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Analysis of outpatient consumption of propulsives in Ukraine compared with Norway and the Baltic states

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Abstract. Disorders involving impaired gastrointestinal peristalsis are widely prevalent both globally and in Ukraine. Propulsives drugs, which enhance the motor activity of the gastrointestinal tract and prevent antiperistaltic contractions of the intestinal smooth muscle, are used in the treatment of such conditions. This study aimed to assess the outpatient consumption of medicinal products classified under group A03F propulsives in Ukraine between 2020 and 2022, in comparison with published data on the use of the same drug group in Norway, Estonia, Lithuania, and Latvia. Consumption volumes were determined using the ATC/DDD methodology and expressed in DDDs per 1,000 inhabitants per day (DIDs). The results were compared with corresponding published statistical data from Norway and the Baltic countries. The findings indicated that the consumption of medicines in group A03F ranged from 0.98 to 1.21 DIDs over the study period, with a decrease observed in 2022. Ukraine differed only slightly from Norway and the Baltic states in terms of the consumption levels of these medicines. The leading position in the consumption of A03F group medicines varied by year: in 2020 – Norway; in 2021 – both Ukraine and Norway; and in 2022 – Lithuania. The lowest consumption volumes were recorded in Estonia. During the study period, domperidone was the most commonly used propulsives in Ukraine, while metoclopramide was most widely used in Norway and the Baltic countries. A comparative assessment of approaches to the use of propulsives in these countries was conducted. The findings may be used to determine the level of access in Ukraine to essential medicines for patients with gastrointestinal motility disorders and to support decision-making by healthcare authorities regarding regulatory measures

Keywords: pharmaceutical market; ATC/DDD methodology; medicine consumption; gastrointestinal motility disorders; metoclopramide; domperidone; itopride hydrochloride; mosapride

Introduction

Disorders of peristalsis play a significant role in the patho-genesis of many gastrointestinal (GI) diseases and conditions. According to the Rome Foundation Global Epidemiology Study (RFGES), the global prevalence of functional GI disorders averages 40.3%. These conditions have substantial economic implications for healthcare systems

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and adversely affect patients' quality of life [1]. As reported by A. Vernon-Roberts *et al.* [2], functional GI disorders account for approximately 5% of visits to primary care physicians and are a common reason for referrals to tertiary care services for further investigation or to exclude serious organic diseases. A. Fikree *et al.* [3] note that such disorders are associated with 30% of outpatient gastroenterology consultations and represent 12% of the workload in primary care. Motor function disorