdy trening oporowy skutecznie wspiera pamięć i ma potencjał spowolnienia regresji poznawczej w grupach klinicznych. Najnowsze dowody wskazują, że trening łączony (multimodalny), zwłaszcza kombinacja ćwiczeń aerobowych i oporowych, prowadzi do synergicznych i maksymalnych korzyści dla funkcji wykonawczych, co jest dodatkowo wzmacniane przez integrację elementów poznawczych. **Wnioski:** Aktywność fizyczna jest kluczową, niefarmakologiczną interwencją. Optymalną strategią maksymalizacji i rozszerzenia korzyści poznawczych jest trening łączony, promujący zarówno wydolność fizyczną, jak i koordynację poznawczą. Ze względu na utrzymujące się luki w wiedzy dotyczące optymalnych protokołów (dawka–reakcja) i mechanizmów leżących u podstaw tych procesów, konieczne jest prowadzenie dalszych badań wysokiej jakości nad synergicznymi efektami interwencji multimodalnych.

Keywords: physical exercise; cognitive functions; elderly; aging; types of physical activity

Słowa kluczowe: ćwiczenia fizyczne; funkcje poznawcze; osoby starsze; starzenie się; rodzaje aktywności fizycznej

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Introduction

Population aging represents one of the major challenges facing contemporary societies, with significant implications for the mental health and cognitive functions of older individuals. As the proportion of older adults continues to grow, urgent adaptations and thorough research are needed across healthcare and academic domains.

Preserving the mental health and cognitive functions of older adults has become a major priority. This encompasses a wide range of preventive approaches, including regular exercise, adequate nutrition, social engagement, and cognitive stimulation, alongside early detection, access to specialized geriatric care, and the development of novel therapeutic and supportive strategies [1].

A growing body of research has investigated the beneficial effects of physical activity on cognitive functions, especially for older individuals. In the context of ageing societies, where cognitive functions like memory, attention, and information processing speed are progressively declining, physical activity plays an important role as both a preventive and therapeutic strategy.

Given the complexity of these issues and the rapid pace of new discoveries, a review of the latest scientific literature discussing the effects of physical activity on cognitive functions in older adults is needed. Remaining abreast of the latest research is essential to understand the underlying mechanisms, identify optimal intervention strategies, and develop effective policies to improve the quality of life of this population.

This review aims to determine which forms of exercise prove most beneficial for specific cognitive functions, like memory, attention, planning abilities, and processing speed, particularly in older adults.

Materials and methods

Our study is based on the analysis of domestic and foreign literature retrieved from "Google Scholar," "PubMed," and other scientific publications. The sources included in this work are limited to those published within the past few years to ensure the most up-to-date information. Data were collected using the following keywords: physical exercise, cognitive functions, elderly, aging, and types of physical activity. All co-authors contributed equally to the literature search, data analysis and interpretation.

Artificial intelligence (AI)

The sole purpose of using artificial intelligence was to improve the scholarly English of the manuscript. The tool assisted in enhancing clarity, consistency, and adherence to scientific writing standards by refining the language, grammar, and style, and ensuring clear presentation of the results. It should be emphasized that the AI tool was used solely as a supportive aid under human supervision. Its role was limited to improving linguistic precision and efficiency, while all data interpretation, analysis, and conclusions remained exclusively under the judgment of human authors.

Results

Impact of aging on cognitive functions

Aging affects the brain through multiple different pathways, causing changes in its structure and chemicals that are critical for cognitive function. These changes can lead to cognitive slowing. Recent research has shown that older adults tend to lose brain volume, particularly in the hippocampus, which plays an important role in episodic memory. A study using magnetic resonance imaging (MRI) in non-demented individuals found that the extent of brain volume loss is age-dependent and significantly associated with cognitive performance [2]. Furthermore, studies show that hippocampal atrophy accelerates around 60 years of age, and is associated with declining episodic memory [3].

Age-related changes in brain chemicals also play a significant role. For example, dopamine, a neurotransmitter linked to focus and decision-making, is progressively reduced in older adults, contributing to deficits in attention and planning abilities [4]. Other studies have found that dysregulation of dopaminergic, noradrenergic, and cholinergic neurotransmitter systems is associated with impaired memory and information processing in older adults [5]. A drop in acetylcholine levels, manifesting as reduced acetylcholine receptor responsiveness, is often associated with deficits in new memory and sustained attention [6]. More recent studies combining positron emission tomography (PET) and MRI have found that progressive reductions in neurotransmitter activity are linked to declining memory performance in individuals with early memory loss or dementia [7].

However, these changes do not occur in isolation. The trajectory of brain aging depends on many different

factors, including genes, lifetime cognitive engagement, and lifestyle choices, which can collectively modulate the extent to which these changes influence behaviour. Although these changes unfold over time, the effects vary from person to person, as demonstrated by recent research [4].

Forms of physical activity

Physical activity is generally classified into the following well-established categories [8]:

- Aerobic (Endurance) Activity – this category encompasses activities such as brisk walking, running, swimming, cycling, and dancing, which are characterized by increased respiratory demand and elevated heart rate.
- Resistance (Strength) Training – this category encompasses exercises designed to build muscle strength, often using weights, resistance bands, or body weight.
- "Mind–Body" Exercises (e.g., Tai Chi, Yoga) (Flexibility and Neuromotor – Balance, Agility, Coordination) – these activities integrate movement with mental focus, breathing, and meditation.

Impact of specific forms of activity on cognitive functions

Aerobic activity

Regular aerobic exercise has been shown to enhance cognitive abilities in older adults, particularly across domains such as memory, executive functions, and overall mental sharpness. Recent evidence shows that these benefits extend to individuals with early signs of memory deficits, known as mild cognitive impairment (MCI).

A study by Zhang et al. found that six months of aerobic exercises improved memory and attention in older adults with MCI [9]. Huang et al. reached similar conclusions, showing that regular aerobic activity improves cognitive functions in individuals with mild to moderate memory impairment [10]. A review by Lu et al. further demonstrated that physical activities, including aerobic exercise, can improve cognitive function in older adults with type 2 diabetes mellitus (T2DM), particularly in the domains of memory and executive function [11]. Aghjayan et al. found that aerobic exercise enhances memory in non-demented adults over 55 years of age, with the magnitude of benefits depending on age and exercise modality [12].

In addition to cognitive benefits, regular aerobic exercise has been shown to improve mood and overall well-being, which may further support cognitive functions. Yang et al. reported that aerobic exercise beneficially impacts patients with Alzheimer's disease by improving both their cognitive function and quality of life [13].

Resistance training

Resistance training also exerts a strong impact on cognitive functions in older adults, particularly in the domains of memory, executive functions, and mental health.

Research shows that these benefits extend to individuals with mild cognitive impairment. Li et al. found that regular resistance training helps improve overall cognitive skills in older adults and those with Alzheimer's disease, enhancing memory, focus, and attention [14]. Similar findings were reported by Zhang et al., showing that resistance training helps maintain cognitive health, particularly in older adults and those in medical settings [15]. A review by Han et al. found that regular resistance training significantly boosts cognitive function in older individuals, especially in the domain of inhibitory control. The most optimal results were seen with training frequency of twice a week for 45 minutes over 12 weeks [16]. Jerez-Salas et al. found that resistance training improves working memory and attentional performance in non-demented adults over 65 years of age, with the magnitude of benefits depending on age and the type of exercise [17]. Wu et al. showed that combining online and in-person resistance training is safe and effective for older adults with cognitive impairment, yielding moderate improvements in executive function, attention, physical strength, and overall well-being [18].

Mind–body exercise

Mind–body exercises, such as Tai Chi and yoga, are also linked to improved cognitive performance in older adults. Liu et al. found that Qigong Baduanjin exercises enhance cognitive functions in community-dwelling older adults, though the exact mechanisms are not fully understood [19]. A review by Han et al. (2025) suggested that mind–body exercises exert the greatest impact on memory among different forms of physical activity. The most optimal outcomes were achieved through high-frequency sessions (at least three times a week) of moderate (45 to 60 minutes) and longer periods (12 to 24 weeks) [16]. Cai et al. and Barney reported that mind–body exercises improve memory, reduce depressive symptoms, and improve balance, while also increasing levels of a neuroprotective protein and lowering a protein implicated in Alzheimer's disease [20, 21].

Comparison of the effectiveness of different forms of physical activity

When comparing different forms of physical activity, mind–body exercises often demonstrate superior outcomes. A comprehensive review published in 2023 showed that mind–body exercises exerted the greatest positive effect on global cognitive function in adults aged 55 years and older [22]. The cumulative effect size (measured by Cohen's Effect Size, d = 0.48) was substantially greater than that of general physical exercise (d = 0.22), suggesting that combining movement with focused attention and breathing can bring significant neuroprotective benefits. Other studies confirm that mind–body exercises enhance executive function, learning, and memory in individuals aged 60 years and older [23].

Resistance training is also highly effective. Research comparing resistance and aerobic training shows that both modalities improve global cognitive function, memory, and mental abilities in older adults [24]. While some studies suggest that resistance training might be more effective at slowing cognitive decline, the overall evidence shows that its efficacy is comparable to that of aerobic exercise [25]. The latest reviews strongly suggest

that combining aerobic and resistance exercises (known as concurrent training, CT) is more beneficial for cognitive health than either modality alone, particularly in older adults [15]. This is attributable to the synergistic mechanisms of the two forms of exercise – aerobic exercises improve blood flow and neurogenesis, while resistance training increases brain-friendly chemicals associated with muscle strength, which collectively support cognitive function.

Traditionally, aerobic exercise has been recognised for its pronounced effects on tasks that involve planning and attention [26]. These benefits are well-supported by scientific evidence, as aerobic activity enhances cerebral blood flow and upregulates the levels of brain-derived neurotrophic factor (BDNF), thereby promoting neuronal growth and connections [22].

In conclusion, while mind–body exercises may have the greatest impact on the global cognitive function in older adults, optimal outcomes are achieved through the integration of multiple exercise modalities, such as resistance and aerobic training, as shown by Gavelin et al. in their review [27].

Discussion

This review demonstrates that physical activity represents a key and multifaceted strategy for the prevention and attenuation of age-related cognitive decline. The purpose of the review, which was to determine which forms of exercise are optimal for different aspects of cognitive function, was met by comparing the evidence for aerobic, resistance, and mind–body exercises.

The main insight emerging from this discussion concerns the optimal implementation of these interventions. Our findings suggest that while each form of exercise offers certain benefits, combining aerobic and resistance training represents the most effective approach for use in real-world settings. This is corroborated by a 2024 meta-analysis [26], which demonstrated that concurrent aerobic and resistance exercises have a greater positive effect on executive function than either modality alone. This synergistic effect is attributable to a broader spectrum of physical benefits, such as enhanced cerebral blood flow and improved neuromuscular communication, which allows for more effective neuroplasticity.

Furthermore, when physical activity is paired with cognitive tasks, as in mind–body exercises involving complex movement sequences, additional benefits are observed. One study [27] found that combining physical and cognitive activities is more effective at supporting executive functions than physical activity alone, underscoring the value of attentional engagement during movement.

However, there are some challenges. A substantial proportion of the research, especially when comparing different forms of exercise, is characterized by inconsistency. For example, exercise protocols differ in terms of frequency, intensity, and duration. Study groups also vary, ranging from healthy older adults to those with mild cognitive impairment. For instance, optimal outcomes for resistance training were seen with a protocol of two sessions per week for 45 minutes over a 12-week period [16], whereas mind–body exercises may require longer periods. These differences make it difficult to determine the optimal amount of exercise (dose-response) for each group.

Despite these limitations, the primary finding remains unequivocal: a combination of different forms of physical activity is recommended to support global cognitive health in older adults. This includes regular aerobic and resistance exercises, which offer the greatest physiological benefits, alongside activities that integrate attentional engagement and motor coordination, such as mind–body or cognitive-physical exercises, which yield the most pronounced cognitive benefits.

Conclusion

In conclusion, our review confirms that physical activity represents a key, non-pharmacological strategy for supporting cognitive function in older adults. While mind–body exercises exert the greatest effect on the global cognitive function in healthy seniors, other exercise modalities remain equally important. Aerobic exercise is particularly beneficial for executive functions, whereas resistance training supports memory. The optimal approach for maximizing the benefits of physical activity is to integrate different exercise modalities. Combining endurance and resistance training with cognitive elements yields the greatest improvements in executive function. The impact of physical activity on cognitive function is an important and promising field of inquiry, and further high-quality research is needed, especially to better understand the optimal design of exercise protocols and the underlying mechanisms responsible for the cognitive benefits of multimodal training.

References

1. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet, 2020; 396(10248): 413–446. doi: 10.1016/S0140-6736(20)30367-6. Erratum in: Lancet, 2023; 402(10408): 1132. doi: 10.1016/S0140-6736(23)02043-3
2. Fujita S, Mori S, Onda K, et al. Characterization of brain volume changes in aging individuals with normal cognition using serial magnetic resonance imaging. JAMA Netw Open, 2023; 6(6): e2318153. doi: 10.1001/jamanetworkopen.2023.18153
3. Bråthen ACS, Sørensen Ø, de Lange AMG, et al. Cognitive and hippocampal changes weeks and years after memory training. Sci Rep, 2022; 12(1): 7877. doi: 10.1038/s41598-022-11636-4
4. Brito DVC, Esteves F, Rajado AT, et al. Assessing cognitive decline in the aging brain: lessons from rodent and human studies. NPJ Aging, 2023; 9(1): 23. doi: 10.1038/s41514-023-00120-6
5. Rieckmann A, Nyberg L. Cognitive aging: the role of neurotransmitter systems. In: Thomas AK, Gutchess A, eds. The Cambridge handbook of cognitive aging: a life course perspective. Cambridge: Cambridge University Press; 2020. p. 82–100
6. Gasiorowska A, Wydrych M, Drapich P, et al. The biology and pathobiology of glutamatergic, cholinergic, and dopaminergic signaling in the aging brain. Front Aging Neurosci, 2021; 13: 654931. doi: 10.3389/fnagi.2021.654931

7. Manca R, De Marco M, Soininen H, et al. Changes in neurotransmitter-related functional connectivity along the Alzheimer's disease continuum. Brain Commun, 2025; 7(1): fcaf008. doi: 10.1093/braincomms/fcaf008
8. American College of Sports Medicine. ACSM's Guidelines for exercise testing and prescription. 12th ed. Philadelphia (PA): Wolters Kluwer; 2022
9. Zhang S, Zhen K, Su Q, et al. The effect of aerobic exercise on cognitive function in people with Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. Int J Environ Res Public Health, 2022; 19(23): 15700. doi: 10.3390/ijerph192315700
10. Huang B, Chen K, Li Y. Aerobic exercise, an effective prevention and treatment for mild cognitive impairment. Front Aging Neurosci, 2023; 15: 1194559. doi: 10.3389/fnagi.2023.1194559
11. Lu HH, Zhou Y, Chen C, Gu ZJ. Meta-analysis of the effect of exercise intervention on cognitive function in elderly patients with type 2 diabetes mellitus. BMC Geriatr, 2024; 24(1): 770. doi: 10.1186/s12877-024-05352-z
12. Aghjayan SL, Bournias T, Kang C, et al. Aerobic exercise improves episodic memory in late adulthood: a systematic review and meta-analysis. Commun Med (Lond). 2022; 2: 15. doi: 10.1038/s43856-022-00079-7
13. Yang L, Yuan Z, Peng C. Effects of aerobic exercise on cognitive function and quality of life in patients with Alzheimer's disease: a systematic review and meta-analysis. BMJ Open, 2025; 15(1): e090623. doi: 10.1136/bmjopen-2024-090623
14. Li W, Fang W, Zhang Y, et al. Research progress on resistance exercise therapy for improving cognitive function in patients with AD and muscle atrophy. Front Aging Neurosci, 2025; 17: 1552905. doi: 10.3389/fnagi.2025.1552905
15. Zhang M, Fang W, Wang J. Effects of human concurrent aerobic and resistance training on cognitive health: A systematic review with meta-analysis. Int J Clin Health Psychol, 2025; 25(1): 100559. doi: 10.1016/j.ijchp.2025.100559
16. Han H, Zhang J, Zhang F, Li F, Wu Z. Optimal exercise interventions for enhancing cognitive function in older adults: a network meta-analysis. Front Aging Neurosci, 2025; 17: 1510773. doi: 10.3389/fnagi.2025.1510773
17. Jerez-Salas F, Campos-Jara C, Araya Sierralta S, et al. Effects of resistance training on executive functions of cognitively healthy older adults: a systematic review and meta-analysis protocol. Healthcare (Basel), 2025; 13(2): 165. doi: 10.3390/healthcare13020165
18. Wu T, Wang X, Xu Y, et al. The effect of resistance training for older adults with cognitive frailty: a randomized controlled trial. BMC Geriatr, 2025; 25(1): 681. doi: 10.1186/s12877-025-06311-y
19. Liu J, Yang Y, Shi H, et al. Improving cognitive function in older adults through mind-body Qigong exercise at senior daycare centers: The role of sleep as a moderator and mediator. Explore (NY), 2025; 21(4):103167. doi: 10.1016/j.explore.2025.103167
20. Cai H, Zhang K, Wang M, et al. Effects of mind-body exercise on cognitive performance in middle-aged and older adults with mild cognitive impairment: A meta-analysis study. Medicine (Baltimore), 2023; 102(34): e34905. doi: 10.1097/MD.0000000000034905
21. Barney J. Alzheimer's discovery reveals dire effect of toxic tau protein. UVA Health Newsroom [Internet]. 2023 [access: 09.10.2025]. Available from: https://newsroom.uvahealth.com/
22. Blomstrand P, Tesan D, Nylander EM, Ramstrand N. Mind body exercise improves cognitive function more than aerobic- and resistance exercise in healthy adults aged 55 years and older – an umbrella review. Eur Rev Aging Phys Act, 2023; 20(1): 15. doi: 10.1186/s11556-023-00325-4
23. Zhang Y, Liu S, Luo Z, et al. The effects of mind-body exercise on cognitive performance in elderly: a systematic review and meta-analysis. Int J Environ Res Public Health, 2018; 15(12): 2791. doi: 10.3390/ijerph15122791
24. Xu L, Gu H, Cai X, et al. The effects of exercise for cognitive function in older adults: a systematic review and meta-analysis of randomized controlled trials. Int J Environ Res Public Health, 2023; 20(2): 1088. doi: 10.3390/ijerph20021088
25. Huang X, Zhao X, Li B, et al. Comparative efficacy of various exercise interventions on cognitive function in patients with mild cognitive impairment or dementia: a systematic review and network meta-analysis. J Sport Health Sci, 2022; 11(2): 212–223. doi: 10.1016/j.jshs.2021.05.003
26. Ren FF, Hillman CH, Wang WG, et al. Effects of aerobic exercise on cognitive function in adults with major depressive disorder: A systematic review and meta-analysis. Int J Clin Health Psychol, 2024; 24(2): 100447. doi: 10.1016/j.ijchp.2024.100447
27. Gavelin HM, Dong C, Minkov R, et al. Combined physical and cognitive training for older adults with and without cognitive impairment: A systematic review and network meta-analysis of randomized controlled trials. Ageing Res Rev, 2021; 66: 101232. doi: 10.1016/j.arr.2020.101232

THE CARDIOVASCULAR EFFECTS OF MILITARY SERVICE UNDER EXTREME CONDITIONS: A NARRATIVE REVIEW

Wpływ służby wojskowej w warunkach ekstremalnych na układ sercowo-naczyniowy: przegląd narracyjny

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Abstract

Introduction: Military service is associated with exposure to intense physical and mental stress, which affects the cardiovascular system. It remains unclear whether the combination of exertion, operational stress, and extreme environmental conditions can lead to cardiac arrhythmias and hypertension. **Materials and methods:** A review of the scientific literature was conducted, including studies on the effects of exertion, stress, and environmental conditions on the circulatory system in soldiers. Sources included PubMed and Google Scholar. **State of knowledge:** Prolonged exercise leads to cardiac adaptation, whereas excessive exercise may give rise to exercise-induced cardiac fatigue. Mental stress activates the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis, thereby increasing blood pressure and heart rate. High ambient temperature and dehydration increase the risk of arrhythmias and myocardial damage. **Conclusions:** Military service places considerable strain on the circulatory system. Preventive measures, including regular medical screening, risk factor control, and adaptation programmes, are essential. Further research is needed to identify effective strategies for safeguarding the cardiovascular health of military personnel.

Streszczenie

Wstęp: Służba wojskowa wiąże się z ekspozycją na intensywny stres fizyczny i psychiczny, który wpływa na układ sercowo-naczyniowy. Wysiłek fizyczny, stres operacyjny oraz ekstremalne warunki środowiskowe mogą prowadzić do zaburzeń rytmu serca i nadciśnienia. **Materiały i metody:** Przeprowadzono przegląd literatury naukowej, obejmujący badania dotyczące wpływu wysiłku, stresu i warunków środowiskowych na układ sercowo-naczyniowy u żołnierzy. Przeszukano bazy PubMed i Google Scholar. **Stan wiedzy**: Długotrwały wysiłek prowadzi do adaptacji serca, lecz przy nadmiernym obciążeniu może wystąpić przemijające upośledzenie funkcji mięśnia sercowego po wysiłku. Stres psychiczny aktywuje układ współczulny i oś podwzgórze–przysadka–nadnercza, zwiększając ciśnienie tętnicze oraz częstość akcji serca. Wysoka temperatura i odwodnienie nasilają ryzyko zaburzeń rytmu oraz uszkodzenia mięśnia sercowego. **Wnioski:** Służba wojskowa wiąże się ze zwiększonym obciążeniem układu sercowo-naczyniowego. Konieczne jest wdrażanie profilaktyki obejmującej regularne badania, kontrolę czynników ryzyka i programy adaptacyjne. Dalsze badania powinny określić skuteczne strategie ochrony zdrowia sercowo-naczyniowego żołnierzy.

Keywords: cardiovascular system; prevention of cardiovascular diseases; military service; military medicine; extreme conditions

Słowa kluczowe: układ sercowo-naczyniowy; profilaktyka chorób układu krążenia; służba wojskowa; warunki ekstremalne; medycyna wojskowa

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Introduction

Military service entails exposure to extreme physical and mental challenges, compelling the body to mobilize its adaptive reserves [1]. Modern battlefield demands, intensive training regimens, and deployments across diverse climate zones place a substantial physiological burden on the military personnel [1]. The cardiovascular system plays a key role in maintaining homeostasis under these conditions. Exposure to multifactorial stressors (intense exercise, sleep deprivation, extreme temperatures, combat stress) initiates a cascade of neurohormonal responses [2]. These include activation of the hypothalamic–pituitary–adrenal axis (HPA) and the sympathetic nervous system (increased catecholamine and cortisol levels) [2, 3]. While these mechanisms are essential for short-term adaptation, their chronic activation may cause cardiovascular dysregulation [2]. A growing body of evidence points to a link between military service and cardiovascular risk, particularly among veterans [4] and individuals with post-traumatic stress disorder (PTSD) [5]. Clinical observations indicate an increased incidence of acute cardiac events, including sudden cardiac arrest [6], Takotsubo cardiomyopathy [7], and long-term sequelae such as hypertension (HT) [5], coronary artery disease (CAD), and insulin resistance [8]. Understanding these interactions is fundamental for the development of effective preventive strategies in military medicine. This paper reviews the current knowledge on the cardiovascular effects of military service under extreme conditions.

Aim

The primary aim of this paper is to synthesize and critically analyse the available literature on the cardiovascular effects of military service under extreme conditions. The article is a narrative review. Specific objectives include:

- Analysis of key pathophysiological mechanisms underlying the cardiovascular response to physical and psychological stressors;
- Characterization of acute clinical manifestations and cardiac events during exposure to extreme conditions;
- Assessment of the long-term cardiovascular consequences of military service, including the risk of chronic diseases;
- Review of available prevention, monitoring, and intervention strategies aimed at protecting the cardiovascular health of military personnel.

Materials and methods

This literature review used PubMed and Google Scholar databases to investigate the cardiovascular effects of military service. Publications were selected and analyzed with respect to physiological and pathological cardiovascular changes arising from stress, environmental conditions, adaptive mechanisms, and preventive interventions.

State of knowledge

Mechanisms underlying the cardiovascular effects of extreme environmental conditions

Autonomic response and the role of stress and hormones

The autonomic nervous system (ANS) maintains homeostasis through the interaction between the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) [9, 10]. In military service, the balance shifts towards SNS (responsible for elevated heart rate and blood pressure) with simultaneous PNS inhibition. This is manifested by reduced heart rate variability (HRV), confirming the predominance of sympathetic activation and reduced adaptive capacity [9, 10]. The ANS response is linked to stress hormones (cortisol, catecholamines) [11]. During prolonged stress associated with military service, their elevated levels increase blood pressure and heart rate. Field studies have shown a correlation between elevated cortisol and impaired physical performance and decreased HRV, particularly in the context of sleep deprivation. These levels normalise following recovery [11].

Haemodynamic and metabolic changes and oxidative stress

Under extreme conditions, haemodynamic changes are observed, such as reduced circulating blood volume and diminished venous return (reduction of preload) [12]. High physical loads increase heart rate and blood pressure, thereby elevating the cardiac workload [12]. These changes are associated with metabolic disturbances and oxidative stress (increased lipolysis and fatty acid oxidation) [13]. Oxidative stress, resulting from the imbalance between free radicals and defence mechanisms, can lead to cellular damage and cardiovascular deterioration [13]. Dehydration, sleep deprivation, and caloric deficit further exacerbate chronic sympathetic activation and haemodynamic and metabolic disturbances [12, 13]. Adaptation involves upregulation of metabolic efficiency and antioxidant mechanisms. Monitoring haemodynamic and metabolic parameters is crucial, as uncompensated changes may progress to myocardial dysfunction. Training and nutritional interventions may contribute to improved performance and health in military personnel [13].

Inflammation and immune response

Exposure to extreme conditions (hypoxia, hyperthermia, oxidative stress, physical exercise) triggers robust activation of the immune system and inflammatory pathways. This leads to increased production of proinflammatory cytokines (IL-6, TNF-α), activation of NF-κB, and migration of immune cells to the vascular endothelium [14]. This sterile inflammatory response promotes endothelial dysfunction, increases oxidative stress, and may lower the threshold for myocardial and vascular damage [14].

Coagulation disorders and the risk of thrombosis

Extreme conditions shift haemostatic balance in a prothrombotic direction. Hyperthermia (heat stroke) activates

the coagulation cascade (tissue factor release, platelet aggregation, inhibition of fibrinolysis), which increases the risk of microthrombosis and disseminated intravascular coagulation (DIC) [15]. Dehydration and haemoconcentration increase blood viscosity, promoting turbulent flow, endothelial injury, and blood stasis, shifting haemostasis toward a prothrombotic state [16].

The impact of individual factors: age, chronic conditions, and lifestyle

Advancing age is associated with a lower cardiovascular adaptive reserve and impaired thermoregulation, increasing susceptibility to circulatory failure under heat stress. Population studies have shown that each 1°C rise in ambient temperature above the optimal value is associated with an approximately 2.1% increase in the risk of cardiovascular death (RR = 1.021; 95% CI: 1.020–1.023), while in individuals over 65 years of age, a short-term 1°C temperature increment may elevate the risk of a cardiovascular event by up to 33% [17]. Individuals with pre-existing chronic conditions (e.g., hypertension, diabetes) already exhibit chronic inflammation, and therefore are particularly vulnerable to decompensation under additional environmental stress. Studies involving military exposure to toxic environments (e.g., smoke from oil well fires) showed that the risk of coronary artery disease was nearly three times higher (OR = 2.95; CI: 1.40–6.19) compared to unexposed individuals [14]. Lifestyle factors, including chronic sleep deprivation and smoking, further promote a pro-inflammatory and pro-thrombotic profile, thereby compromising adaptive capacity. Cohort studies have shown that individuals consuming ≥5 glasses of water daily had more than a two-fold lower risk of CAD mortality compared to those consuming ≤2 glasses [18]. The individual profile thus constitutes the basis for risk stratification

Acute clinical sequelae

Serving under extreme conditions is associated with complex physical, mental, and environmental stress, giving rise to dynamic cardiovascular disturbances, including arrhythmias, coronary events, and cardiomyopathy. Overactivation of the HPA axis and the sympathetic nervous system constitutes a key mechanism [2].

Arrhythmias and sudden cardiac arrest

Arrhythmias and sudden cardiac death (SCD) represent serious acute consequences of military service. A 25-year study among military recruits found SCD to be the most common non-traumatic cause of death accounting for 42% of fatalities, with hypertrophic cardiomyopathy and myocarditis accounting for 33% and 20%, respectively [6]. Intense physical exertion and mental stress upregulate sympathetic activity and catecholamine levels, thereby increasing the risk of ventricular arrhythmias [2]. Neuroendocrine studies have demonstrated alterations in cortisol and DHEA-S levels that correlate with stress response and may modulate susceptibility to arrhythmias [3]. Continuous monitoring of physiological parameters has confirmed that extreme conditions (temperature, dehydration) give rise to clinically significant fluctuations in heart rate [1].

Acute coronary events (including myocardial infarction)

Stress and physical overload can trigger acute coronary events. A meta-analysis by Padhi et al. showed that PTSD increases the risk of myocardial infarction (MI) by approximately 30% [5]. Veterans with PTSD are more likely to meet the diagnostic criteria for metabolic syndrome, including obesity, dyslipidaemia, and HT, which further increases the cardiovascular risk [8]. Acute stress can also lead to transient coronary vasoconstriction and an imbalance between myocardial oxygen supply and demand (type II MI) [2].

Acute heart failure and stress-induced cardiomyopathy (Takotsubo syndrome)

Takotsubo syndrome represents a common complication of acute stress. Kahili et al., who enrolled 3,248 patients in their study, showed a 38% increase in the incidence of this syndrome during periods of increased social stress, such as armed conflicts [7]. The mechanism underlying Takotsubo syndrome involves a rapid release of catecholamines, leading to transient left ventricular systolic dysfunction, with a clinical presentation mimicking MI, yet without significant coronary artery stenosis [2].

Blood pressure disorders in extreme situations

Blood pressure fluctuations are common among military personnel. Data from the Veterans Health Administration indicate that hypertension (HT) is one of the most common chronic conditions in this population (71%) [4]. Field studies have documented episodes of both transient HT (sympathetic activation) and hypotension (dehydration, hyperthermia). Continuous physiological monitoring allows for early detection of cardiovascular overload [1].

Extreme environmental conditions

Military personnel are exposed to dynamic fluctuations in temperature, atmospheric pressure, and oxygen levels. Adaptation to such conditions requires intense activation of regulatory systems (HPA axis, SNS), which may contribute to chronic circulatory dysregulation [2].

High ambient temperature and dehydration

Elevated ambient temperatures prompt blood redistribution to the skin and increase fluid loss, leading to hypovolemia and increased cardiac workload [1]. Dehydration further exacerbates tachycardia and can ultimately lead to circulatory collapse. Activation of the HPA axis in response to heat stress (elevated cortisol and catecholamines) may promote arrhythmia [2]. Chronic exposure carries the risk of heat overload syndromes [1]. A 25-year review of military recruit autopsy findings identified 126 non-traumatic sudden deaths, with structural cardiac abnormalities present in 51% of cases. These were most commonly coronary artery anomalies (61%), myocarditis (20%), and hypertrophic cardiomyopathy (13%) [6]. Hyperthermia and dehydration are both factors contributing to sudden cardiac death in individuals with previously undiagnosed cardiac defects [6].

Low ambient temperatures

Cold exposure triggers cutaneous vasoconstriction and increased peripheral vascular resistance, raising blood pressure and left ventricular workload, which is particularly dangerous for hypertensive individuals [4]. Cold is a potent stressor that stimulates the SNS and may, similarly to emotional stress, give rise to Takotsubo syndrome [7]. Extremely low temperatures can reduce coronary blood flow and impair myocardial repolarization, thereby promoting arrhythmias and endothelial dysfunction [5].

Altitude and hypoxia

Hypobaric conditions induce tissue hypoxia, with early responses including increased heart rate and cardiac output. Prolonged exposure results in increased haematocrit and blood viscosity (risk of thrombosis and pulmonary hypertension). Hypoxic stress further activates the HPA axis (increased cortisol) [2] and affects DHEA-S levels, which may serve an adaptive function [3]. Morgan et al. showed that exposure to severe military survival stress was associated with an increase in DHEA-S from 27.8 µg/dL (± 11.1) to 60.1 µg/dL (± 26.2) and cortisol from 8.6 µg/dL (± 3.8) to 31.1 µg/dL (± 5.8). A higher DHEA-S to cortisol ratio under these conditions correlated with better task performance (r = 0.61) and lower dissociation (r = –0.63) [3]. Real-time monitoring of physiological parameters enables early detection of maladaptive responses under hypoxic conditions [1].

Long-term consequences of military service

Hypertension, coronary artery disease, heart failure

Prolonged exposure to stress leads to activation of the HPA axis and SNS, resulting in stress hyperactivation and disruption of homeostasis. Persistently elevated cortisol and catecholamine levels contribute to raised blood pressure and vascular remodelling [2]. Combat veterans exhibit a higher incidence of HT compared to the general population [4], and exposure to combat trauma increases the risk of CAD and HF. A meta-analysis of over 335,000 participants showed that PTSD was associated with a significantly increased risk of cardiovascular disease (HR = 1.417; 95% CI: 1.313–1.522), including MI (HR = 1.415; 95% CI: 1.331–1.500) and stroke (HR = 2.074; 95% CI: 1.165–2.982) [5].

Cardiac remodelling

The long-term impact of military service on cardiac remodelling remains the subject of intensive research. Structural changes, such as left ventricular hypertrophy, are observed in response to haemodynamic and neurohormonal stress [19]. A 2021 study by Charton et al. enrolled 20 soldiers from special forces units and 38 cadets from a non-elite military unit. In special forces soldiers, intense physical exertion was associated with significant morphological and functional changes in all four heart chambers, including transient impairment of both ventricular and atrial systolic function, as assessed by the 2D-strain method – an advanced echocardiographic technique that quantifies systolic and diastolic myocardial deformation based on 2D image analysis.

Chronic exposure to stress factors, including sleep deprivation, may result in both systolic and diastolic dysfunction [19].

Insulin resistance as a mediator in the relationship between PTSD and metabolic conditions

Metabolic dysregulation, including insulin resistance, is a key mediating mechanism. Chronic activation of the HPA axis leads to increased cortisol and glucose levels and visceral fat accumulation. Veterans with PTSD are more likely to meet the diagnostic criteria for metabolic syndrome [8]. An analysis of 253 veterans (women and men) assessed five key diagnostic factors for metabolic syndrome, including blood pressure, waist-to-hip ratio, as well as fasting HDL, triglyceride, and glucose levels. Metabolic syndrome criteria were met by 40% of subjects, including 43% in the PTSD group. Logistic regression analysis showed a significant correlation between PTSD severity and the prevalence of metabolic syndrome (p = 0.03), suggesting that chronic activation of stress-related pathways may play a central role in the development of metabolic disorders in this population [8]. Insulin resistance is a mediator between neurohormonal dysregulation and endothelial injury and CAD progression [20]. Changes in DHEA-S and cortisol levels in individuals exposed to combat stress have been shown to correlate with impaired glucose metabolism [3], further increasing long-term cardiovascular risk.

Changes in risk factors associated with military service

Alterations in metabolic and cardiac risk factors have been observed during military service. Low dietary fibre intake correlated with higher total and LDL cholesterol levels, as evidenced by a significant positive correlation between changes in fibre intake and variations in total (r = –0.36, p = 0.033) and LDL cholesterol (r = –0.39, p = 0.019).

The study further demonstrated that body fat percentage (BF%) and fat mass were positively correlated with total (r = 0.51; p = 0.002) and LDL cholesterol (r = 0.53; p = 0.001). Mean total cholesterol ranged from 4.64 to 4.71 mmol/L, while LDL cholesterol ranged from 2.27 to 2.87 mmol/L over the six-month follow-up, with body fat percentage remaining stable at approximately 13.5%. These findings highlight the role of diet and body composition in shaping cardiovascular risk profile during military service [21].

Cardiovascular prevention and monitoring among military personnel

Selection and screening

Prior to deploying military personnel to extreme environments, screening tests, encompassing medical history and physical examination, are essential. Soldiers assigned to high-altitude, desert, or polar operations require extensive diagnostic screening, including electrocardiography (ECG). Modern ECG interpretation standards, such as the Seattle Criteria, were developed to improve diagnostic accuracy in highly active individuals, including soldiers [22]. These criteria enable clinicians

to distinguish physiological changes typical of training adaptations that require no further diagnosis, such as sinus bradycardia ≥30/min, first-degree atrioventricular block (PR ≤400 ms), or incomplete right bundle branch block (QRS <120 ms), from actual pathologies that may lead to sudden cardiac arrest, including ST segment depression ≥0.5 mm, pathological Q waves (>40 ms or ≥3 mm), T wave inversion in at least two adjacent leads, or QTc prolongation ≥470/480 ms [23]. The use of the Seattle criteria and automated ECG analysis algorithms based on them significantly reduced the false positive rate (to 3.7%) while maintaining 100% sensitivity in detecting life-threatening conditions [22]. This approach is of particular importance in the military population, where rapid and reliable cardiac assessment is crucial for personnel safety. Extended diagnosis (echocardiography, cardiac stress test) is essential for military personnel at risk (positive family history, syncope, HT, diabetes, etc.) [22]. Soldiers aged 35 years or older and those returning to active duty following a prolonged absence also require special attention due to their increased risk of asymptomatic CAD. Exposure to extreme conditions may reveal previously undiagnosed cardiovascular disorders.

Adaptive training and acclimatization — heat and altitude

Heat acclimatization represents a fundamental strategy for reducing cardiac risk. A two-week programme of progressive high-temperature training (conducted in accordance with NATO guidelines) reduces the need for compensatory increases in cardiac output [24]. Isothermal conditioning has been shown to produce more pronounced cardiac adaptations (average heart rate reduction of 11 beats/min) than traditional training (reduction of 4 beats/min) [25]. Altitude acclimatization (above 1,500 m) is an adaptative response to hypobaric hypoxia. Exposure to low partial pressure of oxygen (PO_2) initiates sympathetic nervous system activation (increased heart rate) [26]. Acute mountain sickness (AMS) represents the primary threat (38% incidence at 3,500 m). Preventive strategies include gradual ascent (altitude limit <305 m per day) and staging (acclimatization at intermediate altitudes) [26].

Risk management: hydration, supplementation

Dehydration-related body weight loss exceeding 2% leads to a 5–10% decline in physical performance, underscoring the critical importance of adequate hydration [24]. Guidelines recommend intake of beverages containing 20–30 mEq/L sodium, 2–5 mEq/L potassium, and 5–10% carbohydrate to prevent fluid, electrolyte, and glycogen depletion. Sodium plays a key role in water absorption and compensation for sweat losses [27].

Post-exposure procedures (rehabilitation, post-event monitoring)

Return to duty following a cardiac event requires an individualized assessment, including cardiac stress test and haemodynamic parameters, conducted under cardiological supervision. Comprehensive cardiac rehabilitation has been shown to reduce mortality by 20–30% and improve exercise tolerance by 25–35% [28].

Psychological interventions to reduce stress and PTSD severity

Meta-analyses indicate that psychological interventions, including trauma-focused cognitive behavioural therapy (TF-CBT) and eye movement desensitization and reprocessing therapy (EMDR), effectively reduce PTSD symptoms in veterans, though the effect is smaller and less durable than that observed in the general population [29].

Special aspects

Gender differences

Female military personnel, female recruits in particular, are exposed to greater cardiovascular strain than their male counterparts during intense physical exercise, as evidenced by higher heart rates and blood pressure during load-bearing marches [30]. Field studies have shown that these differences are particularly visible during long marches (over 8 km), highlighting the need for individualized training programmes, gradually increased load, and continuous physiological monitoring in female recruits [30].

In a cohort of 60 recruits (30 women and 30 men, mean age 20 ± 2 years), women exhibited heart rate higher by a mean of 12–15 beats/min and systolic blood pressure higher by 6–8 mmHg during 8–10 km load-bearing marches, confirming the greater cardiovascular burden experienced by female personnel [30].

Age: young recruits vs older veterans

The MIL-SCORE study, which enrolled 6,487 Polish professional soldiers (mean age 38 ± 9 years, women accounting for 7.8%), identified age as one of the key factors differentiating the health profile of military personnel [31]. Older veterans (>50 years of age) exhibited significantly higher rates of HT (45.2%) and obesity (58.7%) compared to young recruits (<35 years of age), in whom the prevalence of these disorders was 18.9% and 21.4%, respectively [31]. These findings underscore the need to implement cardiometabolic preventive measures already in the early stages of military service [31].

The specificity of international missions compared to national exercises

Soldiers deployed on foreign missions are exposed to significantly greater environmental and psychophysical stress than during domestic exercises [32]. The most frequently mentioned contributing factors include operational stress, prolonged exposure to extreme temperatures, sleep deprivation, and limited capacity for physical recovery [32].

Studies among Polish soldiers have shown that a high prevalence of cardiovascular risk factors, including HT, obesity, and hypercholesterolaemia, may increase susceptibility to the adverse effects of these conditions [31]. Analyses involving 82,341 US soldiers (mean age 27 ± 6 years) demonstrated a 27% higher incidence of new-onset HT and a 19% higher incidence of new-onset hy-

percholesterolaemia among those serving on overseas deployments compared with those participating in domestic exercises [32]. Therefore, it is recommended to implement preventive and monitoring programmes tailored to the specific mission and the climate of the operational area [32].

The perspective of the Polish Armed Forces

Polish epidemiological studies confirm the growing burden of cardiovascular risk among both recruits and veterans [31]. Analyses of military populations have identified HT, overweight, and dyslipidaemia as the most prevalent risk factors [31]. At the same time, international studies have shown that similar trends are also observed in the armed forces of other NATO member states, confirming the global nature of the cardiovascular health problem among professional soldiers [32].

Data from national and international programmes indicate that over 40% of professional soldiers across the surveyed armed forces meet the criteria for at least one major cardiovascular risk factor (HT, obesity, or dyslipidaemia) [31, 32]. These findings highlight the need for regular screening, health education, and the implementation of comprehensive preventive measures, particularly among individuals returning from overseas deployments [31, 32].

Conclusions

Military service imposes substantial physiological and psychosocial demands. Multifactorial stress, including combat exposure, physical exertion, thermal stress, and sleep deprivation, activates the HPA axis and sympathetic nervous system. These responses, while adaptive in the short term, may lead to haemodynamic dysregulation, arrhythmias, and increased risk of cardiovascular disease when chronically activated. Excessive neurohormonal stimulation, oxidative stress, and inflammatory processes contribute to endothelial damage, vascular dysfunction, and cardiac remodelling. Extreme environmental conditions, including temperature, hypoxia, and dehydration, exacerbate this process, increasing the risk of acute cardiovascular events, including sudden cardiac death. In the military population, both acute manifestations (cardiac arrhythmias, left ventricular systolic dysfunction) and long-term consequences (HT, coronary artery disease, metabolic disorders) have been observed. The intensity of these changes depends on individual factors, such as genetic predisposition, training level, and the body's adaptive capacity, which modulate individual resistance to stress. Early risk identification and comprehensive prevention, encompassing cardiac screening, monitoring of exercise capacity, metabolic control, thermal adaptation, hydration, and recovery, are crucial. Further research is needed to develop personalized diagnostic and preventive models for populations exposed to extreme stress.

References

1. Friedl KE. Military applications of soldier physiological monitoring. J Sci Med Sport, 2018; 21(11): 1147–1153. doi: 10.1016/j.jsams.2018.06.004
2. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol, 2009; 5(7): 374–381. doi: 10.1038/nrendo.2009.106
3. Morgan CA 3rd, Southwick S, Hazlett G, et al. Relationships among plasma dehydroepiandrosterone sulfate and cortisol levels, symptoms of dissociation, and objective performance in humans exposed to acute stress. Arch Gen Psychiatry, 2004; 61(8): 819–825. doi: 10.1001/archpsyc.61.8.819
4. Yamada M, Wachsmuth J, Sambharia M, et al. The prevalence and treatment of hypertension in Veterans Health Administration, assessing the impact of the updated clinical guidelines. J Hypertens, 2023; 41(6): 995–1002. doi: 10.1097/hjh.0000000000003424
5. Padhi BK, Khatib MN, Serhan HA, et al. Cardiovascular impact of post-traumatic stress disorder: A systematic review and meta-analysis. Curr Probl Cardiol, 2024; 49(8): 102632. doi: 10.1016/j.cpcardiol.2024.102632
6. Eckart RE, Scoville SL, Campbell CL, et al. Sudden death in young adults: a 25-year review of autopsies in military recruits. Ann Intern Med, 2004; 141(11): 829–834. doi: 10.7326/0003-4819-141-11-200412070-00005
7. Kahila Y, Barel MS, Bruoha S, et al. The effect of national stress events on the incidence of Takotsubo syndrome. IJC Heart Vasc, 2025; 59: 101697. doi: 10.1016/j.ijcha.2025.101697
8. Heppner PS, Crawford EF, Haji UA, et al. The association of posttraumatic stress disorder and metabolic syndrome: a study of increased health risk in veterans. BMC Med, 2009; 7: 1. doi: 10.1186/1741-7015-7-1
9. Bustamante-Sánchez A, Tornero-Aguilera JF, Fernández-Elías VE, et al. Effect of stress on autonomic cardiovascular response to stress in military populations: A systematic review. Cardiol Res Pract, 2020; 2020: 7986249. doi: 10.1155/2020/7986249
10. Stephenson MD, Thompson AG, Merrigan JJ, et al. Applying heart rate variability to monitor health and performance in tactical personnel: A narrative review. Int J Environ Res Public Health, 2021; 18(15): 8143. doi: 10.3390/ijerph18158143
11. Tait JL, Drain JR, Corrigan SL, et al. Impact of military training stress on hormone response and recovery. PLoS One, 2022; 17(3): e0265121. doi: 10.1371/journal.pone.0265121
12. Stein JA, Farina EK, Karl JP, et al. Biomarkers of oxidative stress, diet and exercise distinguish soldiers selected and non-selected for special forces training. Metabolomics, 2023; 19: 39. doi: 10.1007/s11306-023-01998-9
13. Radulescu D, Mihai FD, Trasca ET, et al. Oxidative stress in military missions-impact and strategies: A narrative analysis. Life (Basel). 2024; 14(5): 567. doi: 10.3390/life14050567
14. Alfaddagh A, Martin SS, Leucker TM, et al. Inflammation and cardiovascular disease: from mechanisms to therapeutics. Am J Prev Cardiol, 2020; 4: 100130. doi: 10.1016/j.ajpc.2020.100130
15. Iba T, Connors JM, Levi M, Levy JH. Heatstroke-induced coagulopathy: biomarkers, mechanistic insights, and patient management. eClinicalMedicine, 2022; 44: 101276. doi: 10.1016/j.eclinm.2022.101276
16. Desai Y, Khraishah H, Alahmad B. Heat and the heart. Yale J Biol Med, 2023; 96(2): 197–203. doi: 10.59249/HGAL4894
17. Peters A, Schneider A. Cardiovascular risks of climate change. Nat Rev Cardiol, 2021; 18: 1–2. doi: 10.1038/s41569-020-00473-5

18. Singh N, Areal AT, Breitner S, et al. Heat and cardiovascular mortality: an epidemiological perspective. Circ Res, 2024; 134(9): 1098–1112. doi: 10.1161/CIRCRESAHA.123.323615
19. Charton M, Kervio G, Matelot D, et al. Exercise-induced cardiac fatigue in soldiers assessed by echocardiography. Front Cardiovasc Med, 2021; 8: 785869. doi: 10.3389/fcvm.2021.785869
20. Ormazabal V, Nair S, Elfeky O, et al. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc Diabetol, 2018; 17(1): 122. doi: 10.1186/s12933-018-0762-4
21. Nykänen T, Pihlainen K, Kyröläinen H, Fogelholm M. Associations of nutrition and body composition with cardiovascular disease risk factors in soldiers during a 6-month deployment. Int J Occup Med Environ Health, 2020; 33(4): 457–466. doi: 10.13075/ijomeh.1896.01541
22. Magee C, Haigney MC. Cardiovascular screening in the U.S. Military: Time to reconsider the electrocardiogram. Mil Med, 2020; 185(7–8): e1039–e1045. doi: 10.1093/milmed/usaa002
23. Drezner JA, Ackerman MJ, Anderson J, et al. Electrocardiographic interpretation in athletes: the 'Seattle Criteria'. Br J Sports Med, 2013; 47(3): 122–124. doi: 10.1136/bjsports-2012-092067
24. Parsons IT, Stacey MJ, Woods DR. Heat adaptation in military personnel: mitigating risk, maximizing performance. Front Physiol, 2019; 10: 1485. doi: 10.3389/fphys.2019.01485
25. Tan SCC, Ang WH, Lim LSX, eaa§t al. Efficacy of isothermic conditioning over military-based heat acclimatization and interval training in tropical native males. Med Sci Sports Exerc, 2022; 54(11): 1925–1935. doi: 10.1249/MSS.0000000000002991
26. Mallet RT, Burtscher J, Richalet JP, et al. Impact of high altitude on cardiovascular health: current perspectives. Vasc Health Risk Manag, 2021; 17: 317–335. doi: 10.2147/VHRM.S294121
27. Jäger R, Kerksick CM, Campbell BI, et al. International Society of Sports Nutrition Position Stand: protein and exercise. J Int Soc Sports Nutr, 2017; 14: 20. doi: 10.1186/s12970-017-0177-8
28. Piotrowicz R, Wolszakiewicz J. Cardiac rehabilitation following myocardial infarction. Cardiol J, 2008; 15(5): 481–487
29. Coventry PA, Meader N, Melton H, et al. Psychological and pharmacological interventions for posttraumatic stress disorder and comorbid mental health problems following complex traumatic events: Systematic review and component network meta-analysis. PLoS Med, 2020; 17(8): e1003262. doi: 10.1371/journal.pmed.1003262
30. Schram B, Orr R, Niederberger B, et al. Cardiovascular demand differences between male and female US Marine recruits during progressive loaded hikes. J Strength Cond Res, 2024; 38(8): e454–e458. doi: 10.1519/JSC.0000000000004816
31. Gielerak G, Krzesiński P, Piotrowicz K, et al. The prevalence of cardiovascular risk factors among Polish soldiers: The results from the MIL-SCORE Program. Cardiol Res Pract, 2020; 2020: 3973526. doi: 10.1155/2020/3973526
32. Vincent SR, Schlenk MA, Horan KA, Moore BA. Incidences and trends of cardiovascular determinants and diagnoses in active duty service members. J Mil Veterans Health, 2024; 32: 42–51. Available from: https://jmvh.org/article/incidences-and-trends-of-cardiovascular-determinants-and-diagnoses-in-active-duty-service-members/ (access: 13.11.2025)

REVIEW ARTICLE

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS AND TIRZEPATIDE IN GYNECOLOGIC CANCER THERAPY: A LITERATURE REVIEW OF THEIR DUAL EFFECTS ON WEIGHT LOSS AND TUMOR CONTROL

Agoniści receptora glukagonopodobnego peptydu 1 i tirzepatyd w terapii nowotworów ginekologicznych: przegląd literatury dotyczący ich równoczesnego wpływu na redukcję masy ciała oraz proces nowotworowy

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and tirzepatide are primarily used in the treatment of type 2 diabetes and obesity. Beyond correcting metabolic imbalance, these agents modulate the tumor microenvironment, enhance apoptosis, downregulate pro-inflammatory signaling, and impair metastatic potential in cancer cells. The primary objective of this review is to evaluate the impact of incorporating incretin-based therapies into the management of gynecologic malignancies, including endometrial, ovarian, and cervical cancers. In endometrial cancer, GLP-1RAs and tirzepatide promote apoptosis, reverse chemoresistance, enhance progesterone receptor signaling, and demonstrate synergy with hormonal therapies. In ovarian cancer, GLP-1RAs have been shown to suppress tumor-promoting pathways, reduce inflammation, and inhibit metastatic processes. In cervical cancer, particularly among patients with type 2 diabetes, GLP-1RAs may offer protective effects by counteracting the pro-inflammatory and tumor-promoting effects of hyperglycemia. GLP-1RAs and tirzepatide target metabolic dysregulation and directly modulate signaling pathways involved in tumorigenesis, which may help redefine existing clinical approaches in gynecologic oncology by combining metabolic control with antineoplastic activity.

Streszczenie

Agoniści receptora glukagonopodobnego peptydu 1 (analogi GLP-1) oraz tirzepatyd są lekami zarejestrowanymi do leczenia cukrzycy typu 2 i otyłości. Oprócz wpływu na regulację zaburzeń metabolicznych, wykazują również działanie na mikrośrodowisko guza, nasilają apoptozę, zmniejszają sygnalizację prozapalną i ograniczają zdolność komórek nowotworowych do tworzenia przerzutów. Głównym celem niniejszej pracy jest ocena potencjalnych korzyści wynikających z dołączenia leków inkretynowych do terapii nowotworów ginekologicznych, w szczególności endometrium, jajnika oraz szyjki macicy. W nowotworach endometrium analogi GLP-1 oraz tirzepatyd indukują apoptozę, odwracają lekooporność na chemioterapię, wzmacniają sygnalizację receptora progesteronowego oraz działają synergistycznie z terapiami hormonalnymi. W leczeniu nowotworów jajnika analogi GLP-1 hamują szlaki sprzyjające progresji nowotworu, zmniejszają stan zapalny oraz ograniczają powstawanie przerzutów nowotworowych. U pacjentek z rakiem szyjki macicy,

szczególnie ze współistniejącą cukrzycą typu 2, analogi GLP-1 wykazują działanie ochronne poprzez redukcję stanu zapalnego i normalizację glikemii, której podwyższony poziom sprzyja rozwojowi nowotworów. Analogi GLP-1 oraz tirzepatyd wpływają na wyrównanie zaburzeń metabolicznych i bezpośrednio modulują szlaki sygnałowe odpowiedzialne za proces nowotworzenia. Mechanizmy te mogą stanowić podstawę do opracowania nowych strategii terapeutycznych w ginekologii onkologicznej, łączących kontrolę metaboliczną z działaniem przeciwnowotworowym.

Keywords: uterine cervical neoplasms; ovarian neoplasms; tirzepatide; glucagon-like peptide-1 receptor agonists; endometrial neoplasms

Słowa kluczowe: nowotwory szyjki macicy; nowotwory jajnika; tirzepatyd; agoniści receptora glukagonopodobnego peptydu 1; nowotwory endometrium

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Introduction

Gynecologic cancers represent a significant global health issue, with a substantial increase in incidence and mortality across various regions [1]. Cervical cancer is considered the most frequent gynecologic malignant neoplasm worldwide, independent of socioeconomic status, and uterine cancer follows as the second most common [2]. Endometrial carcinoma (EC) accounts for more than 90% of uterine malignancies. The prevalence of EC has been increasing [1], and the underlying causes are likely factors including rising rates of obesity and diabetes, and changes in reproductive health, such as decreasing birth rates and delayed childbearing [3]. In particular, obesity significantly increases the risk of developing EC. It results in extended estrogen exposure without sufficient counteraction by progestins [4]. Lifestyle modifications or bariatric surgery can lead to weight loss, which has been demonstrated to substantially decrease the risk of EC [5].

Ovarian cancer remains the most lethal gynecologic malignancy [6]. Its incidence has been decreasing in some regions, for example, in the United States of America, since 1990 [7], yet survival rates remain persistently low as a result of advanced-stage diagnosis [6].

Cervical cancer has shown a decline in both incidence and mortality in developed countries over the past 50 years, due to extensive screening programs and HPV vaccination [8]. However, it continues to be a leading contributor to cancer mortality in developing countries [9]. Cervical adenocarcinoma is associated with particular challenges in early detection and is influenced by estrogen-related risk factors, with recent studies indicating increasing incidence [10].

In Poland, the mortality rate from gynecologic cancers ranks among the highest in Europe [11]. Between 2000 and 2022, both incidence and mortality from endometrial and ovarian cancers increased, with the highest occurrence and number of deaths demonstrated for endometrial cancer. At the same time, cervical cancer rates have shown a declining trend [12].

Considering the increasing impact of gynecologic cancers, novel therapeutic strategies are urgently needed. The function of GLP-1 receptor agonists (GLP-1RAs) and tirzepatide, agents primarily used to treat type 2 diabetes and obesity, is a growing focus of research on antineoplastic effects. In addition to their roles in metabolism, these agents have been shown to regulate cell proliferation, apoptosis, and inflammation. Preclinical and early clinical studies suggest that GLP-1RAs and tirzepatide may influence tumorigenesis in endometrial, ovarian, and cervical cancers. This positions them as potentially viable adjunctive treatment modalities [13, 14].

This review summarizes current evidence on the prospective roles of GLP-1 receptor agonists and tirzepatide in gynecologic oncology, concentrating on their mechanisms of action and therapeutic relevance in endometrial, ovarian, and cervical cancers.

Materials and methods

This narrative review aims to evaluate the influence of GLP-1 receptor agonists (GLP-1RAs) and the dual GIP/GLP-1 receptor co-agonist tirzepatide on pathogenic mechanisms involved in gynecological malignancies, including endometrial, ovarian, and cervical cancers, based on an extensive review of the literature from the PubMed, Web of Science, Scopus, and Google Scholar databases. Record extraction was performed using the search terms: [GLP-1RAs OR "glucagon-like peptide-1 receptor agonists" OR tirzepatide] AND ["endometrial cancer" OR "ovarian cancer" OR "cervical cancer" OR "gynecologic cancers"]. The initial screening of studies was conducted by the authors based on titles and abstracts to determine their relevance and alignment with the review objectives. Relevant records were selected for full-text evaluation, after which eligible studies were included in a qualitative synthesis. Given that this was a narrative review rather than a meta-analysis, no statistical methods were employed.

Mechanisms of action of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and tirzepatide

GLP-1 receptor agonists (GLP-1RAs) can be classified into two categories: short-acting (exenatide administered twice per day, lixisenatide) and long-acting forms (liraglutide, exenatide administered once weekly, dulaglutide, semaglutide). Short-acting GLP-1RAs primarily affect postprandial glucose levels and delay gastric emptying, while long-acting agents provide sustained receptor activation and superior fasting glucose control [15]. Meta-analyses report that all GLP-1RAs significantly lower HbA_{1c} levels and promote weight loss through long-term central appetite inhibition [15].

Tirzepatide is a dual GLP-1 and GIP receptor agonist that has shown greater effectiveness in improving glycemic control and reducing body weight than GLP-1RAs alone [16]. Tirzepatide has been evaluated both as monotherapy and in combination with agents such as metformin, sulfonylureas, or insulin [17].

GLP-1RAs influence the biology of oncogenic pathways and exert pro-apoptotic and anti-proliferative effects. As a result, GLP-1RAs induce apoptosis in certain cancers and inhibit tumor growth in others [14]. These agents interfere with key signaling pathways, including the phosphatidylinositol 3-kinase (PI3K)-Akt pathway and the extracellular signal-regulated kinase 1/2 (ERK1/2) cascade, which are crucial for cancer cell survival and proliferation [18]. GLP-1RAs may activate downstream fibroblast growth factor 21 (FGF-21), an anti-inflammatory mediator [13].

In malignancies such as uterine corpus endometrial carcinoma and cervical squamous cell carcinoma, increased expression of GLP-1 receptors (GLP1R) has been associated with poorer survival outcomes. Conversely, in ovarian cancer, increased GLP1R expression has been associated with improved overall survival. The impact of GLP1R signaling therefore varies by tumor type [13].

Tirzepatide targets both GLP-1 and GIP receptors, which complicates its role in oncological treatment. Through its effects on insulin and blood glucose regulation, it potentially inhibits tumor growth linked to insulin-responsive signaling pathways [19]. Reports from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) indicate a higher likelihood of developing medullary thyroid carcinoma (MTC) after tirzepatide treatment [14]. GLP-1RAs may be associated with a potential risk of MTC, although this has not yet been indisputably established [14]. Reports indicate that tirzepatide use in patients results in a 13.67-fold increased risk of cancer compared to other medications [14]. Tirzepatide and other GLP-1RAs appear to have a comparable overall safety profile [20].

Effects of GLP-1RAs and tirzepatide on specific gynecologic cancers

Endometrial cancer

Obesity contributes to approximately 34% of endometrial cancer (EC) cases [21]. The traditional classification system specifies two clinicopathogenetic types of EC, type I and type II. Type I EC is strongly correlated with obesity, primarily due to increased estrogen levels resulting from adipose tissue activity, which predisposes patients to the development of this malignancy [22]. Increased adiposity stimulates aromatase activity, promoting the conversion of androgens into estrone and estradiol and reducing progesterone levels, particularly among anovulatory women [23]. This estrogen-progesterone imbalance may be involved in the development of endometrial carcinogenesis. Sustained weight loss of 5% over three years leads to a 39% reduction in EC risk [5]. Fluctuations in weight may cause greater harm than persistent obesity [21]. GLP-1 receptor agonists (GLP-1RAs) induce body weight loss through the regulation of insulin sensitivity, delayed gastric emptying, and appetite suppression [15].

GLP-1 receptors (GLP-1Rs) have been identified in both non-cancerous and malignant endometrial cells [24]. Studies in murine EC models have suggested that exenatide suppresses tumor progression [25]. Exenatide possibly exerts its effects by modulating GLP-1R signaling and downregulating the IGF-1R/PI3K/Akt/mTOR pathway. Exenatide and liraglutide promote autophagy and apoptosis in EC cells by stimulating the AMP-activated protein kinase (AMPK) pathway. AICAR, an AMPK activator, may potentiate this effect when co-administered with liraglutide [22, 24]. Through AMPK activation, exendin-4 may reverse resistance to cisplatin chemotherapy induced by hyperglycemia [26].

Endometrial cancer tissues with increased GLP-1R expression correlate with longer progression-free survival, a more favorable hormone receptor profile (estrogen and/or progesterone receptors), and low-grade histology [24]. Stimulation of GLP-1R activates the cyclic AMP/protein kinase A (cAMP/PKA) signaling pathway, regulating apoptosis, differentiation, and gene expression. This mechanism may inhibit tumor growth [27].

Through genomic and non-genomic mechanisms, including activation of PI3K and mitogen-activated protein kinase (MAPK) signaling pathways, estrogen promotes cancer development. Progesterone exerts protective effects by enhancing differentiation, inducing cell cycle arrest, and initiating apoptosis. In EC, epigenetic modifications commonly affect progesterone receptor (PR) expression and activity [23]. GLP-1RAs may augment PR signaling via interaction with membrane-associated proteins such as PGRMC1, stimulate downstream pathways [e.g., proto-oncogene tyrosine-protein kinase (Src) and Erk] that phosphorylate PRB (PR receptor isoform), enhancing its activation and nuclear translocation, and PR gene transcription [23]. Levonorgestrel, used for the prevention and treatment of EC, increases the expression of GLP-1R, PGRMC1, estrogen receptor (ER), androgen receptor (AR), mineralocorticoid receptor (MR), and PR [23]. In vitro analyses of EC cell lines and ex-vivo patient-derived organoids show that dual treatment with levonorgestrel and GLP-1RAs (semaglutide or liraglutide) results in a significantly greater decrease in cell viability compared with either agent alone [23]. Liraglutide leads to elevated progesterone receptor (PGR) levels, improving the efficacy of medroxyprogesterone acetate (MPA), a hormone therapy for EC [28].

Kong et al. (2024) conducted a study involving tirzepatide administered to two groups, obese and lean murine EC models, showing a greater than 60% reduction in EC tumor weight after treatment [19]. Tirzepatide also induced significant weight loss, with a 20.1% reduction in body weight observed in obese mice and 16.8% in lean mice. Tirzepatide reduced the expression of the GLP-1R in lean mice, which was higher in comparison to the obese group, without affecting GIP receptor levels in either group. In both mice groups, tirzepatide treatment decreased the expression of tumoral Ki67, Bcl-xL, and phosphorylated S6, markers associated with tumor proliferation and apoptosis. However, metabolic responses to treatment varied between the murine model groups. In obese mice, tirzepatide suppressed glycolytic and ErbB pathway gene expression, and enhanced fatty acid degradation and immune function. In lean mice, tirzepatide affected alternative metabolic pathways, including phospholipase D signaling, and induced changes in lipid and energy metabolism [19].

Tirzepatide also lowered serum adiponectin, leptin, resistin, and CRP levels, especially in obese mice, exerting systemic anti-inflammatory effects and improving insulin sensitivity [29].

Ovarian cancer

Approximately 95% of ovarian cancer histological subtypes originate from epithelial cells, including high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous types [30]. Ovarian malignancy proliferation and invasion are primarily regulated by activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway [31]. Tumor necrosis factor alpha (TNF-α) and Toll-like receptor 4 (TLR4) initiate the IκB kinase complex, which phosphorylates and degrades IκB. Consequently, nuclear translocation of NF-κB is facilitated, and genes involved in cancer progression are induced [31].

The imbalance between matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) is one of the mechanisms contributing to ovarian cancer progression. Enhanced activity of MMP-9 in the microenvironment leads to extracellular matrix degradation [32], while decreased TIMP levels aggravate the invasive potential [33]. Moreover, increased secretion of vascular endothelial growth factor (VEGF) promotes neoangiogenesis [32], leading to further cancer expansion.

Exendin-4, a GLP-1RA, modulates several key pathways involved in ovarian cancer progression. Exendin-4 reduces the phosphorylation of IκB, thereby directly inhibiting activation of the NF-κB signaling pathway [33]. In vitro analyses have revealed that this GLP-1RA also suppresses the production of MMP-2 and MMP-9, while simultaneously increasing TIMP-1 and TIMP-2 levels. Additionally, Exendin-4 decreases VEGF and TNF-α expression in ovarian cancer cells, protecting endothelial cells from TNF-α-induced apoptosis [33]. Treatment with GLP-1RA further reduces the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), thereby limiting extravasation and dissemination of tumor cells [33].

GLP-1RAs exhibit pleiotropic effects that modulate ovarian cancer progression, leading to body weight reduction, restoration of hormonal balance, and anti-inflammatory activity. Moreover, GLP-1RAs target critical pathways involved in ovarian cancer proliferation, which might offer potentially new strategies for treatment.

Cervical cancer

Cervical cancer is primarily driven by HPV infection. Squamous cell carcinoma and adenocarcinoma represent the most frequently diagnosed histological subtypes of cervical cancer [2]. A hyperglycemic microenvironment may exacerbate inflammation associated with malignancy progression [4]. Reports from The Cancer Genome Atlas (TCGA) show that expression of prostate-specific membrane antigen 2 (PSMA2), an integral component of the proteasome complex, is significantly elevated in cervical cancer. Hyperglycemic conditions further promote enhanced PSMA2 expression in cervical cancer cell lines, while non-malignant cells show no significant changes [34].

Patients with type 2 diabetes have been found to exhibit upregulated GLP-1 receptors (GLP-1R) in cervical cancer tissues. In this group, GLP-1R and PSMA2 demonstrate enhanced co-expression, indicating a positive correlation between these molecules in cervical cancer [34]. Exendin-4, a GLP-1RA, mitigates the hyperglycemic microenvironment, acts as an anti-inflammatory agent, and suppresses PSMA2 expression [34].

Hyperglycemic conditions also increase phosphorylation of p65 and IκB, which activates the NF-κB pathway. Intervention with Exendin-4 reduces phosphorylation of these proteins, thereby suppressing cancer progression [34].

Future perspective

There are ongoing clinical trials evaluating GLP-1 receptor agonists (GLP-1RAs), including "Weight Loss Management in Endometrial Cancer Survivors (ECS Weight)" (NCT06877572), which is primarily focused on weight reduction and its impact on endometrial cancer outcomes. Additional trials are investigating tirzepatide, including "A Study of a Weight Loss Intervention in People With Endometrial Cancer" (NCT06751589), which also addresses the role of obesity in endometrial cancer, and "Weight-loss Drug for Fertility-Sparing Treatment of Atypical Hyperplasia and Grade 1 Cancer of the Endometrium (WE-FiERCE)" (NCT06073184), which aims to evaluate tirzepatide's ability to improve complete response rates to cancer treatment.

Triple-acting GLP-1, GIP, and glucagon receptor agonists, as well as small-molecule oral GLP-1 receptor agonists, are investigational agents, not yet commercially available. By modulating metabolism, inducing substantial body weight reduction, and potentially exhibiting antineoplastic activity, these therapies have the potential to revolutionize therapeutic practices [35].

Conclusions

This review demonstrates that GLP-1 receptor agonists (GLP-1RAs) and the dual GIP/GLP-1 receptor co-agonist

tirzepatide influence multiple pathogenic mechanisms involved in gynecologic cancers, including endometrial, ovarian, and cervical types. These incretin-based therapies, despite being primarily designed to correct metabolic dysregulation by improving insulin sensitivity and reducing adipose mass, also directly modulate signaling pathways involved in tumorigenesis, including PI3K/Akt/mTOR, AMPK, and the NF-κB signaling pathways. The antineoplastic effects of GLP-1RAs and tirzepatide are manifested via modulating the tumor microenvironment, enhancing apoptosis, downregulating pro-inflammatory signaling, and inhibiting metastasis.

GLP-1RAs and tirzepatide may improve the effectiveness of existing cancer treatment protocols, particularly among patients with obesity or type 2 diabetes. Moreover, combining GLP-1RAs with hormonal therapies in endometrial cancer (e.g., levonorgestrel or medroxyprogesterone acetate) has shown promise in improving the efficacy of current hormonal therapy, which could help redefine existing clinical approaches and promote more individualized treatment strategies.

Much of the current evidence is based on preclinical research conducted with murine models or in vitro experiments, which may not fully reflect the complexity of human biological responses. The differential expression and oncologic relevance of GLP-1 receptors across tumor types remain insufficiently understood at the molecular level. Furthermore, the potentially elevated risk of particular cancers, such as medullary thyroid carcinoma, poses a safety concern during treatment with GLP-1RAs and tirzepatide, as suggested by pharmacovigilance data.

The effectiveness and oncological safety of supportive treatments with GLP-1RAs and tirzepatide in cancer patients should be evaluated in further long-term clinical trials.

In conclusion, GLP-1RAs and tirzepatide target metabolic dysregulation, which may help reshape therapeutic approaches in gynecologic oncology by combining metabolic control with antineoplastic activity.

References

1. Siegel RL, Kratzer TB, Giaquinto AN, et al. Cancer statistics, 2025. CA Cancer J Clin, 2025; 75(1): 10–45. doi: 10.3322/caac.21871
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 2021; 71(3): 209–249. doi: 10.3322/caac.21660
3. Smrz SA, Calo C, Fisher JL, Salani R. An ecological evaluation of the increasing incidence of endometrial cancer and the obesity epidemic. Am J Obstet Gynecol, 2021; 224(5): 506.e1–506.e8. doi: 10.1016/j.ajog.2020.10.042
4. Cao Z, Zheng X, Yang H, et al. Association of obesity status and metabolic syndrome with site-specific cancers: a population-based cohort study. Br J Cancer, 2020; 123(8): 1336–1344. doi: 10.1038/s41416-020-1012-6
5. Luo J, Chlebowski RT, Hendryx M, et al. Intentional weight loss and endometrial cancer risk. J Clin Oncol, 2017; 35(11): 1189–1193. doi: 10.1200/JCO.2016.70.5822
6. WHO. Global Cancer Observatory: Ovary fact sheet. Lyon: International Agency for Research on Cancer; 2022 [access: 05.05.2025]. Available from: https://gco.iarc.who.int/media/globocan/factsheets/cancers/25-ovary-fact-sheet.pdf
7. National Cancer Institute. Cancer Stat Facts: Ovarian Cancer [Internet]. Bethesda (MD): SEER Program; [access: 07.05.2025]. Available from: https://seer.cancer.gov/statfacts/html/ovary.html
8. Kjaer SK, Dehlendorff C, Belmonte F, Baandrup L. Real-world effectiveness of human papillomavirus vaccination against cervical cancer. J Natl Cancer Inst, 2021; 113(10): 1329–1335. doi: 10.1093/jnci/djab080
9. Beavis AL, Gravitt PE, Rositch AF. Hysterectomy-corrected cervical cancer mortality rates reveal a larger racial disparity in the United States. Cancer, 2017; 123(6): 1044–1050. doi: 10.1002/cncr.30507
10. Castellsagué X, Díaz M, de Sanjosé S, et al; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. J Natl Cancer Inst, 2006; 98(5): 303–315. doi: 10.1093/jnci/djj067
11. Bręborowicz GH. Położnictwo i ginekologia. T. 2: Ginekologia. Warszawa: Wydawnictwo Lekarskie PZWL; 2021: p. 275
12. Krajowy Rejestr Nowotworów. 1999–2022: Zgony (umieralność) i zachorowania (zachorowalność) [Internet]. Warszawa: Krajowy Rejestr Nowotworów; [access: 05.05.2025]. Available from: https://krajowyrejestrnowotworow.my.canva.site/
13. Ungvari Z, Bartha Á, Ungvari A, et al. Prognostic impact of glucagon-like peptide-1 receptor (GLP1R) expression on cancer survival and its implications for GLP-1R agonist therapy: an integrative analysis across multiple tumor types. Geroscience, 2025; 47(3): 4413–4427. doi: 10.1007/s11357-024-01494-5
14. Kounatidis D, Vallianou NG, Karampela I, et al. Anti-diabetic therapies and cancer: from bench to bedside. Biomolecules, 2024; 14(11): 1479. doi: 10.3390/biom14111479
15. Yao H, Zhang A, Li D, et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. BMJ, 2024; 384: e076410. doi: 10.1136/bmj-2023-076410
16. Karagiannis T, Malandris K, Avgerinos I, et al. Subcutaneously administered tirzepatide vs semaglutide for adults with type 2 diabetes: a systematic review and network meta-analysis of randomised controlled trials. Diabetologia, 2024; 67(7): 1206–1222. doi: 10.1007/s00125-024-06144-1
17. Rosenstock J, Frías JP, Rodbard HW, et al. Tirzepatide vs insulin lispro added to basal insulin in type 2 diabetes: The SURPASS-6 randomized clinical trial. JAMA, 2023; 330(17): 1631–1640. doi: 10.1001/jama.2023.20294. Erratum in: JAMA, 2023; 330(19): 1915. doi: 10.1001/jama.2023.22757. Erratum in: JAMA, 2025; 333(16): 1460. doi: 10.1001/jama.2025.3806
18. Zhao H, Wei R, Wang L, et al. Activation of glucagon-like peptide-1 receptor inhibits growth and promotes apoptosis of human pancreatic cancer cells in a cAMP-dependent manner. Am J Physiol Endocrinol Metab, 2014; 306(12): E1431–1441. doi: 10.1152/ajpendo.00017.2014
19. Kong W, Deng B, Shen X, et al. Tirzepatide as an innovative treatment strategy in a pre-clinical model of obesity-driven endometrial cancer. Gynecol Oncol, 2024; 191: 116–123. doi: 10.1016/j.ygyno.2024.10.004

20. Caruso I, Di Gioia L, Di Molfetta S, et al. The real-world safety profile of tirzepatide: pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database. J Endocrinol Invest, 2024; 47(11): 2671–2678. doi: 10.1007/s40618-024-02441-z
21. Baker-Rand H, Kitson SJ. Recent advances in endometrial cancer prevention, early diagnosis and treatment. Cancers (Basel), 2024; 16(5): 1028. doi: 10.3390/cancers16051028
22. Bourou MZ, Matsas A, Valsamakis G, et al. The potential role of glucagon-like peptide-1 (GLP-1) receptor agonists as a type of conservative treatment of endometrial cancer in women of reproductive age: a review of the literature and a call for study. Cureus, 2024; 16(9): e69678. doi: 10.7759/cureus.69678
23. Hagemann A.R., Hagemann IS, Mutch DG, et al. Enhancing progestin therapy with a glucagon-like peptide 1 agonist for the conservative management of endometrial cancer. Cancers (Basel), 2025; 17(4): 598. doi: 10.3390/cancers17040598
24. Kanda R, Hiraike H, Wada-Hiraike O, et al. Expression of the glucagon-like peptide-1 receptor and its role in regulating autophagy in endometrial cancer. BMC Cancer, 2018; 18(1): 657. doi: 10.1186/s12885-018-4570-8
25. Zhang Y, Xu F, Liang H, et al. Exenatide inhibits the growth of endometrial cancer Ishikawa xenografts in nude mice. Oncol Rep, 2016; 35(3): 1340–1348. doi: 10.3892/or.2015.4476
26. Zhang Y, Cheng J, Li J, et al. The GLP-1R agonist exendin-4 attenuates hyperglycemia-induced chemoresistance in human endometrial cancer cells through ROS-mediated mitochondrial pathway. Front Oncol, 2021; 11: 793530. doi: 10.3389/fonc.2021.793530
27. Li W, Gu Y, Liu S, et al. GLP1R inhibits the progression of endometrial carcinoma through activation of cAMP/PKA pathway. J Clin Lab Anal, 2022; 36(10): e24604. doi: 10.1002/jcla.24604
28. Zhu XX, Feng ZH, Liu LZ, Zhang Y. Liraglutide suppresses the proliferation of endometrial cancer cells through the adenosine 5'-monophosphate (AMP)-activated protein kinase signaling pathway. Chin Med J (Engl), 2021; 134(5): 576–578. doi: 10.1097/CM9.0000000000001363
29. Romanos-Nanclares A, Tabung FK, Sinnott JA, et al. Inflammatory and insulinemic dietary patterns and risk of endometrial cancer among US women. J Natl Cancer Inst, 2023; 115(3): 311–321. doi: 10.1093/jnci/djac229
30. Robboy SJ. Robboy's pathology of the female reproductive tract. Amsterdam: Elsevier Health Sciences; 2009. p. 601
31. Alvero AB. Recent insights into the role of NF-kappaB in ovarian carcinogenesis. Genome Med, 2010; 2(8): 56. doi: 10.1186/gm177
32. Yeung TL, Leung CS, Yip KP, et al. Cellular and molecular processes in ovarian cancer metastasis. A review in the theme: cell and molecular processes in cancer metastasis. Am J Physiol Cell Physiol, 2015; 309(7): C444–456. doi: 10.1152/ajpcell.00188.2015
33. Kosowska A, Gallego-Colon E, Garczorz W, et al. Exenatide modulates tumor-endothelial cell interactions in human ovarian cancer cells. Endocr Connect, 2017; 6(8): 856–865. doi: 10.1530/EC-17-0294
34. Mao D, Cao H, Shi M, et al. Increased co-expression of PSMA2 and GLP-1 receptor in cervical cancer models in type 2 diabetes attenuated by Exendin-4: A translational case-control study. EBioMedicine, 2021; 65: 103242. doi: 10.1016/j.ebiom.2021.103242
35. Rosenstock J, Frias J, Jastreboff AM, et al. Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. Lancet, 2023; 402(10401): 529–544. doi: 10.1016/S0140-6736(23)01053-X

REVIEW ARTICLE

ISOLATED SYSTOLIC HYPERTENSION IN YOUNG ADULTS – DIAGNOSTIC CONTROVERSIES AND CLINICAL SIGNIFICANCE: A REVIEW OF CURRENT DATA

Izolowane nadciśnienie skurczowe u młodych dorosłych – kontrowersje diagnostyczne i znaczenie kliniczne: przegląd aktualnych danych

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Abstract

In recent years, isolated systolic hypertension (ISH) has been increasingly reported in young adults, particularly lean men. This phenomenon, traditionally associated with advanced age and arterial stiffness, is now more frequently diagnosed in individuals under 50 years of age, raising numerous controversies regarding both its clinical interpretation and therapeutic management. In contrast to the older population, where ISH constitutes a significant cardiovascular risk factor, young individuals often present with so-called "pseudo-ISH" – a form of systolic hypertension resulting from physiological pulse-wave amplification, without accompanying pathological changes in the cardiovascular system. The aim of this review is to summarize the current state of knowledge on ISH in young adults, with particular emphasis on its pathophysiology, diagnostic tools (ambulatory blood pressure monitoring, home blood pressure monitoring, central blood pressure measurement, pulse wave velocity), prognostic significance, and therapeutic approach. Current controversies related to differentiating systolic–diastolic hypertension from its physiological variants are discussed, and the need for further research to unequivocally determine the risk and management strategies in this patient population is highlighted.

Streszczenie

W ostatnich latach coraz częściej obserwuje się występowanie izolowanego nadciśnienia skurczowego (ISH) wśród młodych dorosłych, szczególnie szczupłych mężczyzn. Zjawisko to, tradycyjnie kojarzone z podeszłym wiekiem i sztywnością tętnic, jest również częściej diagnozowane u osób poniżej 50. roku życia, co rodzi liczne kontrowersje dotyczące zarówno jego interpretacji klinicznej, jak i leczenia. W przeciwieństwie do starszej populacji, w której ISH stanowi istotny czynnik ryzyka sercowo-naczyniowego, osoby młode często prezentują tzw. „pseudo-ISH" – postać nadciśnienia skurczowego wynikającą z fizjologicznej amplifikacji fali tętna, bez towarzyszących patologicznych zmian w układzie sercowo-naczyniowym. Celem niniejszego przeglądu jest podsumowanie aktualnego stanu wiedzy na temat ISH u młodych dorosłych, ze szczególnym uwzględnieniem jego patofizjologii, narzędzi diagnostycznych (ambulatoryjnego monitorowania ciśnienia tętniczego, domowego monitorowania ciśnienia tętniczego, pomiaru ciśnienia centralnego, prędkości fali tętna), znaczenia rokowniczego oraz podejścia terapeutycznego. Omówiono również aktualne kontrowersje związane z różnicowaniem nadciśnienia skurczowego i rozkurczowego od jego wariantów fizjologicznych, a także wskazano na potrzebę dalszych badań, mających na celu jednoznaczne określenie ryzyka i strategii postępowania w tej populacji pacjentów.

Keywords: cardiovascular risk; young adults; central blood pressure; isolated systolic hypertension; pseudo-ISH

Słowa kluczowe: ryzyko sercowo-naczyniowe; młodzi dorośli; ciśnienie centralne; pseudo-ISH; izolowane nadciśnienie skurczowe

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Introduction

In recent years, an increasing prevalence of cardiovascular diseases and chronic kidney diseases has been observed among young and middle-aged adults. Although this population was previously considered to be at relatively low risk, current data suggest that adverse health trends are also affecting individuals under 40 years of age. One of the factors that may play a key role in this process is arterial hypertension, the rise of which is often associated with the obesity epidemic and unhealthy lifestyle patterns. Despite the growing scale of the problem, the management of hypertension in this age group remains controversial [1, 2].

Isolated systolic hypertension (ISH), an abnormality most commonly observed in older individuals in whom arterial stiffness and increased pulse pressure play a dominant role in its pathogenesis, presents particular diagnostic and therapeutic challenges [1, 3]. However, in recent years, an upward trend in the incidence of ISH has also been observed in young individuals, particularly men. This phenomenon generates many controversies, both in terms of diagnosis and therapy [2, 4]. In young adults, ISH may involve a different pathomechanism and is not always associated with increased cardiovascular risk [5, 6]. Despite a growing body of epidemiological evidence, the clinical significance of ISH at a younger age remains unclear. It is still debated whether it should be treated as an early marker of cardiovascular risk or rather as a physiological variant or "pseudo-hypertension" that does not require aggressive treatment. This review aims to outline the current state of knowledge on ISH in young and middle-aged adults – considering its prevalence, pathophysiological mechanisms, risk of complications, and therapeutic approaches [7, 8].

Definition and diagnostic criteria

Isolated systolic hypertension in young adults, defined as individuals between 18 and 40 years of age, is, according to the 2024 European Society of Hypertension (ESH) guidelines, characterized by systolic blood pressure (SBP) ≥140 mmHg with a concurrent diastolic blood pressure (DBP) <90 mmHg [8]. In this population, particularly among lean men, the phenomenon of pseudo-ISH (apparent arterial hypertension) is frequently observed. This refers to situations in which systolic blood pressure measured in an office setting is elevated, while central blood pressure remains within the normal range. This phenomenon results from an increase in arterial stiffness and pulse-wave amplification within the vascular system, which causes values measured peripherally to be higher than in the aorta. It occurs more frequently among younger, otherwise healthy individuals, and may therefore result in an erroneous diagnosis of arterial hypertension [9, 10].

In light of this, the latest 2024 ESH recommendations draw attention to the necessity of verifying blood pressure measurement results, especially in young individuals presenting with isolated SBP elevation. More accurate diagnostic assessment enables differentiation between true systolic–diastolic hypertension and pseudo-ISH, which is of crucial importance for therapeutic decisions [8].

Pathophysiology

Isolated systolic hypertension in young adults often results from hemodynamic mechanisms that differ from those observed in the older population. In younger patients, the main factor leading to ISH is pulse-wave amplification, a phenomenon in which systolic pressure measured in peripheral arteries (e.g., the brachial artery) is significantly higher than central aortic pressure. This amplification is a result of higher stiffness of peripheral arteries and variability in cardiac output, which are characteristic of younger individuals, particularly those leading an active lifestyle. Furthermore, younger individuals typically exhibit better vascular elasticity, which causes a greater discrepancy between systolic pressure in the brachial artery and central pressure, potentially leading to an erroneous diagnosis of systolic hypertension [11–13].

In such patients, despite elevated systolic blood pressure measured peripherally, central aortic pressure remains within normal limits. This phenomenon, referred to as pseudo-ISH, does not result from pathological changes in the vessel walls (e.g., loss of arterial elasticity), as is the case in older individuals. Instead, it arises from pulse-wave amplification. Pseudo-ISH thus reflects hemodynamic changes that do not indicate true pathological hypertension but rather an increased difference between central and peripheral pressure, which is a physiological phenomenon in many individuals [14, 15].

Diagnostic tools and differentiation

To improve the accuracy of ISH diagnosis in young patients, detailed blood pressure assessment using 24-hour ambulatory blood pressure monitoring (ABPM) is recommended. This method provides a more complete picture of blood pressure variability throughout the day, which is crucial for differentiating systolic–diastolic hypertension from white-coat hypertension, which may occur as a result of stress associated with examination in clinical settings. Additionally, home blood pressure monitoring (HBPM) is recommended, as it enables blood pressure evaluation in the patient's natural environment, eliminating the influence of stress-inducing factors associated with a visit to the doctor's office [10, 8].

In recent years, increasing importance in ISH diagnostics has been attributed to the measurement of central blood pressure, which is obtained using specialized tonomet-

ric or cuff-based devices, often supported by dedicated mathematical algorithms. Central blood pressure measurement allows for the assessment of pressure in the main arterial vessels, including the aorta, providing more precise data than traditional peripheral measurements. Another important tool in ISH diagnostics is the evaluation of arterial stiffness, which can be performed by measuring pulse-wave velocity (PWV). Arterial stiffness is an important indicator of cardiovascular risk and can help differentiate pseudo-ISH from true systolic–diastolic hypertension. Finally, echocardiography remains a key method for assessing cardiac load, enabling a detailed analysis of changes in cardiac function and potential damage related to chronic hypertension. Collectively, these diagnostic methods allow for a more precise assessment of the patient's hemodynamic condition and more reliable exclusion of the pseudo-ISH phenomenon [8, 16, 17].

Prognostic significance

Epidemiological data on isolated systolic hypertension in younger individuals remain inconclusive, and study results vary depending on the length of the observation period, sex, and age group. Several studies indicate that in young men, ISH is not associated with a significant increase in cardiovascular risk in the short-term perspective. Such findings suggest that, in this group of patients, despite elevated systolic blood pressure, diastolic pressure remains normal, which in the short term may not result in a significant increase in the risk of cardiovascular incidents compared with individuals with both systolic and diastolic hypertension [5, 6]. However, other studies indicate that in young women, ISH may be associated with a higher risk of developing cardiovascular disease than in individuals with high-normal blood pressure or isolated diastolic hypertension, although the risk remains lower than in combined systolic–diastolic hypertension [18].

A prospective study published in 2015 demonstrated that among younger adults with ISH, the risk of mortality from cardiovascular diseases, including ischemic heart disease, was higher compared with individuals with normal blood pressure. These findings suggest that although ISH may not lead to cardiovascular complications in the short term, it is associated with a greater risk of cardiac incidents in the long-term perspective [11]. Similar conclusions were reported in the MONICA/KORA cohort study (2021), which found that younger individuals who smoke regularly, are obese, have dyslipidemia, and exhibit elevated blood pressure, are at higher risk of developing ISH. The study highlights that factors such as cigarette smoking and obesity have a significant impact on the occurrence of ISH, particularly in men, and also contribute to an increase in cardiovascular risk in this patient group [3].

Therapeutic approach

In young adult patients with isolated systolic hypertension and SBP values of 140–159 mmHg, in whom no hypertension-related organ damage is found and no additional cardiovascular risk factors are present, a non-pharmacological approach is recommended in the first instance. This treatment should be applied for a period of 6 to 12 months, and its aim is to monitor the body's response to lifestyle changes, such as weight reduction, limitation of salt intake, and increased physical activity, before a decision is made to implement pharmacotherapy. In patients with SBP ≥160 mmHg, or in those with coexisting organ damage related to arterial hypertension and/or the presence of other cardiovascular risk factors, it is necessary to include pharmacotherapy to reduce the risk of cardiovascular complications [19].

Non-pharmacological interventions play a key role in the management of ISH, and their effectiveness is independent of baseline blood pressure values. The most effective methods include lifestyle modification, particularly weight reduction, limitation of salt intake, and regular physical activity. Study results indicate that a weight loss of 5 kg, as well as an increase in the level of physical activity in individuals under 45 years of age, leads to a reduction in SBP by an average of 5 mmHg. Even a modest decrease in body weight has a significant impact on improving blood pressure control, while regular physical activity, including aerobic exercise, effectively lowers SBP and reduces the risk of future cardiovascular events [4].

Controversies and challenges

Isolated systolic hypertension in young adults remains a subject of active debate in the medical community, especially in the context of its association with cardiovascular risk. On the one hand, some researchers suggest that ISH in young individuals, particularly tall, physically active men, may result from pulse-wave amplification in peripheral blood vessels. This mechanism leads to so-called "spurious" systolic hypertension, which is not associated with an actual increase in cardiovascular risk but may be misinterpreted as white-coat hypertension. In such cases, despite elevated systolic blood pressure values, there is no increased risk of cardiovascular events, although blood pressure monitoring outside the doctor's office is still indicated for a more accurate assessment of the patient's condition [14].

On the other hand, a growing body of evidence suggests that ISH in younger patients may indeed be associated with elevated cardiovascular risk, particularly when accompanied by elevated central blood pressure or the presence of organ damage related to hypertension. Cohort studies, including the MONICA/KORA study, have shown that young adults with ISH exhibit a higher risk of cardiovascular mortality compared with individuals with normal blood pressure [3]. These findings indicate the need for a more detailed assessment of patients with ISH to precisely distinguish individuals who require intensive monitoring and treatment from those who may be managed with clinical observation alone, without the need to introduce pharmacological therapy.

In the context of ISH therapy and diagnostics, some experts advocate distinguishing true ISH based on central blood pressure measurements, while treating other cases as physiological variants that do not require intervention [20]. However, ignoring ISH in the young adult population may lead to overlooking the early stages of arterial stiffness, which in the longer term can increase the risk of cardiovascular complications [21]. For this reason, there is an urgent need for further research to enable more precise determination of risk groups in this population and to establish optimal diagnostic and therapeutic strategies.

Conclusions

Isolated systolic hypertension in young adults constitutes a complex and not yet fully understood clinical issue. Unlike older individuals, where ISH is unequivocally associated with reduced vascular elasticity and increased cardiovascular risk, in younger patients, this phenomenon may have a different pathomechanism and, in many cases, may not reflect true cardiovascular risk. In the younger population, particularly among lean and physically active men, ISH is often associated with a phenomenon termed pseudo-ISH. For this reason, advanced diagnostic methods, such as ABPM, HBPM, central blood pressure measurement, and assessment of arterial stiffness (PWV), are of key importance, allowing for a more precise differentiation of true ISH from physiological variants. Although some studies indicate that ISH in young men is not associated with increased short-term cardiovascular risk, others suggest that in young women and individuals with additional risk factors (obesity, tobacco smoking, dyslipidemia), ISH may lead to complications in the longer term. These observations underscore the importance of an individualized approach to risk assessment and therapeutic decisions. Currently, there are no definitive guidelines regarding the management of ISH in young adults. Consequently, further well-designed cohort and randomized studies are needed to clarify the long-term clinical effects of ISH in this population and to optimize diagnostic criteria and therapeutic indications. In light of the available evidence, both overtreatment and trivialization of this phenomenon should be avoided.

References

1. Yano Y, Lloyd-Jones DM. Isolated systolic hypertension in young and middle-aged adults. Curr Hypertens Rep, 2016; 18(11): 78. doi: 10.1007/s11906-016-0686-x
2. Saladini F, Palatini P. Isolated systolic hypertension in young individuals: pathophysiological mechanisms, prognostic significance, and clinical implications. High Blood Press Cardiovasc Prev, 2017; 24(2): 133–139. doi: 10.1007/s40292-017-0199-y
3. Atasoy S, Middeke M, Johar H, et al. Cardiovascular mortality risk in young adults with isolated systolic hypertension: findings from population-based MONICA/KORA cohort study. J Hum Hypertens, 2022; 36(12): 1059–1065. doi: 10.1038/s41371-021-00619-z. Erratum in: J Hum Hypertens, 2023; 37(4): 330. doi: 10.1038/s41371-023-00804-2
4. Scott H, Barton MJ, Johnston ANB. Isolated systolic hypertension in young males: a scoping review. Clin Hypertens, 2021; 27(1): 12. doi: 10.1186/s40885-021-00169-z
5. Lee H, Yano Y, Cho SMJ, et al. Cardiovascular risk of isolated systolic or diastolic hypertension in young adults. Circulation, 2020; 141(22): 1778–1786. doi: 10.1161/CIRCULATIONAHA.119.044838
6. Yano Y, Neeland IJ, Ayers C, et al. Hemodynamic and mechanical properties of the proximal aorta in young and middle-aged adults with isolated systolic hypertension: the Dallas Heart Study. Hypertension, 2017; 70(1): 158–165. doi: 10.1161/HYPERTENSIONAHA.117.09279
7. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. Hypertension, 2020; 75(6): 1334–1357. doi: 10.1161/HYPERTENSIONAHA.120.15026
8. McEvoy JW, McCarthy CP, Bruno RM, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J, 2024; 45(38): 3912–4018. doi: 10.1093/eurheartj/ehae178. Erratum in: Eur Heart J, 2025; 46(14): 1300. doi: 10.1093/eurheartj/ehaf031. Erratum in: Eur Heart J, 2025; 46(45): 4949. doi: 10.1093/eurheartj/ehaf659
9. Espeche W, Minetto J, Stavile N, et al. Isolated systolic hypertension in young adults and its relationship with ambulatory blood pressure measurements. Arch Clin Hypertens, 2024; 10(1): 001–006. doi: 10.17352/ach.000034
10. Palatini P, Saladini F, Mos L, et al. Clinical characteristics and risk of hypertension needing treatment in young patients with systolic hypertension identified with ambulatory monitoring. J Hypertens, 2018; 36(9): 1810–1815. doi: 10.1097/HJH.0000000000001754
11. Yano Y, Stamler J, Garside DB, et al. Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. J Am Coll Cardiol, 2015; 65(4): 327–335. doi: 10.1016/j.jacc.2014.10.060
12. Protogerou AD, Blacher J, Safar ME. Isolated systolic hypertension: 'to treat or not to treat' and the role of central haemodynamics. J Hypertens, 2013; 31(4): 655–658. doi: 10.1097/HJH.0b013e32835f7e2b
13. Huang QF, An DW, Aparicio LS, et al. An outcome-driven threshold for pulse pressure amplification. Hypertens Res, 2024; 47(9): 2478–2488. doi: 10.1038/s41440-024-01779-4
14. Lurbe E, Redon J. Isolated systolic hypertension in young people is not spurious and should be treated: con side of the argument. Hypertension, 2016; 68(2): 276–280. doi: 10.1161/HYPERTENSIONAHA.116.06548
15. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol, 2010; 55(13): 1318–1327. doi: 10.1016/j.jacc.2009.10.061
16. Thijs L, Den Hond E, Nawrot T, Staessen JA. Prevalence, pathophysiology and treatment of isolated systolic hypertension in the elderly. Expert Rev Cardiovasc Ther, 2004; 2(5): 761–769. doi: 10.1586/14779072.2.5.761
17. Laurent S, Cockcroft J, Van Bortel L, et al.; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J, 2006; 27(21): 2588–2605. doi: 10.1093/eurheartj/ehl254
18. Gu Q, Meng J, Hu X, et al. Isolated systolic hypertension and insulin resistance assessment tools in young and middle-aged Chinese men with normal fasting glucose: a cross-sectional study. Sci Rep, 2022; 12(1): 758. doi: 10.1038/s41598-021-04763-x
19. Prejbisz A, Dobrowolski P, Doroszko A, et al. Guidelines for the management of hypertension in Poland 2024 – the position of the Polish Society of Hypertension/Polish Cardiac Society Experts. Arterial Hypertension, 2024; 28: 91–146. doi: 10.5603/ah.103916
20. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation, 2010; 121(4): 505–511. doi: 10.1161/CIRCULATIONAHA.109.886655
21. Cheng YB, Li Y, Cheng HM, et al. Central hypertension is a non-negligible cardiovascular risk factor. J Clin Hypertens (Greenwich), 2022; 24(9): 1174–1179. doi: 10.1111/jch.14561

REVIEW ARTICLE

THE PEDIATRIC GUT MICROBIOME AND ITS ROLE IN CHILDHOOD DISEASES: FROM DEVELOPMENT TO THERAPEUTIC POTENTIAL

Mikrobiom jelitowy u dzieci i jego rola w chorobach wieku dziecięcego: od rozwoju do potencjału terapeutycznego

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Abstract

The gut microbiome plays a fundamental role in child development, influencing metabolic regulation, immune maturation, and neurodevelopment from early life onward. Increasing evidence links disturbances in gut microbial composition to pediatric disorders, including obesity, allergic diseases, autoimmune conditions, neurodevelopmental disorders, and gastrointestinal pathologies. This review summarizes current knowledge on the developmental trajectory of the pediatric gut microbiome, the major environmental and biological factors shaping its composition, and key disease-related microbial patterns described in recent literature. Particular attention is given to mechanisms involving immune modulation, intestinal barrier function, microbial metabolites, and the microbiota–gut–brain axis. Finally, the potential role of probiotics as a microbiome-targeted strategy is discussed, emphasizing both their therapeutic promise and existing limitations. Overall, the pediatric gut microbiome emerges as a modifiable determinant of health, warranting further longitudinal and interventional research.

Streszczenie

Mikrobiom jelitowy odgrywa fundamentalną rolę w rozwoju dziecka, wpływając na regulację metabolizmu, dojrzewanie układu odpornościowego oraz rozwój układu nerwowego od najwcześniejszych etapów życia. Coraz więcej dowodów wskazuje, że zaburzenia składu mikrobioty jelitowej są powiązane z występowaniem chorób wieku dziecięcego, w tym otyłości, chorób alergicznych, schorzeń autoimmunologicznych, zaburzeń neurorozwojowych oraz patologii przewodu pokarmowego. Niniejszy artykuł podsumowuje aktualny stan wiedzy na temat rozwoju mikrobiomu jelitowego u dzieci, głównych czynników środowiskowych i biologicznych kształtujących jego skład, a także charakterystycznych wzorców mikrobiologicznych związanych z chorobami, opisanych w najnowszym piśmiennictwie. Szczególną uwagę poświęcono mechanizmom obejmującym modulację odpowiedzi immunologicznej, funkcję bariery jelitowej, rolę metabolitów bakteryjnych oraz komunikację w osi mikrobiota–jelito–mózg. Na zakończenie omówiono potencjalną rolę probiotyków jako strategii terapeutycznej ukierunkowanej na mikrobiom, podkreślając zarówno ich obiecujące możliwości kliniczne, jak i ograniczenia. Ogólnie rzecz biorąc, mikrobiom jelitowy dzieci jawi się jako modyfikowalny czynnik warunkujący zdrowie, co uzasadnia potrzebę dalszych badań podłużnych i interwencyjnych.

Keywords: probiotics; gut microbiome; microbiota–gut–brain axis; immune system development

Słowa kluczowe: probiotyki; mikrobiom jelitowy; oś mikrobiota–jelita–mózg; rozwój układu odpornościowego

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Introduction

The gut microbiome is increasingly recognized as a central regulator of childhood development, influencing biological, cognitive, and emotional processes from birth through adolescence. Childhood encompasses four major stages – infancy, early childhood, middle childhood, and adolescence – and deviations from expected developmental milestones at any of these stages may indicate emerging health concerns. These include conditions such as malnutrition, obesity, neurodevelopmental disorders, including autism spectrum disorder (ASD), food allergies, and asthma. Growing evidence indicates that alterations in gut microbiota composition and function contribute to the onset and progression of many of these disorders, positioning the microbiome as a potentially modifiable determinant of pediatric health outcomes [1].

The pediatric gut microbiome is a complex ecosystem composed of bacteria, viruses, fungi, archaea, and parasites, with bacteria constituting the most abundant and diverse group. Although microbial interactions shape health across the lifespan, their influence is particularly critical during infancy, when key physiological processes are established. Recent research demonstrates that early-life microbial communities interact closely with nutrition, host genetics, and immune system maturation, collectively shaping both immediate and long-term health trajectories [2].

Environmental and physiological factors strongly influence the establishment and subsequent maturation of the gut microbiome. Although the existence of prenatal colonization remains debated, there is broad consensus that extensive microbial colonization begins after birth. Early gut communities are dominated by facultative anaerobes, which are gradually replaced by obligate anaerobes as the intestinal environment stabilizes. Compared with the adult microbiota, the infant microbiome is less diverse and more dynamic [1]. Key determinants of early microbial composition include delivery mode, feeding practices (breastfeeding versus formula feeding), antibiotic exposure, and environmental conditions [1, 2]. The introduction of solid foods marks a major ecological transition: populations such as *Proteobacteria* typically decline, while overall microbial diversity and functional stability increase. Throughout childhood, the microbiome becomes progressively more complex and resilient, and by adolescence it shifts toward a more adult-like profile characterized by reduced aerobic and facultative anaerobic populations and an expansion of obligate anaerobes [1].

Studying the gut microbiota during childhood is particularly important because it differs substantially from the adult microbiome and plays a critical role in establishing metabolic pathways that may persist throughout life. Disruptions in early microbial development have been linked to metabolic disorders such as pediatric obesity, suggesting that interventions targeting early-life microbial dynamics may help prevent obesity and its associated comorbidities [3]. Understanding these mechanisms is essential not only for metabolic health but also for immune and neurodevelopmental maturation, underscoring the microbiome's multidimensional role in shaping pediatric health outcomes [2, 3].

Given the interplay between microbial maturation, metabolism, immune function, and neurodevelopment, examining the pediatric gut microbiome offers a unique opportunity for early interventions and preventive strategies. This review synthesizes current knowledge on the developmental trajectory of the pediatric gut microbiome, the factors influencing its composition, and its implications for metabolic, immune, and neurodevelopmental health, while identifying key knowledge gaps that require further investigation.

Methodology

This narrative review was based on a structured literature search conducted in PubMed, Scopus, and Google Scholar. The search focused on studies published within the past five years to ensure inclusion of the most recent and clinically relevant evidence reflecting current advances in microbiome research. Predefined keywords were used to identify publications related to pediatric gut microbiome development, disease associations, and probiotic interventions.

Approximately 50 articles were screened at the title and abstract level. Following full-text evaluation for relevance, 24 publications were included in the final narrative synthesis and are listed in the reference section. Eligible studies focused on pediatric populations and addressed microbiome-related mechanisms, disease associations, or therapeutic implications.

Given the narrative nature of this review, no formal risk-of-bias assessment tool was applied. Instead, study selection prioritized peer-reviewed publications in reputable journals that provided clear methodological descriptions and reported biologically or clinically plausible associations between gut microbiome alterations and pediatric health outcomes.

Factors shaping the pediatric gut microbiome

The development of the pediatric gut microbiome is a dynamic and highly sensitive process that begins before birth and continues throughout early childhood. This complex ecosystem is shaped by a combination of prenatal influences, perinatal exposures, nutrition, environmental interactions, and medical interventions. Because the gut microbiome plays a critical role in metabolic programming, immune maturation, and neurodevelopment, understanding the factors that modulate its early assembly is essential for promoting long-term health and preventing disease later in life [1].

Maternal influences and prenatal programming

The maternal gut microbiome plays a pivotal role in shaping fetal immune development even before birth. During pregnancy, the maternal microbiota undergoes physiological changes that parallel shifts in immune and metabolic function. Microbial components and metabolites, including short-chain fatty acids (SCFAs), lipopolysaccharides, bacterial DNA, and immune-active peptides, can cross the placental barrier and influence fetal immune programming [4].

Evidence suggests that immune education begins in utero and is partly regulated by maternal microbiota-derived molecules that interact with fetal immune cells, promoting immune tolerance and developmental priming. Although the existence of a true fetal microbiome remains debated, accumulating data support prenatal exposure to microbial products. Moreover, maternal infections – even those occurring prior to conception – may modulate immune outcomes in offspring, highlighting the long-lasting biological consequences of maternal microbial signaling [4].

After birth, breast milk continues this biologically mediated maternal microbial transfer by delivering live bacteria, metabolites, antibodies, and oligosaccharides that shape neonatal microbiota composition and immune maturation. Exclusive breastfeeding should therefore be regarded as a critical extension of maternal influence on early microbial assembly [4, 5].

Mode of delivery and initial colonization

The mode of delivery represents one of the earliest environmental determinants of microbial colonization. Vaginally delivered infants are exposed primarily to maternal vaginal and intestinal microbes, including species from the genera *Lactobacillus*, *Prevotella*, and *Bacteroides*. In contrast, infants born via cesarean section acquire a microbiota dominated by maternal skin and oral bacteria, resulting in delayed colonization by beneficial obligate anaerobes such as *Bacteroides* and *Bifidobacterium* [1].

These early microbial differences are not merely transient but have lasting implications for microbiome stability and immune development. Cesarean-born infants frequently exhibit reduced microbial diversity, delayed establishment of commensal taxa, and increased abundance of opportunistic pathogens such as *Klebsiella* and *Enterococcus* during infancy. Such alterations have been associated with an increased risk of immune dysregulation and metabolic disorders later in life [1].

Infant nutrition and microbial maturation

Among all postnatal influences, infant feeding practices exert the strongest selective pressure on microbiome composition. Breastfed infants typically harbor microbiota enriched in *Bifidobacterium*, *Lactobacillus*, and other species capable of metabolizing human milk oligosaccharides (HMOs) – complex carbohydrates that selectively nourish beneficial microbes [2, 5].

In contrast, formula feeding is associated with greater microbial diversity and accelerated maturation toward an adult-like microbial profile. Although increased diversity is conventionally regarded as beneficial, premature microbial maturation may promote low-grade inflammation and metabolic dysregulation during a critical developmental window [2, 5]. The duration and exclusivity of breastfeeding further shape microbial trajectories in a dose-dependent manner [6]. Discontinuation of breastfeeding induces a marked ecological shift characterized by increased representation of *Firmicutes* and fiber-fermenting taxa typical of the adult microbiome [2, 5].

Beyond taxonomic changes, the functional capacity of the microbiome evolves in parallel. Breastfeeding is associated with enrichment of metabolic pathways involved in carbohydrate utilization, fatty acid synthesis, and vitamin production. In contrast, the microbiota of formula-fed infants is characterized by enhanced bile acid metabolism and amino acid turnover – features indicative of microbial functional maturity [2, 5].

Antibiotic exposure and microbial disruption

Antibiotic administration during early life constitutes one of the most disruptive influences on microbiome development. Exposure is consistently associated with decreased microbial diversity and persistent structural changes in microbial communities. Broad-spectrum antibiotics, particularly macrolides and penicillins, disproportionately deplete beneficial taxa such as *Bifidobacterium* and *Lactobacillus*, thereby compromising SCFA production and immune regulation [7].

Macrolide exposure – especially to azithromycin – has been linked to sustained loss of alpha diversity and depletion of *Akkermansia muciniphila*, a bacterium associated with intestinal barrier integrity and anti-inflammatory effects. Antibiotic treatment is also associated with reductions in regulatory immune-inducing taxa, including *Clostridium* clusters IV and XIVa, which contribute to regulatory T-cell induction [7].

In addition, early antimicrobial exposure promotes the emergence of antimicrobial resistance through selective pressure on microbial populations and perturbation of microbial gene expression. Among neonates treated empirically for suspected early-onset sepsis, alterations in microbiome composition and resistome persistence have been documented months after treatment cessation. Narrow-spectrum regimens, such as penicillin combined with gentamicin, appear to exert fewer ecological effects and are increasingly favored when treatment is unavoidable [8].

Prematurity and hospital-associated colonization

The microbiome development of preterm infants differs fundamentally from that of term neonates. Instead of maternal microbial seeding, premature infants are predominantly colonized by microorganisms originating from the hospital environment, including opportunistic and antibiotic-resistant strains [7].

Distinct fungal colonization patterns also characterize this population, with *Candida* species dominating early development before transitioning toward *Saccharomyces* species following dietary diversification. Gastrointestinal immaturity further compromises microbial establishment. Structural abnormalities – including shortened villi and crypts, decreased mucus and antimicrobial peptide production, increased gut permeability, and impaired motility – foster an intestinal environment unfavorable to obligate anaerobes and susceptible to dysbiosis [7].

Collectively, these vulnerabilities increase the risk of infectious complications, necrotizing enterocolitis, and long-term metabolic and immunological consequences,

underscoring the need for targeted microbial interventions in neonatal care settings [7].

Diet and environmental influences across childhood

Beyond infancy, diet remains a dominant force shaping microbial ecology. Diets high in saturated fat, refined sugar, and animal protein – the so-called Western diet – are associated with reduced microbial diversity and enrichment of taxa linked to obesity, cardiovascular disease, and metabolic syndrome [3].

In contrast, carbohydrate-rich dietary patterns support a *Prevotella*-dominant enterotype associated with improved metabolic functions. Data from the Integrative Human Microbiome Project demonstrate that microbial composition shifts dynamically in disease states such as inflammatory bowel disease and diabetes, emphasizing the central role of nutrition in modulating microbial resilience [3].

Environmental exposures further influence microbial assembly. Children raised in households with siblings or domestic animals exhibit greater microbial diversity, consistent with increased microbial exchange and enhanced immune training through environmental contact [1].

Gut microbiome and childhood diseases

Neurodevelopmental and neurological disorders (ASD and related conditions)

Both the gut microbiome and the central nervous system undergo rapid and dynamic development during early childhood. Accumulating evidence suggests that intestinal microorganisms play a fundamental role in shaping neurodevelopmental trajectories during this critical period [9–13]. Communication between the gut and the brain is mediated by the microbiota–gut–brain axis (MGBA), a bidirectional network integrating neural, immune, endocrine, and metabolic pathways [9, 12].

Several complementary mechanisms are involved in early-life gut–brain signaling. Microbial metabolites – particularly SCFAs and tryptophan-derived compounds – modulate blood–brain barrier integrity, microglial maturation, and neuroinflammatory pathways. These metabolites also influence systemic and intestinal immune tone, including cytokine production and T-cell differentiation, thereby impacting neuroimmune development. Additionally, the vagus nerve and the enteric nervous system transmit neural signals from the gastrointestinal tract to brainstem and cortical regions, enabling rapid bidirectional communication between the gut and the central nervous system [9, 11, 12].

Dysregulation of the MGBA has been implicated in multiple neurodevelopmental, psychiatric, and neurodegenerative disorders. Disruption of gut–brain communication has been associated with mood disorders, Alzheimer's disease, and autism spectrum disorder (ASD) [13]. In children with ASD, recurring alterations in gut microbiota composition include an increased abundance of *Clostridium* species and reduced representation of *Bifidobacterium*. Certain *Clostridium* species are capable of producing neurotoxic and pro-inflammatory metabolites that may enter systemic circulation and influence neurological function. Given the relative instability of the pediatric microbiome, early childhood appears to represent a sensitive window during which microbiota-targeted interventions may exert long-term neurodevelopmental effects [12].

Emerging evidence also links the MGBA to rare pediatric neurological disorders. In pediatric-onset leukodystrophies, microbiome disturbances may contribute to neuroinflammation, immune dysregulation, and altered metabolic signaling, thereby influencing disease progression and neurological outcomes [10]. Similarly, in neonates with necrotizing enterocolitis, disruption of gut–brain communication has been associated with subsequent neurodevelopmental impairment, potentially mediated through inflammatory signaling and altered microbial metabolite profiles [11].

Although much of the mechanistic insight originates from preclinical research, an increasing number of observational studies in pediatric cohorts support a clinically relevant role of the gut microbiome in neurodevelopment. However, further longitudinal and interventional studies are required to determine causality and evaluate the therapeutic potential of microbiome-modifying strategies in pediatric neurological and neurodevelopmental conditions [9–13].

While numerous studies report alterations in gut microbiota composition in children with neurodevelopmental disorders, most human data remain associative. Evidence is largely derived from cross-sectional or case–control studies, whereas causal relationships are primarily supported by preclinical models. Consequently, direct causality between microbiome alterations and neurodevelopmental outcomes in children has not yet been firmly established.

Importantly, findings across studies are not fully consistent. Variability in reported microbial signatures may reflect differences in age at sampling, dietary patterns, gastrointestinal comorbidities, medication use, and analytical methodologies, complicating direct comparison between cohorts.

Key knowledge gaps remain regarding the temporal stability of microbiome alterations, critical developmental windows of vulnerability, and the long-term neurodevelopmental impact of microbiome-targeted interventions in pediatric populations.

Allergic diseases and atopic disorders

Disruption of the gut microbiome is increasingly recognized as a significant contributor to allergic disease development in children [14–16]. Studies in atopic dermatitis (AD) report pronounced differences in gut microbial composition between affected and healthy children, characterized by reduced microbial diversity and shifts in dominant taxa [14]. In many cases, these alterations precede clinical manifestations, suggesting that dysbiosis may contribute to disease initiation rather than arise solely as a consequence of inflammation [14, 15].

The gut and skin microbiota function as interconnected ecosystems that modulate immune responses. Children with AD commonly exhibit reduced levels of *Lactobacillus* and *Bifidobacterium* and increased abundance of *Clostridium* species and *Staphylococcus aureus*. Experimental data support the immunoregulatory role of *Lactobacillus* species in attenuating allergic inflammation [14].

Across pediatric allergic conditions, gut dysbiosis frequently involves an increased Firmicutes-to-Bacteroidetes ratio together with overrepresentation of *Ruminococcus gnavus*. This species has been identified as a major contributor to allergic phenotypes. Disruption of intestinal epithelial integrity associated with dysbiosis facilitates antigen translocation into systemic circulation, promoting abnormal immune activation and increasing allergic susceptibility [16].

Microbial metabolites, particularly SCFAs derived from dietary fiber fermentation, are critical for maintaining epithelial integrity and immune tolerance. Reduced fecal SCFA concentrations have been consistently reported in allergic children, and depletion of microbial genes related to fiber metabolism has been associated with an elevated risk of allergic sensitization [16].

Although most available evidence is associative, experimental studies provide support for causality. Selected members of the *Clostridia* class have been shown to improve gut barrier integrity and reduce allergen sensitivity, while microbiota transfer from healthy infants protects against allergic responses in animal models [16]. In contrast, increased abundance of *Clostridium* species has been reported in pediatric asthma, and early colonization with this genus has been associated with a higher risk of allergic disease development [17].

Most human studies linking gut microbiome alterations to pediatric allergic diseases are observational and therefore demonstrate associations rather than definitive causality. Experimental models provide supportive mechanistic evidence; however, translation of these findings to human pediatric populations remains limited.

Conflicting results have been reported regarding the role of specific taxa, including members of the *Clostridium* genus, which have been associated with both protective and adverse immune effects depending on timing, strain specificity, and host context.

Further research is required to define strain-specific effects, optimal timing for microbial modulation, and the durability of microbiome-related immune programming across childhood.

Obesity and metabolic dysregulation

Growing evidence indicates that the gut microbiome plays a critical role in metabolic regulation, energy homeostasis, and immune function, and that disturbances in microbial composition are strongly associated with the development of childhood obesity [3,18–19]. Experimental studies in animal models provide compelling evidence for causality. Transplantation of fecal microbiota from obese donors into germ-free mice has been shown to induce metabolic traits characteristic of obesity, including increased adiposity and altered energy regulation. Similarly, gut microbiota derived from mice that developed obesity following early antibiotic exposure induced comparable metabolic alterations in recipient germ-free animals. Moreover, microbial communities from obese hosts exhibit enhanced capacity for dietary energy extraction, and transfer of these communities results in increased fat deposition in previously lean recipients [3].

The gut microbiome is also involved in endocrine regulation and metabolic signaling. In children with obesity accompanied by central precocious puberty, gut microbial profiles differ significantly from those of normal-weight peers. These alterations include an increased abundance of *Firmicutes* and a reduction of *Bacteroidetes*, as along with elevated levels of *Alistipes*, *Klebsiella*, and *Sutterella*, and decreased representation of beneficial genera such as *Anaerostipes*, *Bacteroides*, and *Bifidobacterium*. Such compositional changes have been linked to disruptions in inositol metabolism and SCFA production, contributing to impaired metabolic regulation and excess adiposity [19].

The microbiome further influences neuroendocrine regulation through its interaction with metabolic pathways. SCFAs produced by bacterial taxa such as *Ruminococcus* and *Roseburia* modulate leptin gene expression via activation of free fatty acid receptors, thereby affecting hypothalamic signaling and pubertal timing. Notably, microbial profiles in girls with coexisting obesity and precocious puberty differ from those observed in children with either condition alone, suggesting a distinct microbial pattern associated with combined pathology [19].

Emerging evidence suggests that gut microbiota dysregulation may represent a biological link between obesity and asthma. Children with obesity-related asthma exhibit heightened immune dysregulation and persistent low-grade inflammation, and both clinical and experimental studies have reported microbial disturbances in individuals affected by both conditions. However, disease-specific microbial signatures remain insufficiently characterized, and further clinical research is required to define precise associations [18].

Evidence for a causal role of the gut microbiome in obesity is strong in experimental animal models; however, pediatric human studies remain predominantly associative. Although consistent microbial patterns have been described in children with obesity, causality cannot be inferred due to the observational nature of most available data.

Reported microbial signatures in pediatric obesity vary substantially across studies, likely reflecting differences in age, pubertal status, diet, ethnicity, and methodological approaches, underscoring the heterogeneity of obesity-associated microbiome profiles.

Major knowledge gaps include the identification of disease-specific microbial signatures, clarification of bidirectional host–microbiome interactions, and determination of whether microbiome modulation can sustainably influence metabolic outcomes in children.

Autoimmune diseases (T1D, celiac disease)

Type 1 diabetes (T1D) results from complex interactions between genetic predisposition and environmental factors, with the gut microbiome increasingly recognized as a major contributor to disease pathogenesis. Significant alterations in microbial composition and function have been observed in association with islet autoimmunity and progression to clinical disease [20].

Reported microbial changes include reduced SCFA production, altered bile acid and tryptophan metabolism, and increased intestinal permeability, collectively promoting immune dysregulation. Functional remodeling of the microbiome during disease progression is further characterized by decreased bile acid metabolism and increased biosynthesis of inflammatory components such as lipopolysaccharides [20].

Defects in intestinal barrier proteins and alterations in exocrine pancreatic function have been identified in both individuals with T1D and in genetically predisposed children prior to disease onset, suggesting that intestinal dysfunction may precede autoimmune processes. Moreover, gut microbiome structure has been associated with glycemic control, disease duration, and vascular complications, indicating that microbial variability contributes to interindividual differences in clinical outcomes [20].

Gastrointestinal disorders (IBD, functional constipation)

Inflammatory bowel disease

The gut microbiome is a central factor in the pathogenesis of inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis [13, 21, 22]. Pediatric IBD is characterized by reduced microbial diversity, decreased *Firmicutes*, and increased *Enterobacteriaceae* [21, 22].

Loss of beneficial taxa, including *Faecalibacterium prausnitzii* and *Bifidobacterium*, is frequently observed, while pro-inflammatory bacteria including *Escherichia coli* are enriched. Microbiome composition varies with disease severity, with microbial profiles during remission more closely resembling those of healthy controls compared to those seen during active disease [21, 22].

Ruminococcus gnavus has been linked to severe disease phenotypes and increased inflammatory activity. Mechanistic evidence suggests that this organism promotes inflammation through TLR4-mediated induction of tumor necrosis factor-α (TNF-α) [21]. Although establishing causality remains challenging, family and twin studies suggest that microbial profiles correlate more strongly with disease state than with shared genetic background. Inflammation itself may also perpetuate dysbiosis by altering the intestinal metabolic environment [22].

Functional constipation

In functional constipation (FC), accumulating evidence suggests that gut microbiota dysregulation contributes to altered intestinal motility [23, 24]. SCFAs, particularly butyrate, have been proposed as modulators of bowel motility, although findings remain inconsistent and causality has not been established [23].

Comparative studies have demonstrated significant microbial differences between children with FC and healthy controls, including reduced *Firmicutes* and increased abundance of *Actinobacteria* and *Bifidobacterium* in specific subgroups [24]. Although mechanistic pathways remain incompletely defined, these findings support a contributory role of dysbiosis in pediatric FC [23, 24].

Potential use of probiotics in pediatric disease management

Interest in probiotics has expanded substantially in recent years, coinciding with increased recognition of the gut microbiome as an active regulator of immune, metabolic, and neurodevelopmental processes in children. Although probiotics are often discussed as a heterogeneous group, clinical effects appear to be strain-specific, not class-wide. The most consistent evidence in pediatric populations has been reported for selected strains, particularly *Lactobacillus rhamnosus* GG, *Bifidobacterium infantis*, *Bifidobacterium breve*, and *Saccharomyces boulardii*. In contrast, results for other strains and multi-strain formulations remain variable, underscoring the importance of strain-level characterization when interpreting clinical outcomes [12–24].

Currently, the strongest clinical evidence supports probiotic use in the prevention and management of acute infectious diarrhea, antibiotic-associated diarrhea, and necrotizing enterocolitis in preterm infants. For other indications, including allergic diseases, obesity, autoimmune disorders, and neurodevelopmental conditions, available data remain limited and largely heterogeneous, with inconsistent clinical endpoints and modest effect sizes.

One of the most consistently reported effects of probiotics is the stabilization of intestinal epithelial integrity. Selected strains of *Bifidobacterium*, *Lactobacillus*, and specific members of the *Clostridia* class have been shown to strengthen tight junctions and reduce gut permeability, thereby limiting the systemic translocation of microbial products and dietary antigens. Preservation of mucosal barrier function is particularly relevant in conditions characterized by chronic inflammation or immune dysregulation, such as allergic diseases, type 1 diabetes, and inflammatory bowel disease (IBD) [16, 20, 21, 23].

In addition to their barrier-related effects, probiotics exert immunomodulatory activity by influencing cytokine production, promoting regulatory T-cell differentiation, and attenuating pro-inflammatory pathways. Bacterial metabolites, most notably SCFAs such as butyrate, contribute to immune tolerance and epithelial health. Impairment in microbial metabolic activity has been reported across several pediatric disease states, including obesity, allergic disorders, and autoimmune diseases, indicating that functional restoration of the microbiome may represent a therapeutically relevant target [16,18–22].

Neurodevelopmental and neurological disorders

The microbiota–gut–brain axis provides a mechanistic framework through which probiotics may influence neurodevelopmental outcomes. Microbial metabolites regulate neuroimmune crosstalk, blood–brain barrier integrity, and microglial maturation during critical windows of early development. Altered abundance of *Clostridium* and *Bifidobacterium* species has been reported in children with autism spectrum disorder and related neuropsychiatric conditions, supporting the hypothesis that targeted modulation of microbial composition may influence neurological function [9–13].

Allergic and immune-mediated diseases

In pediatric allergic disease, probiotics are being investigated for their capacity to support immune maturation and promote oral tolerance. Reduced levels of *Bifidobacterium* and selected *Clostridia* have been associated with amplified allergic inflammation, whereas restoration of these taxa is linked to improved immune regulation [14–16]. Experimental studies further indicate that early-life microbial modulation may influence long-term susceptibility to allergic disease through immune-programming mechanisms [16].

Obesity and metabolic regulation

Potential metabolic effects of probiotics include modulation of energy extraction from the diet, regulation of lipid metabolism, and interaction with endocrine pathways. Gut microbial activity influences leptin signaling and SCFA production, both of which contribute to adiposity regulation and pubertal timing. Distinct microbial patterns observed in children with coexisting obesity and precocious puberty suggest that microbiota composition may contribute to metabolic heterogeneity within pediatric obesity and may inform individualized therapeutic approaches [18, 19].

Autoimmune diseases

In autoimmune conditions such as type 1 diabetes and pediatric IBD, probiotics may support restoration of disease-associated dysbiosis by enhancing colonization resistance and modulating inflammatory cascades. Alterations in bile acid metabolism, increased lipopolysaccharide production, and disruption of epithelial defenses have been reported in both disorders, reinforcing the concept that microbial intervention may help re-establish intestinal homeostasis and immune balance [20–22].

Functional gastrointestinal disorders

In functional gastrointestinal disorders, including pediatric functional constipation, modulation of the gut microbiota may influence motility patterns through fermentation processes and SCFA production. Distinct microbial signatures have been identified in constipated children compared with healthy controls, providing further rationale for microbiota-oriented therapeutic strategies in this population [23, 24].

Interpretation of probiotic efficacy in pediatric populations is complicated by substantial heterogeneity across studies. Variability in probiotic strains, dosing regimens, treatment duration, age at intervention, and clinical outcome measures limits comparability between trials. In addition, many studies involve small sample sizes, short follow-up periods, and lack mechanistic validation, collectively reducing the strength of clinical inference.

Translation of probiotic research into routine pediatric practice remains challenging. The absence of standardized formulations, limited regulatory oversight, and inconsistent reporting of strain-specific effects hinder clinical decision-making. Furthermore, interindividual variability in baseline microbiome composition may influence therapeutic response, suggesting that a uniform probiotic approach may not be universally effective. As a result, despite promising experimental and clinical findings, evidence-based implementation of probiotics in pediatric care remains limited.

Conclusion

The pediatric gut microbiome plays an essential role in shaping metabolic, immune, and neurodevelopmental outcomes from infancy through adolescence. Accumulating evidence indicates that disruptions in microbial maturation are associated with a broad spectrum of childhood diseases, including obesity, allergic disorders, autoimmune conditions, neurodevelopmental abnormalities, and gastrointestinal pathologies.

Environmental exposures, maternal health, mode of delivery, feeding practices, antibiotic use, and dietary patterns collectively influence microbial assembly during critical developmental windows. When these processes are perturbed, long-term consequences for immune balance, metabolic regulation, and neurological development may arise.

Probiotics represent a promising tool for microbiome modulation in pediatric populations, with potential applications across multiple disease categories. Their effects include enhancement of epithelial barrier integrity, immune regulation, and restoration of microbial metabolic capacity. However, current evidence is limited by heterogeneity in probiotic strains, dosing regimens, and clinical outcome measures.

Future research should prioritize well-designed randomized controlled trials, longitudinal cohort studies, and mechanistic investigations to establish causality and define optimal intervention strategies. A deeper understanding of strain-specific effects and developmental timing will be necessary to translate microbiome science into evidence-based pediatric therapies.

References

1. Ronan V, Yeasin R, Claud EC. Childhood development and the microbiome: the intestinal microbiota in maintenance of health and development of disease during childhood. Gastroenterology, 2021; 160(2): 495–506. doi: 10.1053/j.gastro.2020.08.065
2. Catassi G, Aloi M, Giorgio V, et al. Role of diet and nutritional interventions in shaping the infant gut microbiome. Nutrients, 2024; 16(3): 400. doi: 10.3390/nu16030400

3. Akagbosu CO, Nadler EP, Levy S, Hourigan SK. The role of the gut microbiome in pediatric obesity and bariatric surgery. Int J Mol Sci, 2022; 23(23): 15421. doi: 10.3390/ijms232315421
4. Ianiro G, Tilg H, Gasbarrini A, Cammarota G. Maternal gut microbiome in pregnancy: implications for immune development. Nat Rev Gastroenterol Hepatol, 2023; 20(2): 77–94. doi: 10.1038/s41575-023-00864-2
5. Donovan SM, Wang M, Li M, et al. Gut microbiome and breastfeeding: implications for immune development. J Allergy Clin Immunol, 2022; 150(3): 523–534. doi: 10.1016/j.jaci.2022.07.014
6. McDonnell L, Gilkes A, Ashworth M, et al. Association between antibiotics and gut microbiome dysbiosis in children: systematic review and meta-analysis. Gut Microbes, 2021; 13(1): 1–18. doi: 10.1080/19490976.2020.1870402
7. Sarafidis K, Pateras K, Kampouri M, et al. Probiotics and the gut microbiome in preterm infants. Gut Microbes, 2023; 15(1): 2201160. doi: 10.1080/19490976.2023.2201160
8. Reyman M, van Houten MA, Watson RL, et al. Effects of early-life antibiotics on the developing infant gut microbiome and resistome: a randomized trial. Nat Commun, 2022; 13(1): 893. doi: 10.1038/s41467-022-28525-z
9. Wang Q, Yang Q, Liu X. Microbiota–gut–brain axis and neurodevelopmental disorders. Proc Nutr Soc, 2023; 82(Suppl 1): E284. doi: 10.1093/procel/pwad026
10. Vaia Y, Bruschi F, Tagi VM, et al. Microbiota gut-brain axis: implications for pediatric-onset leukodystrophies. Front Nutr, 2024; 11: 1417981. doi: 10.3389/fnut.2024.1417981
11. Wang Y, Hang C, Hu J, et al. Role of gut–brain axis in necrotizing enterocolitis-related neurodevelopmental impairment. Front Neurosci, 2023; 17: 1059552. doi: 10.3389/fnins.2023.1059552
12. Romano K, Shah AN, Schumacher A, et al. The gut microbiome in children with mood, anxiety, and neurodevelopmental disorders: an umbrella review. Gut Microbiome (Camb), 2023; 4: e18. doi: 10.1017/gmb.2023.16
13. Person H, Keefer L. Psychological comorbidity in gastrointestinal disease: update on the brain–gut–microbiome axis. Prog Neuropsychopharmacol Biol Psychiatry, 2020; 110: 110209. doi: 10.1016/j.pnpbp.2020.110209
14. Liu Y, Du X, Zhai S, et al. Gut microbiota and atopic dermatitis in children. BMC Pediatr, 2022; 22: 323. doi: 10.1186/s12887-022-03390-3
15. Akagawa S, Kaneko K. Gut microbiota and allergic diseases in children. Allergol Int, 2022; 71(3): 301–309. doi: 10.1016/j.alit.2022.02.004
16. De Filippis F, Paparo L, Nocerino R, et al. Specific gut microbiome signatures and the associated pro-inflammatory functions are linked to pediatric allergy and acquisition of immune tolerance. Nat Commun, 2021; 12: 5958. doi: 10.1038/s41467-021-26266-z
17. Al-Mutairi AM, Alharbi AS, Aljohani AS, et al. Paediatric asthma and the microbiome: systematic review. Microorganisms, 2023; 11(4): 939. doi: 10.3390/microorganisms11040939
18. Hu M, Zhao X, Liu Y, et al. Gut microbiota in childhood obesity and asthma. Front Microbiol, 2023; 14: 1264356. doi: 10.3389/fmicb.2023.1264356
19. Wang LY, Qin X, Liu H, et al. Gut microbiota in childhood obesity and precocious puberty. BMC Microbiol, 2024; 24: 461. doi: 10.1186/s12866-024-03461-8
20. Blok L, Hanssen N, Nieuwdorp M, Rampanelli E. Gut microbiome in type 1 diabetes: microbiota–metabolite interactions. Metabolites, 2024; 14(2): 138. doi: 10.3390/metabo14020138
21. Fitzgerald RS, Sanderson IR, Claesson MJ. Pediatric inflammatory bowel disease and its relationship with the microbiome. Microb Ecol, 2021; 82(4): 833–844. doi: 10.1007/s00248-021-01697-9
22. Jauregui-Amezaga A, Smet A. Microbiome in inflammatory bowel disease. J Clin Med, 2024; 13(16): 4622. doi: 10.3390/jcm13164622
23. Avelar Rodriguez D, Popov J, Ratcliffe EM, Toro Monjaraz EM. Functional constipation in children and gut microbiome. Front Pediatr, 2020; 8: 595531. doi: 10.3389/fped.2020.595531
24. Zhao H, Lu X, Ye Y, et al. Dysbiosis of gut microbiota in children with functional constipation and damp-heat constitution: a cross-sectional multi-omics analysis. Sci Rep, 2025; 15: 42256. doi: 10.1038/s41598-025-26439-6

ORIGINAL ARTICLE

THE QUALITY OF LIFE WITH OBESITY (QUOLO) QUESTIONNAIRE – A VALIDATION STUDY

Kwestionariusz jakości życia pacjentów leczonych z powodu otyłości „QUOLO" – badanie walidacyjne

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Abstract

Introduction and objective: As the prevalence of obesity continues to rise, understanding its impact on quality of life has become increasingly important for healthcare providers and researchers. The aim of the study was to validate the Quality of Life with Obesity (QUOLO) questionnaire, a tool designed to assess quality of life among individuals with obesity. **Material and methods:** The QUOLO questionnaire is a comprehensive health and wellness survey with a total of 67 questions covering demographics, health conditions, psychological well-being, and social factors. This cross-sectional study included 117 participants. **Results:** The study revealed several unexpected patterns, with underweight individuals reporting slightly higher quality-of-life scores and obese individuals showing lower general health scores but similar overall quality of life. Higher BMI was associated with lower levels of shame and reduced fear of social contact. Male participants reported higher levels of psychological distress across multiple domains compared with females, which diverges from typical population patterns. **Conclusions:** The absence of strong associations between BMI and quality of life in this sample suggests that body weight may not be as deterministic of subjective well-being as commonly assumed.

Streszczenie

Wprowadzenie i cel: W obliczu światowej epidemii otyłości zrozumienie jej wpływu na jakość życia staje się coraz ważniejsze dla pracowników ochrony zdrowia oraz badaczy zajmujących się leczeniem pacjentów z nadmierną masą ciała. Celem badania była walidacja kwestionariusza Quality of Life with Obesity (QUOLO) służącego do oceny jakości życia osób z otyłością. **Materiał i metody:** Kwestionariusz jakości życia pacjentów leczonych z powodu otyłości (QUOLO) to kompleksowa ankieta zawierająca 67 pytań dotyczących demografii, stanu zdrowia, dobrostanu psychicznego i czynników społecznych. Badanie ma charakter przekrojowy, objęło 117 uczestników. **Wyniki:** W badaniu zaobserwowano kilka nieoczywistych zależności. Pacjenci z niedowagą uzyskali wyższe wyniki świadczące o jakości życia i ogólnym stanie zdrowia niż pacjenci z nadmierną masą ciała. Osoby z wyższym wskaźnikiem masy ciała zgłaszały niższy poziom poczucia wstydu i mniejsze obawy przed kontaktami społecznymi. Mężczyźni wykazywali wyższy poziom stresu psychicznego w wielu obszarach w porównaniu z kobietami, co odbiega od typowych wzorców populacyjnych. **Wnioski:** Brak silnych zależności między wskaźnikiem masy ciała a jakością życia w badanej grupie sugeruje, że masa ciała może nie być tak istotnym czynnikiem determinującym subiektywny dobrostan, jak powszechnie się przypuszcza.

Keywords: quality of life; obesity; validation; self-worth; life satisfaction

Słowa kluczowe: jakość życia; otyłość; walidacja; poczucie własnej wartości; satysfakcja z życia

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Introduction

Obesity is recognized as one of the major public health challenges of the 21st century, affecting millions of individuals worldwide. It is not merely a physiological condition characterized by excessive body fat but a complex state with far-reaching implications for mental, emotional, and social well-being [1]. As the prevalence of obesity continues to rise, understanding its impact on quality of life (QoL) has become increasingly vital for healthcare providers, researchers, and policymakers [2, 3].

The experience of living with obesity often leads to a range of psychological challenges, including depression, anxiety, and low self-esteem [4, 5]. These mental health issues frequently stem from societal stigma and discrimination, which can result in social withdrawal and diminished life satisfaction. Many individuals with obesity struggle with self-acceptance in the context of prevailing beauty standards and pressure to conform to idealized body images. This relentless pressure may exacerbate feelings of inadequacy and unworthiness, which are detrimental to mental health [6]. Consequently, the negative psychological outcomes associated with obesity require thorough assessment and targeted intervention.

The social aspects of living with obesity are equally significant [7]. Social interactions may become increasingly complex as individuals navigate a world that often marginalizes larger bodies. Experiences of bullying, social exclusion, and difficulties in forming intimate relationships are commonly reported [8]. Such social barriers can hinder personal development and contribute to diminished QoL [9]. Understanding the intricate relationship between obesity and social dynamics is critical for fostering inclusive environments that support individuals in their journey towards improved health and self-acceptance [10].

In light of these multifaceted challenges, the need for reliable measurement tools is paramount. The Quality of Life with Obesity (QUOLO) questionnaire has been designed to capture the unique experiences of individuals living with obesity, encompassing psychological, social, and self-acceptance dimensions. By providing a comprehensive assessment of QoL specific to this population, QUOLO aims to identify areas where individuals may need the most support and intervention. Psychometric validation of the questionnaire is essential to ensure its utility and reliability, enabling clinicians and researchers to gauge the impact of obesity on QoL effectively.

This manuscript presents a validation study of the QUOLO questionnaire, detailing its development, psychometric evaluation, and relevance for understanding the complex relationship between obesity, mental health, social functioning, and self-acceptance. Establishing QUOLO as a robust tool for assessment may enhance the ability of healthcare providers to address the holistic needs of individuals with obesity, contributing to improved health outcomes and quality of life. This research aims to contribute to a deeper understanding of how obesity influences daily life experiences and to promote resources that empower individuals on their path to self-acceptance and well-being.

Material and methods

The Quality of Life with Obesity (QUOLO) is an original questionnaire created by the authors of the study. It is a comprehensive health and quality-of-life instrument developed to evaluate the quality of life of patients before and after bariatric surgery. The survey is focused on understanding how weight and health conditions impact various aspects of life, from psychological well-being to social functioning and healthcare experiences.

Before presenting the survey to the target group, a short validation study was conducted among medical students training to become physicians. It was distributed online to third and fourthyear students of the medical faculty, yielding 117 completed responses (response rate: 85%). Respondents were also asked to provide any remarks regarding the construction of the survey that that could ameliorate its quality. The survey was available online for two months for participants who received the link (March and April 2025). Approval from the Bioethics Committee of the Military Institute of Warsaw was obtained (code KB/12/24).

The QUOLO questionnaire is a comprehensive health and wellness survey with a total of 67 questions covering demographics, health conditions, psychological well-being, and social factors.

QUOLO questions include:

- Demographics (gender, age, education, employment, living situation)
- Health status (weight, height, medical conditions, medications)
- Quality-of-life measures (general health, physical fitness, self-worth)
- Psychological symptoms (sadness, mood swings, anxiety, concentration issues)
- Social impact (work difficulties, social interactions, body image)
- Physical limitations (daily activities, mobility, exercise)
- Physical symptoms (pain, breathing issues, sleep problems)
- Healthcare experiences (treatment by medical staff)

Statistical analysis

Statistical analysis was performed with Julius.ai.

All statistical analyses were conducted using Python (version 3.x) with the pandas, numpy, and scipy libraries. The dataset consisted of survey responses from 117 participants who completed a comprehensive health and quality-of-life questionnaire.

Continuous variables, including body mass index (BMI), were calculated from self-reported height and weight. BMI categories were defined according to WHO standards: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). Quality-of-life and mental-health measures were assessed on 5-point Likert scales and converted to numeric values for analysis.

Descriptive statistics, including means, standard deviations, and frequencies, were calculated for all variables.

Pearson correlation coefficients were computed to examine linear relationships between BMI and mental-health measures. Correlation strengths were interpreted according to Cohen's conventions: small (r = 0.10), medium (r = 0.30), and large (r = 0.50) effect sizes. All statistical tests were performed with a significance level of p = 0.05.

Results

The BMI data show a healthy distribution, with a mean of 22.6 (±4.0), which falls within the normal range (range: 16.4–36.6). The majority of participants (n = 78) were in the normal BMI category. The distribution of BMI in the study group is presented in Table 1.

The analysis revealed no significant correlations between BMI and any of the quality-of-life measures. Correlation results are presented in Table 2.

ANOVA analyses showed no significant differences between BMI categories for any quality-of-life measure. However, the data indicate some counterintuitive patterns, with underweight individuals reporting slightly higher quality-of-life scores and obese individuals showing lower general health scores but similar overall quality of life. The relationship between QoL scores and BMI is presented in Figure 1.

The analysis also revealed several patterns between BMI and mental-health symptoms. Interestingly, BMI showed no significant correlations with general quality-of-life measures such as overall life satisfaction, health, physical fitness, or self-worth.

Positive correlations suggest that higher BMI is associated with more frequent mental-health symptoms, while the negative correlations for shame and social contact anxiety are counterintuitive, indicating that individuals with higher BMI reported lower levels of shame. Feelings of shame showed the strongest relationship with BMI, with higher BMI associated with lower shame scores. Mood swings (r = 0.190) and concentration problems (r = 0.185) showed moderate positive correlations with BMI. The need to cry (r = 0.161) also demonstrated a positive relationship with BMI. Correlations between BMI and mental-health measures are presented in Figure 2.

Table 1. Distribution of BMI

BMI	*n*
Obesity	6
Overweight	27
Normal	78
Underweight	11

Table 2. Correlation with BMI results

Overall quality of life	r = 0.021, p = 0.827
General health	r = −0.050, p = 0.594
Physical fitness	r = −0.046, p = 0.622
Self-worth	r = −0.074, p = 0.434

The analysis of the results reveals that individuals with higher BMI reported less shame (r = −0.293, p = 0.001) – a moderate negative correlation, and less fear of social contact (r = −0.206, p = 0.027) – a weak but significant negative correlation (Fig. 3).

The sample included 85 female (72.6%) and 32 male (27.4%) respondents. The data acquired in the survey show that males reported higher levels of psychological distress across multiple domains compared with females, which contrasts with typical population patterns. This may be specific to this sample or the particular measures being validated.

Overall quality-of-life scores were very similar between genders, with no significant differences. The analysis revealed several statistically significant differences in psychological symptoms. Males reported significantly higher scores for the need to cry (p <0.001), mood swings (p <0.001), and concentration problems (p = 0.026). Male participants also presented higher levels of health anxiety (p = 0.001), general anxiety (p = 0.001), and shame (p = 0.043) than female participants.

Discussion

This cross-sectional study of 117 Polish adults examined the relationships between body mass index (BMI) and various dimensions of quality of life and mental health. The findings reveal a complex pattern of associations that challenges conventional assumptions about weight and psychological well-being. Contrary to expectations, no significant correlations were observed between BMI and core quality-of-life measures, including overall quality of life, general health perceptions, physical fitness, or self-worth (all r <0.15, p >0.05).

The mental-health analysis yielded particularly noteworthy results, with the most prominent finding being a negative correlation between BMI and feelings of shame (r = −0.293), suggesting that individuals with higher BMI reported lower levels of shame. This counterintuitive pattern may reflect cultural factors, adaptive coping mechanisms, or body-acceptance attitudes within this population. Modest positive correlations were observed between BMI and mood swings (r = 0.190), concentration problems (r = 0.185), and emotional lability (r = 0.161), suggesting some association between higher weight and specific psychological symptoms.

This Polish survey results challenge common stereotypes about weight and psychological well-being. Rather than showing the expected positive correlation between BMI and psychological distress, the data suggest that individuals with higher BMI in this sample reported lower levels of shame and less social anxiety. This may indicate resilience, acceptance, or cultural factors specific to this population. The most striking finding is that higher BMI is significantly associated with lower levels of shame and social anxiety, which is counterintuitive to common assumptions. The finding related to shame is particularly interesting, as it contradicts common assumptions about weight and self-perception.

In this Polish validation sample, body weight is not a major determinant of perceived quality of life, which contrasts

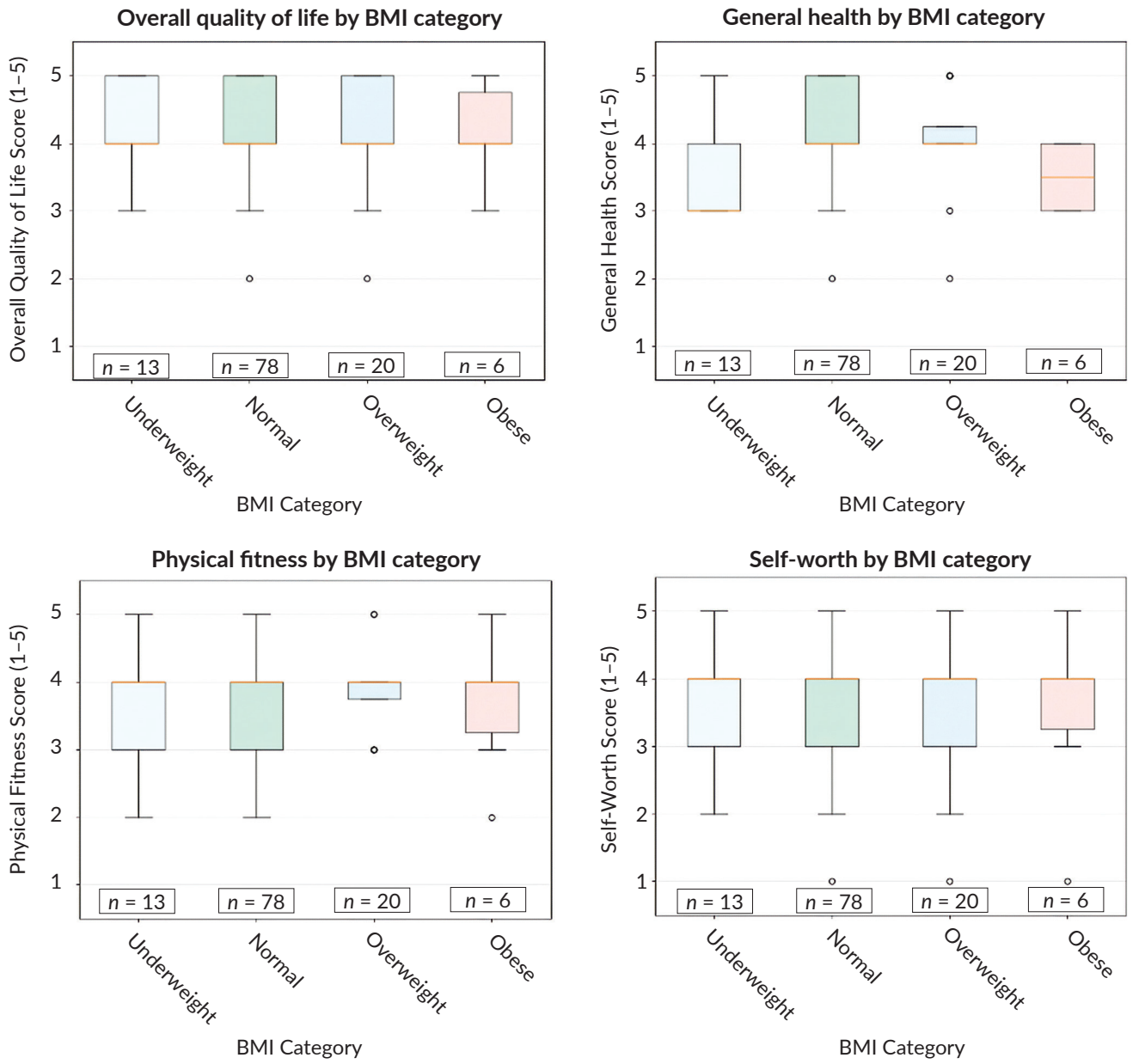

Figure 1. Quality-of-life scores by BMI category

with some population studies but may reflect characteristics specific to this validation cohort. The analysis suggests that while there are some relationships between BMI and mental-health symptoms, they are complex and not uniformly aligned with expected patterns. The negative correlation with shame might indicate resilience or different cultural attitudes toward body weight within this population.

The study also showed unexpected results regarding psychological distress and heath anxiety, with higher levels presented by male participants. This contrasts with typical population assumptions that females are more emotionally affected by life stressors.

Participants in the validation survey were asked for comments on the structure and questions included. The feedback provided a comprehensive critique of a survey focused on health and lifestyle. Respondents expressed a need for options indicating uncertainty about their health status, as well as clearer differentiation in physical-activity levels and tolerances, highlighting that perceived effort can vary significantly across activities. Suggestions were also made to incorporate combinations of work and study, alongside an option of "not applicable" for items related to hospitalization or work status. Some of the participants emphasized the importance of adding questions about headaches, comorbid conditions related to obesity, and the quality of medical care, particularly regarding treatment attitudes and support for patients. Following these suggestions, the structure of the survey will be revised to improve its quality and create a more nuanced and inclusive approach in survey design to capture a diverse range of experiences and perspectives.

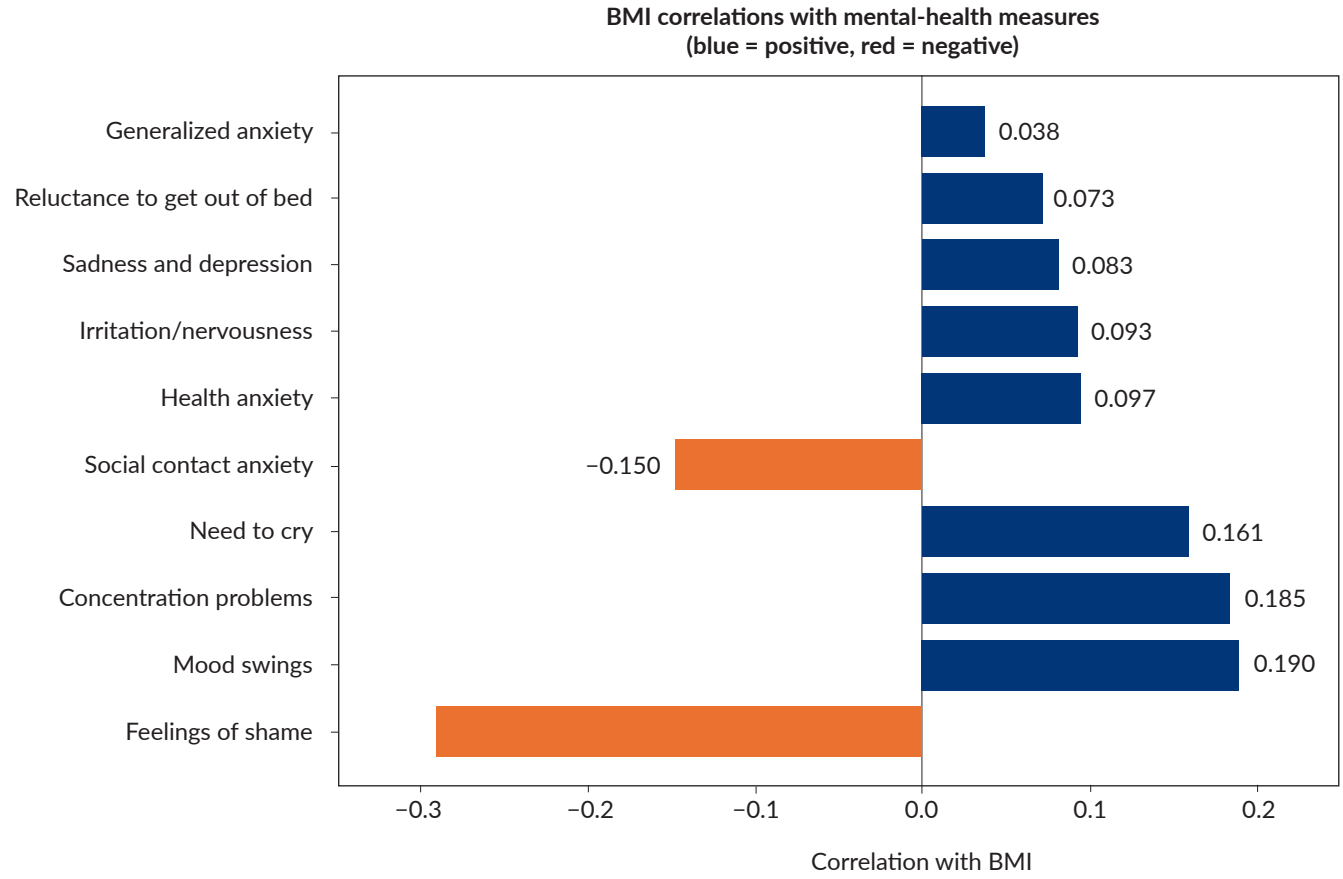

Figure 2. BMI correlations with mental-health measures

These findings represent a notable departure from established literature on BMI and psychological well-being. Previous research has consistently demonstrated positive associations between higher BMI and increased psychological distress, with meta-analyses reporting significant correlations between obesity and depression (r = 0.15–0.25) and anxiety disorders [11, 12]. However, this study of Polish adults revealed markedly different patterns, particularly the unexpected negative correlation between BMI and feelings of shame (r = −0.293), which contradicts findings from Western populations where weight stigma and shame typically increase with BMI [13, 14].

The absence of significant correlations between BMI and quality-of-life measures in this sample contrasts sharply with large-scale studies such as the Nurses' Health Study and the Health Professionals Follow-up Study, which demonstrated clear inverse relationships between BMI and health-related quality-of-life scores. Similarly, the modest correlations with mood symptoms (r = 0.19 for mood swings) are considerably weaker than those reported in longitudinal cohort studies, where obesity has been associated with a 25–55% increased risk of developing depression [12].

These discrepancies may reflect important cultural and contextual factors [15–17]. Research in Eastern European populations has suggested different body-image ideals and weight-related attitudes compared with Western societies [17]. Additionally, the Polish cultural context may include protective factors such as stronger family support systems or different social norms regarding body acceptance that buffer against weight-related psychological distress [18]. The negative shame correlation in particular warrants consideration of cultural adaptation theories, which propose that individuals in certain cultural contexts develop resilience mechanisms against weight stigma [19, 20].

Alternatively, these findings may reflect methodological differences, including the cross-sectional design, reliance on self-reported measures, or sample characteristics that differ from previous studies. The relatively small sample size (n = 117) may also limit the ability to detect weaker associations identified in larger epidemiological studies.

Limitations of the study

The number of participants was small, and the sample consisted primarily of young adults, the majority of whom did not have obesity. Most participants (78/115) had normal BMI, which may limit the power to detect differences. Therefore, conclusions from this survey validation study cannot be extrapolated to clinical populations with obesity.

Conclusions

The analysis included 117 participants and shows that BMI alone is not a strong predictor of overall quality-of-

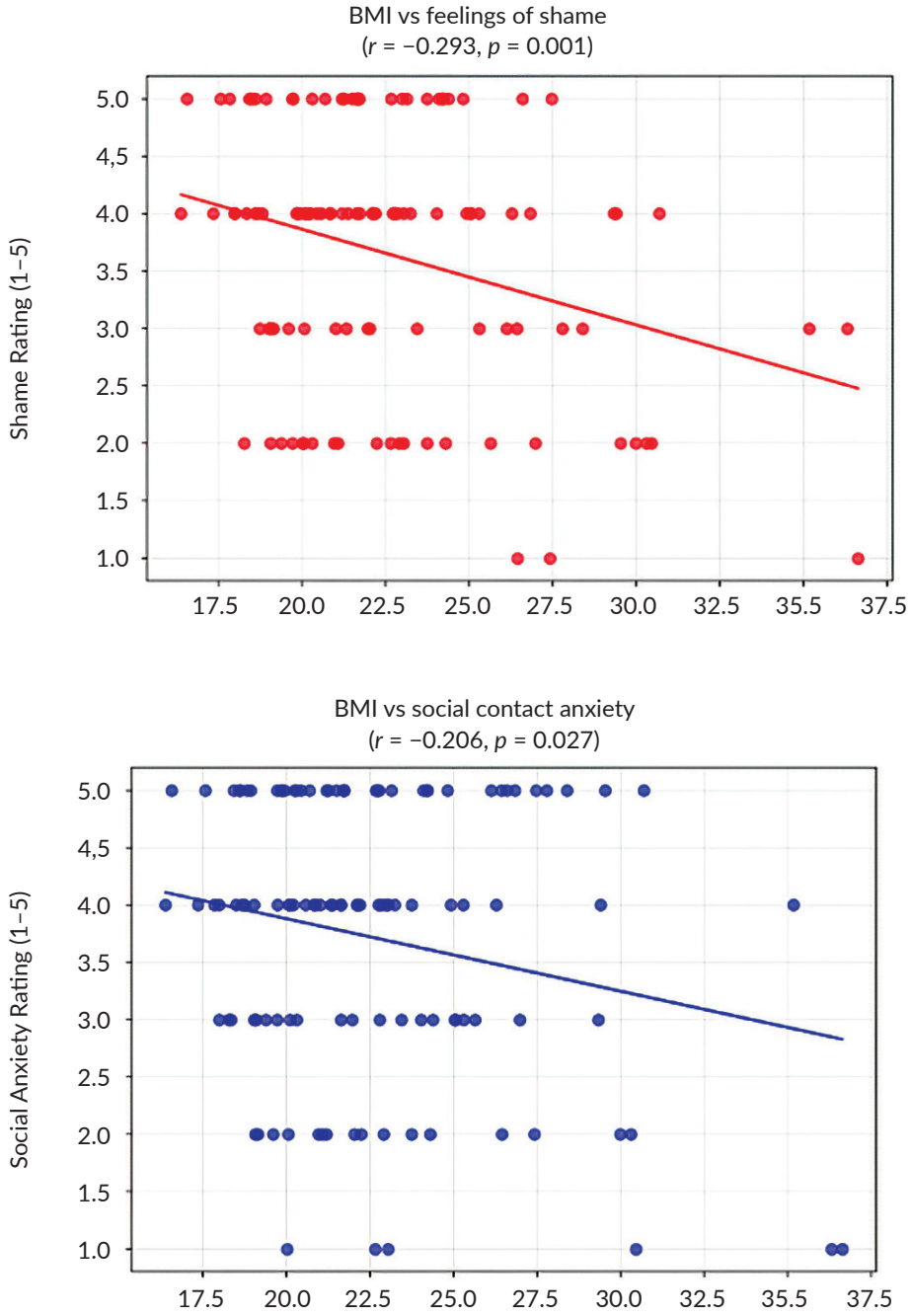

Figure 3. Significant BMI-psychological symptom correlations

life measures in this sample. However, because the validation group included mostly participants without increased BMI, statistically robust conclusions will require studies conducted in larger groups of patients with obesity.

The absence of strong BMI-quality of life relationships in this sample suggests that body weight may not be as deterministic of subjective well-being as commonly assumed. These findings have important implications for healthcare approaches to weight management, emphasizing the need for individualized, culturally sensitive interventions that consider the complex interplay between physical and psychological factors. The unexpected negative correlation with shame warrants further investigation in larger, longitudinal studies to better understand mechanisms underlying weight-related psychological adaptation.

Future research should explore mediating factors such as social support, cultural attitudes toward body image, and coping strategies that may influence the BMI-mental health relationship. Additionally, longitudinal designs would help establish temporal relationships and identify potential causal pathways between weight status and psychological outcomes.

References

1. Vallis M. Quality of life and psychological well-being in obesity management: improving the odds of success by managing distress. Int J Clin Pract, 2016; 70(3): 196–205. doi: 10.1111/ijcp.12765
2. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism, 2022; 133: 155217. doi: 10.1016/j.metabol.2022.155217
3. Mejaddam A, Krantz E, Höskuldsdóttir G, et al. Comorbidity and quality of life in obesity – a comparative study with the general population in Gothenburg, Sweden. PLoS One, 2022; 17(10): e0273553. doi: 10.1371/journal.pone.0273553
4. Barber TM, Kabisch S, Pfeiffer AFH, Weickert MO. Dietary and lifestyle strategies for obesity. Nutrients, 2024; 16(16): 2714. doi: 10.3390/nu16162714
5. Robinson E, Haynes A, Sutin A, Daly M. Self-perception of overweight and obesity: A review of mental and physical health outcomes. Obes Sci Pract, 2020; 6: 552–561. doi: 10.1002/osp4.424
6. Rozjabek H, Fastenau J, LaPrade A, Sternbach N. Adult obesity and health-related quality of life, patient activation, work productivity, and weight loss behaviors in the United States. Diabetes Metab Syndr Obes, 2020; 13: 2049–2055. doi: 10.2147/DMSO.S245486
7. Hemmingsson E. Early childhood obesity risk factors: socioeconomic adversity, family dysfunction, offspring distress, and junk food self-medication. Curr Obes Rep, 2018; 7(2): 204–209. doi: 10.1007/s13679-018-0310-2
8. Steptoe A, Frank P. Obesity and psychological distress. Philos Trans R Soc Lond B Biol Sci, 2023; 378(1888): 20220225. doi: 10.1098/rstb.2022.0225
9. Okolo D, Akpanumo B, Okeke CH, et al. The influence of obesity on quality of life: a systematic review. J Adv Med Med Res, 2024; 36(11): 267–279. doi: 10.9734/jammr/2024/v36i115637
10. Stephenson J, Smith CM, Kearns B, et al. The association between obesity and quality of life: a retrospective analysis of a large-scale population-based cohort study. BMC Public Health, 2021; 21(1): 1990. doi: 10.1186/s12889-021-12009-8
11. DeJesus RS, Breitkopf CR, Ebbert JO, et al. Associations between anxiety disorder diagnoses and body mass index differ by age, sex and race: a population based study. Clin Pract Epidemiol Ment Health, 2016; 12: 67–74. doi: 10.2174/1745017901612010067
12. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry, 2010; 67(3): 220–229. doi: 10.1001/archgenpsychiatry.2010.2
13. Pearl RL, Puhl RM. Weight bias internalization and health: a systematic review. Obes Rev, 2018; 19(8): 1141–1163. doi: 10.1111/obr.12701
14. Puhl RM, Heuer CA. The stigma of obesity: a review and update. Obesity (Silver Spring). 2009; 17(5): 941–964. doi: 10.1038/oby.2008.636
15. Kouidrat Y, Louhou R, Mondot C, et al. Quality of life in patients with obesity: the role of multidisciplinary rehabilitation medicine. Obesities, 2024; 4(2): 160–168. doi: 10.3390/obesities4020015
16. Kolotkin RL, Andersen JR. A systematic review of reviews: exploring the relationship between obesity, weight loss and health-related quality of life. Clin Obes, 2017; 7(5): 273–289. doi: 10.1111/cob.12203
17. Swami V, Frederick DA, Aavik T, et al. The attractive female body weight and female body dissatisfaction in 26 countries across 10 world regions: results of the International Body Project I. Pers Soc Psychol Bull, 2010; 36(3): 309–325. doi: 10.1177/0146167209359702
18. Buratta L, Delvecchio E, Capurso M, Mazzeschi C. Health-related quality of life in children with overweight and obesity: An explorative study focused on school functioning and well-being. Contin Educ, 2023; 4(1): 96–104. doi: 10.5334/cie.58
19. Brewis A, SturtzSreetharan C, Wutich A. Obesity stigma as a globalizing health challenge. Global Health, 2018; 14(1): 20. doi: 10.1186/s12992-018-0337-x
20. Fields ND, Whitcomb BW, Bertone-Johnson ER, et al. Race-specific associations between psychological distress and obesity: the role of social cohesion. Ethn Health, 2023; 28(3): 446–457. doi: 10.1080/13557858.2022.2052713

CEREBROLYSIN IN NEUROLOGY AND INTENSIVE CARE: NEW CLINICAL TRIALS AND THEIR IMPLICATIONS FOR ROUTINE CARE

Cerebrolizyna w neurologii i intensywnej terapii: nowe badania kliniczne oraz ich implikacje praktyczne

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Abstract

Introduction and objective: Cerebrolysin is a multimodal cerebroprotective agent that may improve the function of the blood–brain barrier, the neurovascular unit, and plasticity-related processes following central nervous system injury. This study aims to provide a comprehensive overview and critical evaluation of new clinical data (published after 2020) on the use of cerebrolysin in the acute phase of ischaemic stroke, including combination therapy with reperfusion strategies, and in neurointensive care for patients with traumatic brain injury (TBI). **Materials and methods:** A narrative review of randomised clinical trials (RCTs) involving cerebrolysin, meta-analyses, and prospective/observational studies was conducted, including analysis of the primary endpoints: National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), haemorrhagic transformation (HT/sHT), safety, and treatment feasibility. **Results:** In the acute phase of ischaemic stroke, a meta-analysis of 14 RCTs showed a modest benefit in NIHSS scores without a consistent effect on 90-day mRS outcomes; CEREHETIS reported lower sHT when cerebrolysin was added early to thrombolysis, while the multinational C-REGS2 registry demonstrated a favourable ordinal shift in 90-day mRS and improved cognition without additional safety concerns. Observational post-thrombectomy studies, including cyclic regimens with 12-month follow-up, suggested higher odds of functional independence and reduced HT, although causal inference remains limited. In TBI, the CAPTAIN trial (185 moderate-to-severe cases) demonstrated a benefit on a multidomain global outcome at 90 days with comparable safety. Broader meta-analyses suggested improvement in Glasgow Outcome Scale scores, without a clear effect on mortality and with substantial heterogeneity across studies. **Conclusions:** Cerebrolysin appears most promising as an adjunct to reperfusion and rehabilitation in the acute phase of ischaemic stroke and as supportive therapy in TBI. Definitive multicentre RCTs are needed to refine patient selection, timing, and dosing.

Streszczenie

Wprowadzenie i cel: Cerebrolizyna jest preparatem o wielomodalnym działaniu cerebroprotekcyjnym, mogącym wpływać na działanie bariery krew–mózg, jednostki nerwowo-naczyniowej, oraz procesy plastyczności po uszkodzeniu ośrodkowego układu nerwowego. Celem pracy jest syntetyczna prezentacja i krytyczna ocena nowych danych klinicznych (opublikowanych po 2020 roku) dotyczących zastosowania cerebrolizyny w ostrej fazie udaru niedokrwiennego, w tym jako terapii skojarzonej z reperfuzją, oraz w neurointensywnej opiece u pacjentów z pourazowym uszkodzeniem mózgu. **Materiał i metody:** Przeprowadzono przegląd narracyjny randomizowanych badań klinicznych, metaanaliz oraz badań prospektywnych i obserwacyjnych, uwzględniając analizę NIHSS (National Institutes of Health Stroke Scale), zmodyfikowaną skalę Rankina (mRS), transformację krwotoczną (HT), w tym objawową (sHT), a także bezpieczeństwo i wykonalność leczenia. **Wyniki:** Badania nad terapią łączoną cerebrolizyną z dożylną trombolizą z użyciem tkankowego aktywatora plazminogenu (CEREHETIS, CERE-LYSE) wykazały redukcję sHT po trombolizie i szybszą poprawę ocenianą w skali NIHSS, przy braku różnic w 90-dniowym mRS. W rejestrze C-REGS2 u chorych z umiarkowaną ostrą fazą udaru niedokrwiennego cerebrolizyna wiązała się z korzystnym przesunięciem rozkładu mRS i lepszymi wynikami funkcji poznawczych. Trzy badania obserwacyjne po trombektomii, w tym jedno z 12-miesięczną obserwacją (CEREBROLYSIN-WIM Study) sugerują większą szansę uzyskania niezależności funkcjonalnej i redukcję HT/sHT, jednak brak randomizacji ogranicza możliwość wyciągania wniosków przyczynowych.

W pourazowym uszkodzeniu mózgu projekt CAPTAIN (185 chorych) wykazał korzystny wpływ na globalny wielowymiarowy punkt końcowy oceniany w 90. dobie, przy porównywalnym bezpieczeństwie. Metaanalizy wskazują na poprawę wyników w skali Glasgow, bez redukcji śmiertelności, przy istotnej heterogenności danych. **Wnioski:** Istnieją obiecujące przesłanki dotyczące roli cerebrolizyny jako terapii wspomagającej reperfuzję/rehabilitację w ostrej fazie udaru niedokrwiennego oraz jako interwencji wspomagającej w pourazowym uszkodzeniu mózgu. Potrzebne są jednak wieloośrodkowe randomizowane badania kliniczne z precyzyjną selekcją pacjentów oraz optymalizacją czasu, dawki i długości leczenia.

Keywords: cerebrolysin; reperfusion; acute ischaemic stroke; spinal stroke; traumatic brain injury

Słowa kluczowe: cerebrolizyna; reperfuzja; udar niedokrwienny; udar rdzenia; pourazowe uszkodzenie mózgu

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Introduction

The treatment of acute ischaemic stroke (AIS) has undergone a fundamental transformation with the widespread adoption of reperfusion therapies – intravenous thrombolysis using tissue plasminogen activator (tPA) and mechanical thrombectomy (MT). The primary therapeutic goal remains the rapid restoration of blood flow in the occluded vessel responsible for the ischaemia. However, growing clinical experience indicates that the technical success of recanalisation does not always translate into full functional recovery. This issue is particularly relevant in strokes caused by large vessel occlusion (LVO), where, despite successful recanalisation, secondary injury mechanisms may predominate, including neurovascular unit dysfunction, cytotoxic and vasculogenic oedema, microthrombi, microcirculatory disturbances, and blood–brain barrier (BBB) disruption leading to haemorrhagic transformation (HT). In clinical practice, this results in a discrepancy between the technical success of the procedure (usually >90%) and functional outcomes, as 30–50% of patients remain dependent in the long term (the so-called phenomenon of futile recanalisation).

Consequently, there has been a resurgence of interest in cytoprotective and neuroregenerative strategies, both as adjuncts to reperfusion therapy and as components supporting rehabilitation aimed at inducing brain plasticity [1]. In parallel, other adjuvant approaches are being explored (including therapeutic hypothermia, hyperbaric oxygen therapy, and ischaemic preconditioning). However, their implementation in routine clinical practice remains challenging because of both technical limitations and variability in individual treatment responses. These responses may depend on stroke location (subcortical, cortical, posterior fossa), aetiology (microangiopathy, macroangiopathy), treatment timing, collateral circulation, and other patient-specific factors [2].

Cerebrolysin is one of the most extensively studied neuroprotective agents for disorders of the central nervous system (CNS), in both preclinical and clinical settings [3]. It is a parenterally administered peptide-amino acid preparation whose composition and multimodal mechanism of action mimic those of endogenous neurotrophic factors, which translates into beneficial cytoprotective and neuromodulatory effects observed in ischaemic stroke, traumatic brain injury (TBI), mild cognitive impairment, Alzheimer's disease, vascular dementia, cerebral amyloid angiopathy, monogenic dementias (e.g. cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL), and other neurological disorders [4, 5]. The action of cerebrolysin involves diverse mechanisms of neuroprotection, neuroregeneration, and neuronal and synaptic plasticity. The neurotrophic components of cerebrolysin (including brain-derived neurotrophic factor and ciliary neurotrophic factor, nerve growth factor, orexins, and enkephalins) cross the BBB, initiate the intracellular Shh (sonic hedgehog) signalling pathway, lead to the activation of transcription factors, increased expression of endogenous neurotrophins, and inhibition of excitotoxic processes and oxidative stress, and also have a beneficial effect on microglial function. Preclinical and clinical studies have demonstrated a significant effect of cerebrolysin on endothelial and BBB function, including a reduced risk of haemorrhage following tPA administration through restoration of endothelial cell integrity and improvement of BBB function [6]. Encouraging results have also been reported in the subacute and chronic phases of stroke. In patients receiving cerebrolysin as an adjunct to early and intensive post-stroke rehabilitation, improvements in neurological status and the recovery of motor function and speech ability were observed, together with good tolerability and safety profiles [7]. Based on these data, cerebrolysin has received recommendations from numerous scientific societies (including the Vascular Diseases Section of the Polish Neurological Society (2019), the European Academy of Neurology together with the European Federation of Neurorehabilitation (2021), and the German Society for Neurorehabilitation (2020) for adjunctive use in early post-stroke rehabilitation, particularly in patients with moderate-to-severe stroke [8].

Similarly to the ischaemic cascade observed after stroke, TBI triggers complex processes of secondary injury involving glutamate-induced excitotoxicity, Ca^{2+} influx, mitochondrial dysfunction, oxidative stress, neuroinflammation, and damage to the BBB accompanied by oedema and microcirculatory disturbances. These mechanisms lead to progressive apoptosis, neurodegeneration, and deterioration of neurological function (Fig. 1) [9]. Preclinical models have demonstrated that cerebrolysin may also exert beneficial pharmacological effects in TBI by enhancing the brain's endogenous neuroprotective mechanisms through the maintenance of cellular neurotrophism, neuroprotection, and neuroplasticity [10]. In accordance with the recommendations of the STAIR XI scientific committee, cerebroprotective interventions targeting various stages of the ischaemic or post-traumatic cascade, when administered within an appropriate therapeutic window, are considered essential for improving treatment efficacy [11].

To date, evidence from randomised controlled trials (RCTs) and meta-analyses regarding the efficacy of cerebrolysin in combination with reperfusion therapies in AIS, or as part of intensive management in patients with moderate-to-severe TBI remains scarce and somewhat inconsistent. This is partly due to the inclusion of heterogeneous patient populations, including those with AIS not treated with reperfusion therapy or those with mild TBI. In recent years, however, results from new studies on cerebrolysin in neurological intensive care settings have emerged. These findings justify the need for a broader evaluation of the role of cerebrolysin as an adjunct to tPA or mechanical thrombectomy in ischaemic stroke, and as a supportive therapy alongside standard intensive care after TBI, where it is crucial to translate early radiological success following thrombectomy or stabilisation of vital functions after trauma into meaningful long-term functional recovery.

Objective

The aim of this study is to provide a comprehensive overview and critical evaluation of current data from clinical trials (with particular emphasis on studies published between 2020 and 2025) regarding the use of cerebrolysin in (1) the treatment of AIS, including in combination with reperfusion therapies, (2) intensive neurological care, particularly in TBI and subarachnoid haemorrhage (SAH).

Materials and methods

This paper is a narrative review based on key RCTs, meta-analyses, and more recent prospective and observational studies (including matched-cohort analyses) evaluating the efficacy of cerebrolysin in patients with AIS treated with reperfusion therapy (mechanical thrombectomy or thrombolysis), as well as in patients with TBI or SAH. The analysis focused on endpoints of practical and clinical significance, including neurological deficit severity assessed using the NIHSS (National Institutes of Health Stroke Scale), functional outcome measured with the modified Rankin Scale (mRS), independence evaluated by the Barthel Index (BI), the incidence of HT, including symptomatic haemorrhagic transformation (sHT), safety outcomes (adverse events), and the feasibility of and adherence to treatment protocols.

Results

Acute ischaemic stroke – new data in the era of reperfusion

Previous studies and meta-analyses involving patients with AIS who received non-interventional treatment and started cerebrolysin therapy within 48 hours of stroke onset have demonstrated an overall favourable safety

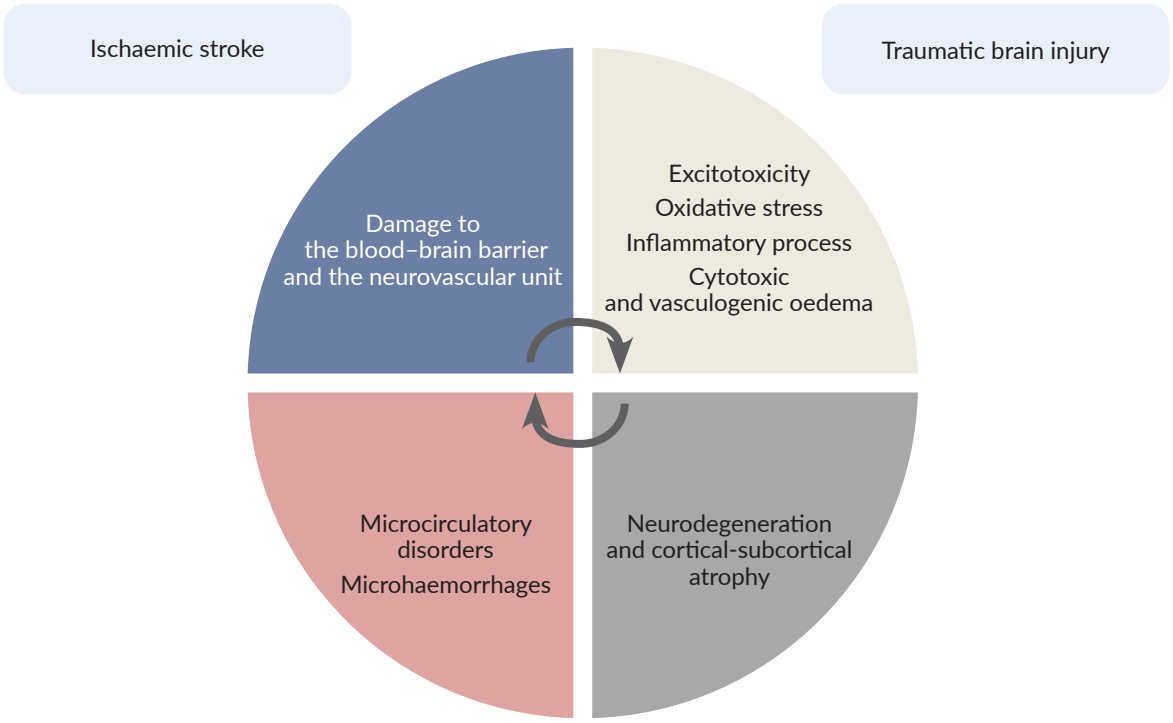


Figure 1. Common pathomechanisms of acute ischaemic stroke and traumatic brain injury

profile and suggested a possible trend towards accelerated neurological recovery, particularly in patients with moderate-to-severe stroke [12]. However, the populations analysed and the cerebrolysin treatment protocols used were highly heterogeneous, which adversely affected the quality of the analysed data [13]. In the recently published largest meta-analysis comprising 14 RCTs conducted between 2004 and 2025 (n = 2,884), which included two studies involving patients treated with thrombolysis, a significant improvement in neurological deficit was demonstrated in patients treated with cerebrolysin (mean difference in NIHSS reduction during hospitalisation vs the control group: 1.39 points; 95% CI: 0.53–2.25; p = 0.02), with no significant differences in functional independence, although this outcome was assessed over a broad time window (days 21–90) [14]. The authors of the meta-analysis emphasised the need for further high-quality studies to confirm the impact on long-term (90-day) functional outcomes.

In the era of reperfusion therapy, more recent studies have focused on two main objectives:

- increasing the proportion of patients achieving functional independence at 90 days;
- reducing HT/sHT and other reperfusion complications.

CEREHETIS – adjunctive thrombolytic therapy and the risk of HT

The prospective, randomised, open-label, multicentre CEREHETIS trial (2024) evaluated the early addition of cerebrolysin as an adjunctive therapy to tPA in patients with AIS involving the middle cerebral artery [15]. In the analysed cohort, patients in the intervention group (IG, n = 126) received 30 ml of cerebrolysin intravenously for 14 days in combination with tPA and standard care, while the control group (CG, n = 215) received tPA and standard care. The endpoints were haemorrhagic complications, including sHT and any HT, as well as functional outcome measured on the mRS at 90 days after onset. In the intention-to-treat (ITT) analysis, a significant reduction in sHT was observed in the cerebrolysin group (3.2% vs 9.3%; OR 0.248; 95% CI: 0.072–0.851; p = 0.019) with a trend towards a lower incidence of HT (15.9% vs 23.3%; p = 0.078). In the PP (per-protocol) analysis, the reduction was significant for both HT (13.7% vs 22.9%; OR 0.417; p = 0.032) and sHT (2.6% vs 9.0%; OR 0.171; p = 0.022). A post hoc analysis found that the reduction in HT risk was greatest in patients with a high predicted risk of haemorrhage according to the HTI scale (including low ASPECTS, signs of a hyperdense middle cerebral artery, atrial fibrillation) [16]. Additionally, a significant early improvement in neurological status was noted in the IG group (median NIHSS score on day 14: 2 vs 3 points; p <0.05), with no significant differences in functional status on the mRS at 90 days. The treatment was well tolerated. In the subgroup of patients undergoing advanced imaging (n = 33), a significant improvement in BBB permeability parameters on perfusion CT (product of permeability and surface area) and a smaller infarct volume at 14 days were observed in the cerebrolysin group. These findings support the hypothesis that stabilising the BBB through cerebroprotective treatment may contribute to reducing the incidence of haemorrhagic complications following reperfusion. The authors noted that the reduction in haemorrhagic risk achieved with cerebrolysin may allow anticoagulant therapy to be resumed 1–2 days earlier in patients at high risk of HT.

The results of the CEREHETIS trial were consistent with those of another prospective, randomised, double-blind, placebo-controlled trial (CERE-LYSE, 2013), which evaluated the safety and efficacy of combining alteplase with cerebrolysin in 119 patients with acute ischaemic stroke [17]. Treatment was initiated within 3 hours of symptom onset; 1 hour after thrombolysis, 30 ml of cerebrolysin or placebo was administered intravenously for 10 consecutive days. The trial was discontinued after the third interim analysis because no improvement in mRS at day 90 (primary endpoint) was demonstrated compared with placebo; however, in the secondary analysis, significantly more (p <0.01) patients in the cerebrolysin group achieved neurological improvement on the NIHSS score, including at 2 (45.8% vs 25.3%), 5 (66.1% vs 37.3%), 10 (72.1% vs 50.8%), and 30 (75.8% vs 57.6%) days.

Therapy added to mechanical thrombectomy

Several observational studies and pragmatic clinical trials have been published to date in populations treated with mechanical thrombectomy (MT), suggesting potential improvement in functional outcomes at 3 months and a significant reduction in haemorrhagic complications with the use of cerebrolysin.

In a pilot observational study, Poljakovic et al. (2021) evaluated patients with moderate or severe AIS (NIHSS >8) following unsuccessful recanalisation following treatment with MT (TICI (Thrombolysis in Cerebral Infarction) score <2b) and/or tPA [18]. The study included 44 patients, allocated to treatment with cerebrolysin (30 ml/day for 14–21 days, treatment initiation ≤24 hours from symptom onset; n = 23) or standard therapy (n = 21). At day 90, no significant differences were observed in the distribution of clinical outcomes (mRS); however, at 12 months, a trend towards a higher proportion of patients with mRS 0–3 was noted (70% vs 48%; p = 0.1), along with a significantly lower incidence of HT (13% vs 38%; p <0.05) and a favourable safety profile for cerebrolysin. The findings of this pilot study were important for the design of subsequent trials, as they indicated a potential therapeutic role for neuroprotective treatment for patients in whom standard reperfusion therapy had not yielded the expected results.

The study by ElBassiouny et al. (2025) involved a prospective assessment of the clinical course of AIS in patients receiving cerebrolysin as adjunctive therapy following successful MT (NIHSS ≥10, age 18–80 years; mTICI 2b/3, cardiogenic stroke) [19]. The analysis included 150 patients: 75 received 30 ml of cerebrolysin intravenously once daily for 14 days, initiated ≤8 hours after MT, while 75 formed the historical control group (MT ± IV rt-PA without cerebrolysin). The primary endpoint was the proportion of patients with mRS 0–2 at day 90, and secondary endpoints included NIHSS and mRS scores at days 14, 30 and 90, cognitive impairment assessed on the MoCA scale at day 90, symptomatic and asymptomatic HT, as well as mortality and adverse

events. The authors demonstrated a significantly higher proportion of patients achieving mRS 0–2 at 90 days in the cerebrolysin group compared with the control group (64% vs 34.7%, respectively; p <0.001) and statistically significantly (p <0.05) lower NIHSS and mRS scores at subsequent time points (14–90 days), alongside a significant (p <0.01) reduction in the incidence of any HT (20% vs 57.3%) and sHT (2.7% vs 41.3%), and lower three-month overall mortality (5.3% vs 32%). In the subgroup analysis of patients with ASPECTS ≤10, better functional outcomes (mRS 0–2 at 3 months) were observed with cerebrolysin compared with controls (ASPECTS 8–10: 50.7% vs 32%; ASPECTS 6–7: 13.3% vs 2.7%). All results were consistent both in the primary analysis cohort and in groups matched for stroke characteristics in the PSM analysis (n = 51 pairs).

The Cerebrolysin-WIM Study, conducted by Polish researchers (2025), assessed the efficacy of treatment in patients selected on the basis of a small infarct core, adequate collateral circulation (CTA-CS 2–3) and successful recanalisation (mTICI 2b–3) [20]. This was a single-centre, prospective, open-label study with blinded outcome assessment, compared with a historical control group matched using the PSM method (50 patients treated with cerebrolysin vs 50 controls). Cerebrolysin was administered in two cycles: 30 ml IV within 8 hours of symptom onset up to day 21 (cycle I) and again during the rehabilitation phase between days 69 and 90 (cycle II). The primary endpoint was the achievement of functional independence (mRS 0–2) by day 90, which occurred more frequently in the cerebrolysin group (68% vs 44%; p = 0.016; OR 2.7; 95% CI: 1.2–6.1; NNT 4.2) (Fig. 2). Treatment was also associated with a lower risk of secondary HT (14% vs 40%; p = 0.02; RR 0.37), faster neurological recovery (NIHSS on day 7: median 3 vs 6; p = 0.01), and better outcomes on functional scales (Barthel Index on day 30 and at 3 months). No differences in mortality at 30 and 90 days were observed between groups. The proportion of patients with mRS 0–2 at 90 days was higher among those who received tPA bridging therapy (80% vs 47.6%; p = 0.03; OR 4.4; 1.1–17.7), with ASPECTS <10 (61.3% vs 26.3%; p = 0.02; OR 4.4; 1.3–15.5), with a trend towards functional independence in patients without sHT (65.3% vs 34.7%; p = 0.07; OR 2.39; 0.9–6.4).

The Cerebrolysin-WIM trial is, to date, the only published study with a 12-month follow-up demonstrating that cerebrolysin use was associated with a higher likelihood of functional independence at 12 months after adjustment for potential confounding factors (aOR 6.10; 95% CI: 1.64–22.66; p <0.01) and a favourable shift towards lower disability across the entire 12-month mRS distribution (pooled OR for favourable shift 3.57; 95% CI: 1.42–8.93; p <0.01) [21]. Cumulative mortality at 12 months was similar in both groups (18% each). Among survivors, 6% of patients in the cerebrolysin group compared with 19% in the control group required institutional care (unadjusted OR 0.26; 95% CI: 0.07–0.99; NNT 8). In multivariate analysis, treatment with cerebrolysin (alongside mTICI 3 and CTA-CS 3) was a significant predictor of functional independence at 12 months (OR 3.5, 95% CI: 1.4–8.6, p <0.05).

A comparison of the four studies discussed suggests a significant beneficial effect of cerebrolysin on prognosis and functional independence by day 90, as well as on reducing the risk of secondary haemorrhage (Fig. 3). The clinical significance of these findings is potentially high (improved

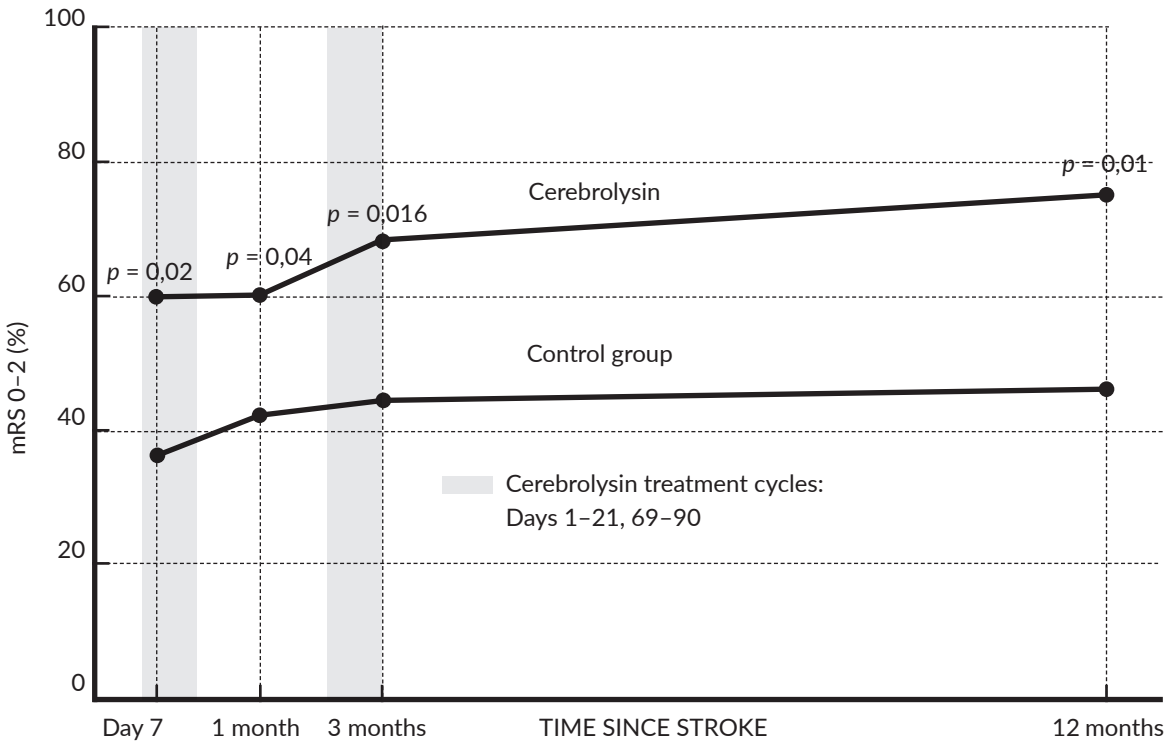
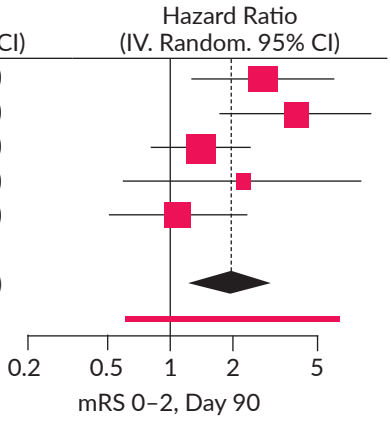


Figure 2. Comparison of the 12-month course of stroke in the cerebrolysin-treated group and the control group. mRS – modified Rankin Scale

A.

Study	logHR	SE	Weight	Hazard Ratio (IV. Random. 95% CI)
Staszewski et al. 2025	0.9953	0.4148	20.1%	2.71 (1.20; 6.10)
ElBassiouny et al. 2025	1.3695	0.4280	19.3%	3.93 (1.70; 9.10)
Khasanova et al. 2023	0.3240	0.2856	28.9%	1.38 (0.79; 2.42)
Poljakovic et al. 2021	0.7882	0.6801	10.1%	2.20 (0.58; 8.34)
Lang et al. 2013	0.0699	0.3893	21.6%	1.07 (0.50; 2.30)
Total (95% CI):			**100%**	**1.92 (1.19; 3.10)**
Prediction interval				**(0.58; 6.32)**

Heterogeneity: Tau² ≈ 0.1234; Chi² = 7.01. df = 4 (P = 0.1356); I² = 42.9%
Test for overall effect: Z = 2.68 (P ≈ 0.0074)



B.

Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio (MH. Random. 95% CI)
Staszewski et al. 2025	1	50	12	50	17.4%	0.08 (0.01; 0.62)
ElBassiouny et al. 2025	2	51	22	51	32.1%	0.09 (0.02; 0.37)
Poljakovic et al. 2021	1	23	1	21	10.0%	0.91 (0.06; 13.69)
Khasanova et al. 2023	3	117	18	201	40.5%	0.29 (0.09; 0.95)
Total (95% CI):		**241**		**323**	**100%**	**0.18 (0.07; 0.43)**
Prediction interval						**(0.03; 1.12)**

Heterogeneity: Tau² ≈ 0.1275; Chi² = 3.53. df = 3 (P = 0.3173); I² = 14.9%
Test for overall effect: Z ≈ −3.81 (P ≈ 0.0001)

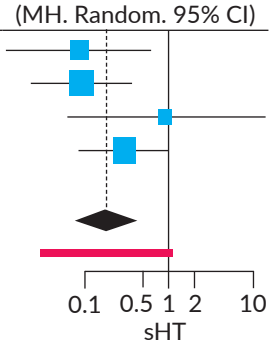


Figure 3. Summary of studies evaluating cerebrolysin as an adjunct to reperfusion therapy in acute ischaemic stroke. **A.** Effect on functional outcome (mRS 0–2) at 90 days. **B.** Effect on symptomatic secondary transformation (sHT) at 24 hours. mRS – modified Rankin Scale, sHT – symptomatic secondary transformation

functional outcomes and safety of reperfusion following MT); however, interpretation is limited by the single-centre, non-randomised study design, and the results should therefore be regarded as preliminary and requiring confirmation in multicentre randomised trials.

Therapy complementing routine care in AIS

C-REGS2 (Cerebrolysin REGistry Study in Stroke 2) was a prospective, open-label, controlled trial evaluating the efficacy of cerebrolysin treatment in routine clinical practice compared with standard therapy; it was conducted in 16 countries between 2018 and 2024 in accordance with the GRACE guidelines [22]. Patients with AIS and moderate neurological deficit (NIHSS 8–15) were included in the study. A total of 1,769 patients were analysed (1,021 in the treatment group vs 748 in the control group). The median NIHSS score was 10; the cerebrolysin treatment regimen was individualised and most commonly involved a dose of 30 ml administered over 10 days. The effect size was reported as the generalised Mann–Whitney measure (MW), interpreted probabilistically as the likelihood of a better outcome in the active treatment group compared with the control group, where MW >0.50 indicates a treatment advantage. In the assessment of the primary endpoint (ordinal mRS analysis at 90 days), cerebrolysin proved significantly more effective than standard therapy (MW 0.6157; 95% CI: 0.59–0.64; p <0.0001; OR 2.03, NNT 8.6). The beneficial effect was also maintained in subgroup analyses (e.g. regardless of prior thrombolysis, which was received by only a small proportion of patients, approximately 20%). The superiority of cerebrolysin was also evident in secondary endpoints (mRS at day 21, NIHSS at days 21 and 90), with a moderate increase in the proportion of very good functional outcomes (mRS 0–1, OR 2.74; 95% CI: 2.12–3.60; p <0.0001) and functional independence (mRS 0–2; OR 2.88; 95% CI: 2.28–3.68; p <0.0001). Better results were also observed on the MoCA scale (MW 0.55; 95% CI: 0.53–0.58; p <0.0001), especially in patients with baseline cognitive deficits. No differences in safety were observed between the groups.

Acute spinal ischaemia and retinal ischaemia

Acute spinal cord ischaemia (Beck's syndrome) and retinal embolism, caused by occlusion of the anterior spinal artery and the central retinal artery respectively, are classified within the spectrum of ischaemic stroke of the CNS. They usually have a poor long-term prognosis, with persistent, significant long-term disability (including bilateral paresis or paralysis of the limbs below the level

of injury, loss of pain and temperature sensation, and autonomic dysfunction affecting the bladder or bowels) or monocular blindness. This report describes the case of a 78-year-old patient treated conservatively (anticoagulants, steroid therapy, intensive neurological rehabilitation) for spinal cord ischaemia, in whom clinical and radiological improvement was observed following administration of cerebrolysin (in two 10-day cycles). In this case, the favourable outcome following the use of cerebrolysin may have resulted primarily from stabilisation of the blood–spinal cord barrier, as well as potential neuroprotective and anti-oedema effects, which may have limited secondary spinal cord damage and promoted clinical improvement [23]. A similar beneficial effect has also been described in patients with retinal stroke, likely related to its effect on the blood–retinal barrier [24]. These findings require confirmation in further studies.

Intensive care and neurological care

Traumatic brain injury

In the field of intensive neurological care, the available evidence regarding cerebrolysin is also encouraging. The most frequently analysed aspect has been the effect of cerebrolysin on the course of TBI. Studies have included patients in varying neurological conditions and at different time points following TBI. Various doses of the drug (10–50 ml/day) and durations of therapy (5–30 days) have also been used. Most studies reported a favourable safety profile and a moderate, population-dependent trend toward potential benefits of cerebrolysin treatment in improving cognitive function and independence.

The CAPTAIN project comprised a prospective analysis of two randomised, double-blind, placebo-controlled phase IIIb/IV trials, which enrolled 185 patients with moderate or severe TBI (Glasgow Coma Scale, GCS 6–12) who received cerebrolysin in three cycles (50 ml/day for 10 days, followed by two cycles of 10 ml/day for 10 days) as an adjunct to standard care. Given the clinical complexity of TBI sequelae, including motor and cognitive deterioration (impairments in communication, processing speed, working memory, and mood), the primary multidimensional endpoint comprising 13 functional and neuropsychological measures was analysed using the Wei–Lachin method (a test for the global comparison of multiple correlated variables), with effect size expressed as a generalised MW measure for the composite outcome (MWcombined).

CAPTAIN I enrolled 46 patients (including 22 in the cerebrolysin group). In the analysis of individual scales, advantages were observed, among others, in the Stroop test and the Colour Connect the Dots Test Part 1/2 (Table 1) [25]. In the analysis of the primary endpoint in the ITT population, the result was borderline (p <0.1; MW = 0.63; 95% CI: 0.48–0.77; OR = 2.1), whereas in the PP analysis, patients treated with cerebrolysin showed significant improvement (p = 0.02; MW = 0.69; 95% CI: 0.53–0.85; OR = 3.2), with a safety profile comparable to that of placebo.

The CAPTAIN II trial enrolled 142 patients (mean age 47.4 years; mean GCS on admission 10.4) [26]. In the analysis of the primary endpoint in both the ITT and PP populations, a significant effect in favour of cerebrolysin was demonstrated at day 90 (MW = 0.59; 95% CI: 0.52–0.66; p = 0.01; MW = 0.602; 95% CI: 0.53–0.68; p <0.01; n = 74/55), with an advantage in favour of cerebrolysin on all 13 individual scales. Survival in patients treated with cerebrolysin did not differ from that in the control group. Subgroup analyses revealed a statistically significant reduction in anxiety levels in patients with moderate or severe post-traumatic disability, with a large effect size (standardised *mean difference*, SMD = 0.73) in the cerebrolysin-treated group [27].

A prospective meta-analysis of the CAPTAIN series (total of 185 patients; mean GCS 10.3; age 45.3 years) confirmed the beneficial effect of cerebrolysin on the global endpoint, which was significant at day 30 (MWcombined = 0.60; 95% CI: 0.52–0.66; p = 0.02; SMD = 0.31; OR = 1.69) and at day 90 (MWcombined = 0.60; 95% CI: 0.52–0.68; p = 0.015; SMD = 0.34; OR = 1.77), with good consistency between studies (I^2 = 0 in pooled analyses) and comparable safety [28].

A broader perspective is provided by a meta-analysis recently published by Polish authors, comprising 10 studies (n = 8,749) with varying treatment regimens (10–50 ml/day IV), treatment durations of 5–30 days, and treatment initiation ranging from 24 hours to over 20 months after injury; three of the studies were blinded [29]. The endpoints were the GCS, GOS (Glasgow Outcome Scale), mortality, and length of hospital stay. The results showed a significant improvement in GOS in favour of cerebrolysin (mean difference, MD: 0.42; 95% CI: 0.262–0.581; p <0.001, with significant heterogeneity between groups (I^2 = 70.55). A less consistent signal for improvement was observed on the GCS (MD 1.34; 95% CI: −0.258 to 2.945, with very high heterogeneity (I^2 = 94.20). No effect was found on length of hospital stay (MD −1.255 days; 95% CI: −6.422 to 3.913; p = 0.634; I^2 = 85.14) or on mortality. The meta-analysis suggested a potentially beneficial effect of treatment on clinical or functional outcomes as measured by the GOS (and probably also the GCS), but also highlighted limitations arising from heterogeneity, varying dosing regimens, and the lack of large RCTs, underscoring the need for further research to determine the optimal treatment protocol.

The largest retrospective cohort study to date (2015), involving 6,151 patients, demonstrated an improvement in the level of consciousness and functional status in the cerebrolysin group (as assessed by the GOS and mRS cores, respectively) compared with the control group [30]. In another retrospective study (2017), involving 129 patients with severe TBI, a beneficial effect of treatment with 10 ml/day for 30 days on functional status improvement at 3 and 6 months was observed [31]. Similarly, a meta-analysis of 8 studies conducted prior to 2018, with varying methodological quality, demonstrated that patients treated with cerebrolysin (n = 112) achieved a favourable outcome on the GOS more frequently than controls (OR 3.01; 95% CI: 1.7–5.1; p = 0.003) and that the likelihood of improved cognitive function was significantly higher in this group (OR 3.4; 95% CI: 1.8–5.2; p <0.001) [32].

Table 1. Summary of the results of the CAPTAIN I and II trials in traumatic brain injury (TBI) [25–28]

Study/ population	Intervention	Primary endpoint	Primary outcomes	Selected secondary outcomes	Safety analysis
CAPTAIN I RCT, DB, placebo; moderate/ severe TBI; GCS 6–12; *N* = 46 (active/ control group: 22/24)	Cerebrolysin 50 ml/day (10 days), then 10 ml/day (days 31–40 and 61–70) vs placebo; and standard medical care	Multidimensional composite endpoint of functional and neuropsychological scales (Wei–Lachin test; MWcombined) at days 10, 30 and 90	**IITT:** *p* <0.1; MW = 0.63 (95% CI: 0.48–0.77); SMD = 0.45; OR = 2.1 **PP:** *p* = 0.0240; MW = 0.69 (0.53–0.85); SMD = 0.69; OR = 3.2	Stroop Word/Dots *p* = 0.0415; MW = 0.6816; Colour Trails 1 *p* = 0.0223; MW = 0.72; Colour Trails 2 p = 0.0170; MW = 0.73	Comparable to placebo
CAPTAIN II RCT, DB, placebo; moderate/ severe TBI; *N* = 139 in analysis (80/59); age 47.4; GCS 10.4; BPRS 2.6	As above	As above	Day 90: MW = 0.59 (95% CI: 0.52–0.66); *p* = 0.0119	PP: Day 90: MW = 0.6026; p = 0.0058. Digit Symbol *p* = 0.0068; Stroop Word/Dots *p* = 0.0009; Digit Span Fwd *p* = 0.0164; Bwd *p* = 0.0014; Colour Trails 1 *p* = 0.008; HADS-D *p* = 0.004	Comparable to placebo
Pooled analysis *N* = 185; age 45.3; GCS 10.3; BPRS 2.8	As above	As above	Day 30: MW = 0.60; *p* = 0.0156; SMD = 0.31; OR = 1.69; Day 90: MW = 0.60; *p* = 0.0146; SMD = 0.34; OR = 1.77	PP: Day 90 (summary report) Wei–Lachin: MW = 0.6272; p = 0.0039; I^2 = 0	Cerebrolysin vs placebo: deaths 3.9% vs 8.4% SAEs 7.8% vs 18.1%

RCT – a randomised clinical trial; DB – double-blind; TBI – traumatic brain injury; GCS – the Glasgow Coma Scale; BPRS – Brief Psychiatric Rating Scale; ITT– intention-to-treat analysis; PP – per-protocol analysis; Wei–Lachin test – global test for multiple correlated endpoints; MW – Mann–Whitney effect; MWcombined – generalisation for a composite endpoint (Wei–Lachin); CI – confidence interval; SMD – standardised mean difference; OR – odds ratio; Digit Symbol – Digit Symbol Coding – symbol/ digit coding test; measure of processing speed; Digit Span Fwd/Bwd – forward/backward digit repetition (attention and working memory); HADS-D – Hospital Anxiety and Depression Scale; SAE – serious adverse events; I^2 – heterogeneity statistic in meta-analysis

Subarachnoid haemorrhage

In the only pilot randomised, double-blind, placebo-controlled trial published to date (2020) in patients with SAH from an aneurysm, the safety and feasibility of administering 30 ml/day of cerebrolysin intravenously for 14 days (initiated within ≤96 hours of onset) were assessed in comparison with placebo; 50 patients were enrolled in the study (25 vs 25) [33]. The treatment was logistically feasible (high completeness of dosing and follow-up) and was associated with a safety profile similar to that of placebo. However, no advantage was demonstrated in the primary functional endpoint at 6 months: the proportion of good functional outcomes (defined as GOSE 5–8) was 76% in the cerebrolysin group versus 68% in the placebo group (OR 1.49; 95% CI: 0.43–5.17). In secondary analyses (e.g. mRS), no significant differences were found between the groups. Given the high incidence of secondary ischaemia following SAH and the limited options for preventing vasospasm, further studies are warranted to determine the efficacy of cerebroprotective therapies in this high-risk population.

Discussion

The widespread adoption of intravenous thrombolysis and MT has substantially improved the prognosis in AIS, but has also highlighted the limitations of an approach focused solely on achieving recanalisation. Even with a high proportion of technically successful procedures, some patients remain dependent, suggesting that outcomes are also determined by processes occurring in the microcirculation and at the interface between the neurovascular unit and the blood–brain barrier. Persistent endothelial dysfunction, perfusion disturbances, vascular oedema and activation of the inflammatory response may sustain oxidative stress, adversely affect the metabolic penumbra and exacerbate secondary damage to peri-infarct tissue [34].

Cerebrolysin exerts neuroprotective and neurorestorative effects in ischaemic stroke and following TBI by inhibiting key components of the ischaemic and pro-inflammatory cascade, including glutamate-induced excitotoxicity and oxidative stress. As a result, it reduces DNA and protein damage, as well as cell necrosis and apoptosis. At the same time, it can support various brain

Table 2. Taxonomy of drugs with potential neuroprotective effects and their mechanisms of action in ischaemic stroke

Physiological targets	Mechanism	Examples from studies on cerebrolysin
"*Bridging*" neuroprotection with reperfusion therapy	Slowing the progression of the infarct in the pre- and early post-reperfusion phases. Maintenance of neuronal metabolism by increasing resistance to hypoxia.	1) CEREHETIS study: concurrent administration with an r-tPA infusion prior to reperfusion improved early neurological status [15]. 2) Rat model of transient middle cerebral artery occlusion: administration of cerebrolysin 3 hours after ischaemia reduced infarct volume by limiting the metabolic penumbra (activation of the CREB/PGC-1α pathway and inhibition of free-radical formation prevented lactate accumulation and lactic acidosis) [2].
BBB stabilisers	Improvement in BBB integrity before and after reperfusion.	1) CEREHETIS study: improvement in BBB function demonstrated on neuroimaging [15]. 2) Reduction in the risk of secondary haemorrhage with cerebrolysin demonstrated in various phase studies [15, 18]. 3) Preclinical study: improvement in BBB function following thrombolytic treatment with cerebrolysin via improved function of endothelial tight junctions and reduced pro-inflammatory and pro-coagulant activity [18].
Stabilisation of microcirculation	Protection of the integrity of arteriolar and capillary endothelium, prevention of the no-reflow phenomenon following reperfusion.	A randomised, double-blind, placebo-controlled trial in 46 patients with acute ischaemic stroke demonstrated a significant reduction in the pulsatility index post-stroke, suggesting an improvement in cerebral blood flow dynamics within the microcirculatory bed following cerebrolysin treatment [34]
Early neuroprotection and prevention of reperfusion injury	Slowing of pathological inflammatory and oxidative processes occurring immediately after reperfusion.	Preclinical (*in vitro*) study: cerebrolysin reduced neuronal death in models mimicking ischaemia, including glutamate toxicity, iodoacetate-induced metabolic inhibition, and ionomycin-induced calcium homeostasis deregulation [31]
Anti-oedema effect	Reduction in the risk of cerebral oedema and secondary herniation.	Studies by Woo et al. and Zhang et al. in patients with subarachnoid haemorrhage due to aneurysm or traumatic brain injury demonstrated a significant reduction in pro-inflammatory markers (IL-1β, IL-6, TNF-α and aquaporin-4) associated with vasculogenic oedema, suggesting that cerebrolysin may mitigate the harmful effects of cerebral oedema and thereby reduce secondary damage associated with increased intracranial pressure and herniation [32].
Delayed neuroprotection, induction of neuroplasticity	Reduction of the consequences of reperfusion injury, apoptosis and mitochondrial dysfunction. Promotion of synaptogenesis and neuroplasticity, improved neurovascular unit function.	1) Multiple preclinical studies have shown that cerebrolysin exerts neurotrophic and neuroprotective effects (by protecting against glutamate-induced excitotoxicity, promoting the proliferation of neuronal progenitor cells, which enhances the differentiation of neurons and oligodendrocytes through the upregulation of Shh signalling and its receptors, modulation of endogenous neurotrophin levels), which promotes improved recovery after stroke when administered within <48 hours in middle cerebral artery ischaemia models [31,33]. 2) The CARS study and meta-analyses have shown that cerebrolysin administered once daily for 21 days, starting 24–72 hours after stroke onset, has a beneficial effect on functional ability and overall fitness in patients in the early phase of post-stroke rehabilitation [26, 28].
BBB – blood–brain barrier; r-tPA – recombinant tissue plasminogen activator		

repair processes by promoting neuro-, synapto- and axonogenesis, aiding the restoration of neuronal function. These properties of cerebrolysin – primarily described in preclinical models – align well with the newly proposed taxonomy for neuroprotective drugs (Tab. 2).

Clinical studies have also demonstrated that cerebrolysin exhibits multimodal effects, influencing several elements of the ischaemia-reperfusion injury cascade and supporting neuronal plasticity processes in the subacute phase. The data from reperfusion studies presented in this paper suggest, above all, the potential to reduce haemorrhagic complications while maintaining a good safety profile. In CEREHETIS, early administration of cerebrolysin following tPA was associated with a significant reduction in sHT and a trend toward reduced HT, and in the subgroup with imaging assessment, improvements in BBB permeability parameters and smaller infarct volumes were noted [15]. In CERE-LYSE, despite no improvement in mRS at 90 days (primary endpoint), faster neurological improvement on the NIHSS at subsequent time points was observed, which may support the hypothesis of an early biological effect of the drug [17].

Although the evidence for the efficacy of cerebrolysin following stroke is derived predominantly from observational studies, several independent cohorts have demonstrated a significant reduction in haemorrhagic compli-

cations and a beneficial effect on functional outcomes. A pilot study by Poljakovic et al. suggested a lower risk of HT and a favourable trend at 12 months, although the sample size was small and included patients with suboptimal recanalisation outcomes [18]. The study by ElBassiouny et al. demonstrated a higher proportion of functionally independent patients (mRS 0–2) at 90 days and a significant reduction in HT/sHT compared with the historical control. These findings should be interpreted with caution given potential bias related to differences in care and patient selection [14].

Of particular interest are the results of the CEREBROLYSIN-WIM study, which selected patients with a small infarct core, adequate collateral circulation, and successful recanalisation. Treatment in two cycles was associated with a higher proportion of functional independence (mRS 0–2) at 90 days and a favourable shift in the mRS distribution, persisting up to 12 months after adjustment for key predictors of outcome following EVT [20, 21].

Registers based on real-world evidence provide an important complement to these studies. In the C-REGS2 registry, cerebrolysin used alongside standard therapy in moderate AIS was associated with a favourable shift in the mRS distribution at 90 days toward functional improvement and better cognitive outcomes, with no differences in safety compared with standard care [22].

A common theme across these studies is a reduced risk of haemorrhagic complications and improved functional outcomes, particularly in patients with extensive stroke at baseline. This is likely related to improved BBB function, which regulates many processes crucial for brain homeostasis, including microcirculation and the complex functions of the neurovascular unit. This may explain the beneficial effects of cerebrolysin in other CNS disorders involving primary (TBI, SAH) or secondary BBB damage (neurodegenerative diseases), and may also indicate efficacy in blood–spinal cord and blood–retinal barrier injury. However, the action of cerebrolysin in AIS and TBI extends beyond its beneficial effect on the BBB, as clinical improvement has also been observed in patients without hypertension and during long-term clinical follow-up (e.g. 12 months), where the impact of acute BBB damage is already minimal [21].

Furthermore, the neurotrophic effects of cerebrolysin and its role in improving brain plasticity have been well documented, including in post-stroke aphasia rehabilitation, as demonstrated in the recently published ESCAS study [7]. However, the effect of cerebrolysin on the course of the acute phase of haemorrhagic stroke and SAH remains insufficiently understood, although studies are already underway in these indications (e.g. the Polish CLINCH study) [35].

In TBI, the pathomechanisms of secondary damage (excitotoxicity, Ca^{2+}influx, mitochondrial dysfunction, oxidative stress, neuroinflammation, and BBB damage with microcirculatory disturbances) partially overlap with those observed in AIS, providing a biological rationale for cerebroprotective strategies. The CAPTAIN programme and several meta-analyses have demonstrated a significant effect in favour of cerebrolysin on functional outcomes at day 90, with a safety profile comparable to that of placebo, although these findings are limited by considerable heterogeneity in populations and dosing regimens [25–28]. From the perspective of ICU practice, it is particularly important that studies with higher methodological rigour did not show any signal of impaired safety, which is a prerequisite for conducting further pragmatic trials in patients with severe TBI, who are often burdened by systemic complications.

The most significant limitation of the current evidence remains the predominance of open-label and observational studies in the context of MT, as well as the frequent use of historical controls, which increases the risk of residual confounding (including differences in eligibility for EVT, time to reperfusion, post-reperfusion care standards, complication prevention, and the intensity and quality of rehabilitation). Similarly, in thrombolytic trials, the lack of a consistent effect on the mRS at 90 days may reflect insufficient power, differences in time windows and endpoint selection, and population heterogeneity. Consequently, current data on AIS should be regarded as promising yet still insufficient to draw definitive conclusions regarding efficacy.

From a practical standpoint, it seems most reasonable to focus future multicentre RCTs on patients before or shortly after reperfusion, in whom the risk of vascular complications and reperfusion injury is highest (e.g. low ASPECTS, increased risk of HT, significant neurological deficit, absence of collateral circulation). Research designs should include standardised high-quality rehabilitation, multidimensional endpoints (cognitive function, mood, quality of life, and imaging markers, e.g. BBB permeability) and longer follow-up (≥12 months). Only such an approach will allow a reliable determination of whether combining reperfusion with cerebroprotection translates into sustained improvements in prognosis and reductions in disability.

However, from a clinical perspective, while exercising caution in interpretation, data from recent years support considering cerebrolysin as a personalised adjunctive therapy in patients with moderate or severe stroke, particularly in early post-stroke rehabilitation and in scenarios with an increased risk of reperfusion injury, as well as in patients with moderate or severe TBI. The consistency of results across several cohorts, the favourable safety profile, and emerging recommendations from neurorehabilitation scientific societies suggest that further research is warranted, with key challenges including the identification of the population most likely to benefit, and the optimisation of the timing of initiation, dose, and duration of therapy.

Conclusions

- Cerebrolysin appears to be a promising adjunct to reperfusion therapy in ischaemic stroke, with the potential to mitigate reperfusion injury and improve both early neurological recovery and long-term functional outcomes. Further studies are needed to fully determine the role of cerebrolysin in the standard treatment protocol for acute ischaemic stroke, with particular emphasis on optimal dosing, timing of treatment initiation, and identification of patient subgroups most likely to benefit from this treatment.

- In neurointensive care for patients following TBI, the feasibility and safety of cerebrolysin have been demonstrated, whereas evidence regarding efficacy with regard to hard endpoints remains limited. Additional multicentre RCTs designed to reflect real-world ICU settings are needed.

References

1. Ribó M, Staszewski J, Zeiler SR, et al. Cerebroprotection in acute ischemic stroke: Perspectives on combining cerebrolysin with recanalization therapy. J Stroke Cerebrovasc Dis, 2026; 35(1): 108515. doi: 10.1016/j.jstrokecerebrovasdis.2025.108515
2. Cozene B, Sadanandan N, Gonzales-Portillo B, et al. An extra breath of fresh air: hyperbaric oxygenation as a stroke therapeutic. Biomolecules, 2020; 10(9): 1279. doi: 10.3390/biom10091279
3. Mureșanu DF, Livinț Popa L, Chira D, et al. Role and impact of cerebrolysin for ischemic stroke care. J Clin Med, 2022; 11(5): 1273. doi: 10.3390/jcm11051273
4. Rockenstein E, Mante M, Adame A, et al. Effects of cerebrolysin on neurogenesis in an APP transgenic model of Alzheimer's disease. Acta Neuropathol, 2007; 113(3): 265–275. doi: 10.1007/s00401-006-0166-5
5. Al-Kuraishy HM, Al-Gareeb AI, Zekry SH, et al. The possible role of cerebrolysin in the management of vascular dementia: Leveraging concepts. Neuroscience, 2025; 568: 202–208. doi: 10.1016/j.neuroscience.2025.01.040
6. Rybacka-Mossakowska J, Namysł K, Ciemniejewski B, Michalak S. Prezentacja ustna, ESOC, Basel, 2024
7. Homberg V, Jianu DC, Stan A, et al. Speech therapy combined with cerebrolysin in enhancing nonfluent aphasia recovery after acute ischemic stroke: ESCAS randomized pilot study. Stroke, 2025; 56(4): 937–947. doi: 10.1161/STROKEAHA.124.049834
8. Błażejewska-Hyżorek B, Czernuszenko A, Członkowska A, et al. Wytyczne postępowania w udarze mózgu. Polski Przegląd Neurologiczny, 2019; 15(A): 1–156, doi: 10.5603/ppn.2019.0001
9. Rauchman SH, Zubair A, Jacob B, et al. Traumatic brain injury: mechanisms, manifestations, and visual sequelae. Front Neurosci, 2023;17: 1090672. doi: 10.3389/fnins.2023.1090672
10. Lu W, Zhu Z, Shi D, et al. Cerebrolysin alleviates early brain injury after traumatic brain injury by inhibiting neuroinflammation and apoptosis via TLR signaling pathway. Acta Cir Bras, 2022; 37(6): e370605. doi: 10.1590/acb370605
11. Lyden P, Buchan A, Boltze J, Fisher M; STAIR XI Consortium. Top priorities for cerebroprotective studies – a paradigm shift: report from STAIR XI. Stroke, 2021; 52(9): 3063–3071. doi: 10.1161/STROKEAHA.121.034947
12. Bornstein NM, Guekht A, Vester J, et al. Safety and efficacy of cerebrolysin in early post-stroke recovery: a meta-analysis of nine randomized clinical trials. Neurol Sci, 2018; 39(4): 629–640. doi: 10.1007/s10072-017-3214-0
13. Ziganshina LE, Abakumova T, Nurkhametova D, Ivanchenko K. Cerebrolysin for acute ischaemic stroke. Cochrane Database of Systematic Reviews, 2023; 10(10): CD007026. doi: 10.1002/14651858.CD007026.pub7
14. Patel PN, Mangal D, Patel K. Safety and efficacy of cerebrolysin for neurorecovery after acute ischemic stroke: a systematic review and meta-analysis of 14 randomized controlled trials. Cureus, 2025; 17(8): e91054. doi: 10.7759/cureus.91054
15. Khasanova DR, Kalinin MN. Cerebrolysin as an early add-on to reperfusion therapy: risk of hemorrhagic transformation after ischemic stroke (CEREHETIS), a prospective, randomized, multicenter pilot study. BMC Neurol, 2023; 23(1): 121. doi: 10.1186/s12883-023-03159-w
16. Kalinin MN, Khasanova DR. Heterogeneous treatment effects of cerebrolysin as an early add-on to reperfusion therapy: post hoc analysis of the CEREHETIS trial. Front Pharmacol, 2024; 14: 1288718. doi: 10.3389/fphar.2023.1288718
17. Lang W, Stadler CH, Poljakovic Z, Fleet D; Lyse Study Group. A prospective, randomized, placebo-controlled, double-blind trial about safety and efficacy of combined treatment with alteplase (rt-PA) and cerebrolysin in acute ischaemic hemispheric stroke. Int J Stroke, 2012; 8(2): 95–104. doi: 10.1111/j.1747-4949.2012.00901.x
18. Poljakovic Z, Supe S, Ljevak J, et al. Efficacy and safety of cerebrolysin after futile recanalisation therapy in patients with severe stroke. Clin Neurol Neurosurg, 2021; 207: 106767. doi: 10.1016/j.clineuro.2021.106767
19. ElBassiouny A, Shehata MSA, Zaki AS, et al. Cerebrolysin as an adjuvant therapy after mechanical thrombectomy in large vessel occlusion cardioembolic stroke: a propensity score matching analysis. Front Neurol, 2025; 16: 1510284. doi: 10.3389/fneur.2025.1510284
20. Staszewski J, Dębiec A, Strilciuc S, et al. Efficacy of cerebrolysin treatment as an add-on therapy to mechanical thrombectomy in patients with acute ischemic stroke due to large vessel occlusion in anterior circulation: results of a 3-month follow-up of a prospective, open label, single-center study. Transl Stroke Res, 2025; 16(6): 1931–1946. doi: 10.1007/s12975-025-01355-z
21. Staszewski J, Dębiec A, Gniadek-Olejniczak K, et al. Cerebrolysin after endovascular thrombectomy in stroke: 12-month functional outcomes in a propensitymatched cohort. Transl Stroke Res, 2026; 17(2): 28. doi: 10.1007/s12975-026-01414-z
22. Vosko MR, Sanak D, Do Y, et al. C-REGS2-A multinational, high-quality comparative effectiveness study of cerebrolysin in moderate acute ischemic stroke. Int J Stroke, 2025; 20(9): 1060–1070. doi: 10.1177/17474930251375439
23. Mejer-Zahorowski M, Szewczuk A, Staszewski J. Successful treatment of anterior spinal artery syndrome with cerebrolysin. Prezentacja ustna, World Stroke Congress, Abu Dhabi, October 2024
24. Dębiec A, Kubiak M, Ziękiewicz M, et al. Zator tętnicy środkowej siatkówki leczony trombolitycznie i neuroprotekcyjnie – opis przypadku i przegląd literatury. Prezentacja ustna, XXV Zjazd Polskiego Towarzystwa Neurologicznego, Białystok 10.09.2024
25. Poon W, Matula C, Vos PE, et al. Safety and efficacy of cerebrolysin in acute brain injury and neurorecovery: CAPTAIN I – a randomized, placebo-controlled, double-blind, Asian-Pacific trial. Neurol Sci, 2020; 41(2): 281–293. doi: 10.1007/s10072-019-04053-5. Erratum in: Neurol Sci, 2020; 41(3): 733. doi: 10.1007/s10072-019-04149-y
26. Muresanu DF, Florian S, Hömberg V, et al. Efficacy and safety of cerebrolysin in neurorecovery after moderate-severe traumatic brain injury: results from the CAPTAIN II trial. Neurol Sci, 2020; 41(5): 1171–1181. doi: 10.1007/s10072-019-04181-y
27. Mureșanu I, Grad DA, Mureşanu DF, et al. The effect of cerebrolysin on anxiety, depression, and cognition in moderate and severe traumatic brain injury patients: A CAPTAIN II Retrospective Trial Analysis. Medicina (Kaunas), 2022; 58(5): 648. doi: 10.3390/medicina58050648

28. Vester JC, Buzoianu AD, Florian SI, et al. Cerebrolysin after moderate to severe traumatic brain injury: prospective meta-analysis of the CAPTAIN trial series. Neurol Sci, 2021; 42(11): 4531–4541. doi: 10.1007/s10072-020-04974-6
29. Jarosz K, Kojder K, Andrzejewska A, et al. Cerebrolysin in patients with TBI: systematic review and meta-analysis. Brain Sci, 2023; 13(3): 507. doi: 10.3390/brainsci13030507
30. Mureșanu DF, Ciurea AV, Gorgan RM, et al. A retrospective, multi-center cohort study evaluating the severity-related effects of cerebrolysin treatment on clinical outcomes in traumatic brain injury. CNS Neurol Disord Drug Targets, 2015; 14: 587–599. doi: 10.2174/1871527314666150430162531
31. Khalili H, Niakan A, Ghaffarpasand F. Effects of cerebrolysin on functional recovery in patients with severe disability after traumatic brain injury: A historical cohort study. Clin Neurol Neurosurg, 2017; 152: 34–38. doi: 10.1016/j.clineuro.2016.11.011
32. Ghaffarpasand F, Torabi S, Rasti A, et al. Effects of cerebrolysin on functional outcome of patients with traumatic brain injury: a systematic review and meta-analysis. Neuropsychiatr Dis Treat, 2018; 15: 127–135. doi: 10.2147/NDT.S186865
33. Woo PYM, Ho JWK, Ko NMW, et al. Randomized, placebo-controlled, double-blind, pilot trial to investigate safety and efficacy of cerebrolysin in patients with aneurysmal subarachnoid hemorrhage. BMC Neurol, 2020; 20(1): 401. doi: 10.1186/s12883-020-01908-9
34. Amiri-Nikpour MR, Nazarbaghi S, Ahmadi-Salmasi B, et al. Cerebrolysin effects on neurological outcomes and cerebral blood flow in acute ischemic stroke. Neuropsychiatr Dis Treat, 2014; 10: 2299–2306. doi: 10.2147/NDT.S75304
35. Kobayashi A, Rutkowska K, Gocyla-Dudar K, et al. Safety and feasibility of cerebrolysin in treatment of primary intracerebral hemorrhage (CLINCH) – a prospective, randomized, open-label, blinded endpoint pilot trial. Front Neurol, 2025; 16: 1602956. doi: 10.3389/fneur.2025.1602956

REVERSE SURAL FLAP AS AN EFFECTIVE ALTERNATIVE TO FREE FLAPS IN LOWER-LIMB SOFT-TISSUE RECONSTRUCTION – A CASE REPORT

Odwrócony płat łydkowy jako skuteczna alternatywa dla wolnych płatów w rekonstrukcji ubytków tkanek miękkich kończyny dolnej – opis przypadku

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Abstract

Fasciocutaneous flaps offer a wide range of options for the reconstruction of lower-limb soft-tissue defects. This article presents the case of a 39-year-old patient who underwent sarcoma resection in the knee region, followed by reconstruction using a reverse sural flap. This regional flap is characterised by favourable retrograde perfusion, structural stability, and minimal donor-site morbidity, enabling single-stage defect coverage and protection of the deep structures of the knee joint. Free flaps are frequently considered the method of choice for the reconstruction of larger lower limb defects; however, their use may be limited in the presence of peripheral vascular disease, diabetes mellitus, post-traumatic wounds, or in patients with an increased risk of perioperative complications. In contrast, the reverse sural flap provides effective defect coverage, reduced operative time, and a lower risk of complications while preserving limb function. The presented case confirms that the reverse sural flap is a safe, effective, and practical option for lower-limb soft-tissue reconstruction, offering advantages over free microsurgical flaps in selected clinical scenarios.

Streszczenie

Płaty skórno-powięziowe dostarczają szerokich możliwości rekonstrukcji ubytków tkanek miękkich kończyny dolnej. W niniejszym artykule przedstawiono przypadek 39-letniego pacjenta po resekcji mięsaka w okolicy kolana, u którego zastosowano rekonstrukcję z użyciem odwróconego płata łydkowego. Ten regionalny płat charakteryzuje się korzystnym ukrwieniem wstecznym, stabilnością oraz minimalnym obciążeniem miejsca dawczego, co pozwala na jednoczasowe pokrycie ubytku i ochronę struktur głębokich stawu kolanowego. Wolne płaty niejednokrotnie są metodą z wyboru w rekonstrukcji większych defektów kończyny dolnej, jednak ich zastosowanie bywa ograniczone w przypadku współwystępowania chorób naczyń obwodowych, cukrzycy, ran pourazowych lub u pacjentów obciążonych zwiększonym ryzykiem powikłań okołooperacyjnych. Odwrócony płat łydkowy pozwala natomiast na skuteczne pokrycie ubytku, skrócenie czasu operacji oraz ograniczenie ryzyka powikłań przy zachowaniu funkcji kończyny. Opisany przypadek potwierdza, że odwrócony płat łydkowy jest bezpieczną, efektywną i praktyczną metodą rekonstrukcji ubytków tkanek miękkich kończyny dolnej, oferującą w wybranych sytuacjach przewagę nad wolnymi płatami mikrochirurgicznymi.

Keywords: reverse sural flap; lower limb reconstruction; soft tissue defect; knee; alternative to free flaps

Słowa kluczowe: odwrócony płat łydkowy; rekonstrukcja kończyny dolnej; ubytek tkanek miękkich; kolano; alternatywa dla wolnych płatów

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Introduction

Sarcoma is a tumour of mesenchymal origin that develops in soft tissues such as muscles, adipose tissue, blood vessels, and fasciae. Surgical management of sarcomas typically requires radical resection, which results in substantial soft-tissue defects. Effective reconstruction of these defects is essential for protecting the deep structures of the limb, preserving functionality, and enabling the patient's subsequent rehabilitation [1].

A fasciocutaneous flap is a segment of skin and its underlying fascia, transferred to cover a soft-tissue defect. Unlike free microsurgical flaps, regional flaps retain their intrinsic blood supply, allowing them to be transposed or reversed within adjacent anatomical structures. The reverse sural flap is a fasciocutaneous flap in which perfusion occurs retrogradely via perforators of the peroneal artery. This technique provides stable and reliable coverage of lower-limb defects, reducing operative time and lowering the risk of complications compared with free microsurgical flaps [2].

Case report

A 39-year-old man was admitted on an expedited elective basis to the Clinical Department of Plastic, Reconstructive and Burn Surgery at the Military Institute of Medicine – National Research Institute in Warsaw for reconstruction of a knee-region soft-tissue defect following sarcoma resection using a fasciocutaneous flap.

The patient is professionally active and rides motocross recreationally. He had initially undergone soft-tissue sarcoma resection at another centre, after which the procedure was found to be non-radical (positive margins). He subsequently received radiotherapy, followed by re-excision of residual tumour tissue within the scar left by the initial sarcoma. The patient was admitted electively for the reconstruction of the soft-tissue defect in the knee region using a fasciocutaneous flap retrogradely vascularised by perforators of the peroneal artery. Clinical examination revealed a 6 cm × 3 cm soft-tissue defect on the anterior aspect of the knee.

Upon admission, a detailed clinical assessment was performed, and surgical treatment was planned. The operative technique was meticulously defined prior to the procedure. Vascular perforators were mapped on the skin under ultrasound guidance, and the course of the sural nerve was traced, enabling safe planning and dissection of the fasciocutaneous flap. A wound swab was obtained for microbiological analysis. Preoperative thromboprophylaxis and empirical antibiotic therapy with intravenous clindamycin (300 mg three times daily) were initiated. Analgesic management was also maintained. Following completion of the preoperative workup, the patient was cleared and prepared for surgery. In the present case, a fasciocutaneous flap retrogradely vascularised by perforators of the peroneal artery was selected, allowing effective defect coverage while preserving the integrity of the structures surrounding the knee joint.

Stage I of the operation – excision of the lesion and preparation of the reverse sural flap

During the first stage of surgery, the sural flap was harvested. A skin incision was made along the previously marked course of the sural bundle. After dissection through the subcutaneous tissue, the fascia of the gastrocnemius muscle was reached. The fasciocutaneous flap was subsequently dissected together with the neurovascular bundle to approximately 2 cm below the popliteal fossa. The sural nerve and the short saphenous vein were identified, ligated, and transected. Muscular perforators were likewise ligated and transected. Next, the fasciocutaneous flap was elevated along with the skin island, fascia, nerve, and vein up to the pivot point on the fascial pedicle. The flap relied on retrograde vascularisation originating from the perforators of the peroneal artery and the short saphenous vein. Following dissection, the flap was viable and well-perfused. It was left in its original position and secured to the donor-site margins with skin sutures for postoperative observation.

Stage II of the operation – surgical debridement of the medial knee wound with fixation of the reverse sural flap

The wound in the region of the right knee was cleansed and debrided until a bleeding wound bed was obtained. An incision connecting the flap pivot point to the wound was then made. Skin flaps were dissected, and meticulous haemostasis was achieved. The flap was rotated into the knee-region defect and secured with interrupted sutures. A drain was placed beneath the flap at the distal pole. Subsequently, the margins of the donor-site wound were approximated to the muscle using sutures. The donor site for the split-thickness skin graft (STSG) was cleansed and lubricated. A 0.2 mm STSG was harvested from the right thigh using a dermatome. The harvested graft was carefully unfurled over the defect site, achieving complete coverage (100%). Skin staplers and sutures were applied, and dressings were placed over the donor sites. The intra- and post-operative course was uneventful. The surgical count was correct.

Immediately after surgery, the flap demonstrated normal viability. Pharmacological therapy was initiated, consisting of oral acetylsalicylic acid 75 mg once daily and intravenous pentoxifylline 200 mg twice daily. Analgesic management and thromboprophylaxis were continued.

The first dressing change was performed on the second postoperative day. The upper drain was removed, the flap was massaged to evacuate accumulated sanguineous fluid, and patient mobilisation was initiated. On postoperative day 4, the drain was changed, and subsequent dressing changes were performed every two days. From the third day onwards, targeted antibiotic therapy was introduced based on the results of the pre-operative wound swab. Subsequent dressing changes demonstrated a normal healing process. On postoperative day 10, marginal epidermal maceration of the flap was observed; however, healing of the fasciocutaneous flap itself progressed normally. The patient was discharged with recommendations for regular outpatient dressing changes and follow-up.

During further outpatient follow-up, post-operative healing was monitored. The healing process proceeded normally. Approximately one month later, the patient presented with suspected infection of the residual wounds and was readmitted to the department. The patient was afebrile (body temperature 37°C). Secondary intention healing was noted at the donor site within the upper and lower poles of the flap. A wound swab for microbiological culture was obtained, wound toilet was performed, isolated skin staplers were removed, and an iodoform dressing was applied for local antisepsis. The patient remained in good general condition, with improvement in the local wound status. Hospitalisation lasted two days, after which the patient was discharged home with outpatient recommendations. Follow-up visits confirmed complete flap take and normal limb function.

Discussion

Sarcomas are rare malignant neoplasms originating from mesenchymal tissue. They encompass more than 70 histopathological subtypes. Approximately four-fifths arise from soft tissues, with the remainder originating from bone. In Europe, their incidence is estimated at 4–5 cases per 100,000 population annually [3]. Limb-sparing resection is currently considered the gold standard in the treatment of soft tissue sarcomas [4]. Studies have demonstrated that combining surgery with radiotherapy yields better outcomes than surgery alone. However, radiotherapy adversely affects tissue viability and graft take during subsequent reconstruction. The choice between preoperative and postoperative radiotherapy is made individually, as the baseline condition of the tissues plays a crucial role in determining reconstructive options [5].

Plastic surgery procedures are therefore essential for restoring both the appearance and function of the limb following sarcoma treatment [6]. In 1981, Pontén described the fasciocutaneous flap as a reconstructive option for soft-tissue defects of the lower limb, particularly in the knee region. This flap is now widely used across the lower leg – from the heel and ankle to the knee – though it is most frequently applied in the distal third of the leg [7]. The sural flap is typically located between the popliteal fossa and the mid-calf, overlying the heads of the gastrocnemius muscle. It is one of the longest fasciocutaneous flaps in the lower limb [7]. The reverse sural flap is an island flap innervated by the sural nerve, with retrograde perfusion supplied by perforators of the peroneal artery. Dissection of this flap requires caution, primarily with regard to the peroneal artery [8]. Doppler ultrasonography is highly valuable in preoperative planning, as precise assessment of the vascular supply is essential [7]. Because the flap is pedicled, its harvest does not require microsurgical infrastructure. Consequently, this method is more accessible than other modalities and can be performed by centres with varying resources [9].

In a systematic review, Tripathee et al. reported that complications occurred in approximately one-quarter of patients undergoing reconstruction using a reverse sural flap. The most common complications included partial flap necrosis and venous congestion [9]. Mild venous congestion typically resolves spontaneously within a few days [7]. Total flap necrosis – the most severe complication – occurred in approximately 2.5% of cases. Early detection of signs of impaired flap adaptation can help prevent total necrosis; hence, training medical staff in recognizing early abnormalities is essential [9]. Other reported complications include haematoma and infection of the surrounding tissues. Risk factors for complications include diabetes mellitus, age over 40 years, and vascular diseases [8].

Nevertheless, the reverse sural flap is used to treat defects in patients with diabetic foot ulcers, achieving an excellent healing rate despite the baseline presence of these risk factors [8]. However, although this method can be successfully used in patients with diabetes and peripheral vascular disease, caution is advised in smokers, whose risk of partial necrosis is approximately threefold higher [10]. Venous insufficiency is another significant risk factor, increasing the risk of complications up to ninefold [11]. Because the flap is harvested with its innervation, patients experience temporary sensory loss and paraesthesias on the lateral aspect of the foot, which typically resolve over time [7]. Methods used to manage the most serious complication – partial or total flap necrosis – include leg elevation, catheterisation of the proximal stump of the lesser saphenous vein, and venous 'supercharging'. Some authors also recommend the flap delay technique, which involves transecting a vessel or incising the lateral borders of the skin island to redirect blood flow. A disadvantage of the flap, limited to aesthetic concerns, is the visible donor-site scar; however, it does not result in any functional impairment of the limb [7].

Despite this, the sural flap is widely used in reconstructive surgery and is characterized by a safety profile comparable to other methods of covering tissue defects. Due to the high efficacy of this method in both adult and paediatric populations, the sural flap should be considered a valuable option in reconstructive therapy across all age groups [12]. Its main advantages include relatively simple dissection, preservation of the major arteries supplying the lower limb, and a low incidence of donor-site complications [8]. Importantly, its greatest strength is the ability to perform successful reconstruction without microsurgical expertise, which significantly increases its availability [9].

The lower limb is a surgically demanding region and often presents greater reconstructive challenges than other anatomical areas [13]. Historically, free muscle flaps were considered optimal for defects with exposed bone due to the rich vascularity of muscle tissue. However, subsequent evidence has demonstrated that fasciocutaneous flaps possess higher vascular density and should be regarded as the method of choice for reconstructing defects with exposed bone surfaces [14]. There is no single universal technique for the management and reconstruction of soft-tissue defects that can meet the needs of all patients. Nevertheless, the sural flap remains one of the most commonly used reconstructive methods and is associated with good functional outcomes [15].

The choice between using a reversed sural flap and a free flap remains a topic of debate among reconstruc-

tive surgeons. According to the principle of the "reconstructive ladder", the sural flap occupies an earlier stage than free flaps because of its characteristics. Studies have demonstrated more favourable outcomes of flap adaptation with the sural flap than with free flaps [9]. It is a particularly useful method when contraindications to microsurgical reconstruction using a free tissue flap are present [7]. A study involving 221 paediatric patients compared the use of a pedicled sural flap with that of a free microsurgical flap. The mean surface area of tissue used to cover the defect was significantly larger in the free-flap group. Significantly more patients required a skin graft at the donor site after using the pedicled sural flap, whereas a significantly greater number of patients undergoing reconstruction with a free flap required secondary thinning. Differences in the frequency of postoperative complications were not statistically significant, and both methods demonstrated comparable safety profiles. However, the sural flap is less demanding because it does not require microsurgical skills from the operator, and the operative time is shorter. The surface area of the harvested tissues is smaller, and consequently, the sural flap is intended for the reconstruction of defects of a specific location and size, due to its pedicle and limited dimensions [14].

In cases where the skin and soft tissues of the posterior aspect of the lower leg are intact, the reversed sural flap represents a good and accessible method for the surgical reconstruction of defects of various aetiologies [16]. Another advantage is that any necessary revision and tissue elevation are considerably easier than in the case of a free flap [14].

Conclusions

Following a two-stage sarcoma resection and complementary scar excision, the patient underwent reconstruction of the tissue defect using a reverse sural flap. This treatment enabled him to return to physical activity without any functional limitation of the tumour-affected limb. Although reconstruction using a reverse sural flap – like any surgical procedure – may be associated with complications, it typically does not lead to long-term sequelae. Most complications can be managed conservatively with appropriate wound care and rehabilitation. The reverse sural flap, characterised by retrograde vascularisation, remains one of the primary methods for soft-tissue reconstruction of the lower leg, ankle, and foot. It is a readily accessible option for covering tissue defects and does not require microsurgical expertise.

References

1. Rutkowski P, Nowecki Z (eds.). Mięsaki tkanek miękkich u dorosłych. Warszawa: Medical Tribune Polska; 2009
2. Wei FC, Mardini S. Flaps and reconstructive surgery. Edinburgh: Elsevier Saunders; 2009: 45–78
3. Soomers V, Husson O, Young R, et al. The sarcoma diagnostic interval: a systematic review on length, contributing factors and patient outcomes. ESMO Open, 2020; 5(1): e000592. doi: 10.1136/esmoopen-2019-000592
4. Gatto A, Cavalli EM, Stucchi S, et al. One-stage surgical resection and functional reconstruction for upper limb soft tissue sarcoma. Ann Plast Surg, 2024; 93(5): 575–588. doi: 10.1097/SAP.0000000000004107
5. Guadagnolo BA, Bassett RL, Mitra D, et al. Hypofractionated, 3-week, preoperative radiotherapy for patients with soft tissue sarcomas (HYPORT-STS): a single-centre, open-label, single-arm, phase 2 trial. Lancet Oncol, 2022; 23(12): 1547–1557. doi: 10.1016/S1470-2045(22)00638-6
6. Piper M, Irwin C, Sbitany H. Pediatric lower extremity sarcoma reconstruction: A review of limb salvage procedures and outcomes. J Plast Reconstr Aesthet Surg, 2016; 69(1): 91–96. doi: 10.1016/j.bjps.2015.08.035
7. Ciofu RN, Zamfirescu DG, Popescu SA, Lascar I. Reverse sural flap for ankle and heel soft tissues reconstruction. J Med Life, 2017; 10(1): 94–98
8. Yammine K, Eric M, Nasser J, Chahine A. Effectiveness of the reverse sural flap in covering diabetic foot ulcers: a systematic review and meta-analysis. Plast Surg (Oakv), 2022; 30(4): 368–377. doi: 10.1177/22925503211019617
9. Tripathee S, Basnet SJ, Lamichhane A, Hariani L. How safe is reverse sural flap? A systematic review. Eplasty, 2022; 22: e18
10. Daar DA, Abdou SA, David JA, et al. Revisiting the reverse sural artery flap in distal lower extremity reconstruction: a systematic review and risk analysis. Ann Plast Surg, 2020; 84(4): 463–470. doi: 10.1097/SAP.0000000000002041
11. de Blacam C, Colakoglu S, Ogunleye AA, et al. Risk factors associated with complications in lower-extremity reconstruction with the distally based sural flap: a systematic review and pooled analysis. J Plast Reconstr Aesthet Surg, 2014; 67(5): 607–616. doi: 10.1016/j.bjps.2014.01.044
12. Wang A, Durand JPF, Dadzie AI, et al. Application of reverse sural flaps in pediatric patients: a systematic review. Ann Plast Surg, 2025; 94(2): 236–242. doi: 10.1097/SAP.0000000000004115
13. Serra PL, Boriani F, Khan U, et al. Rate of free flap failure and return to the operating room in lower limb reconstruction: a systematic review. J Clin Med, 2024; 13(15): 4295. doi: 10.3390/jcm13154295
14. Beecher SM, Cahill KC, Theopold C. Pedicled sural flaps versus free anterolateral thigh flaps in reconstruction of dorsal foot and ankle defects in children: a systematic review. Arch Plast Surg, 2021; 48(4): 410–416. doi: 10.5999/aps.2020.00983
15. Crowe CS, Cho DY, Kneib CJ, et al. Strategies for reconstruction of the plantar surface of the foot: a systematic review of the literature. Plast Reconstr Surg, 2019; 143(4): 1223–1244. doi: 10.1097/PRS.0000000000005448
16. Cui Z, Zhang X, Shou J, Yin G. Repeated reverse sural fasciocutaneous flap is an effective surgical strategy for repairing long segmental soft tissue defects of the tibia. J Int Med Res, 2019; 47(10): 5003–5009. doi: 10.1177/0300060519874154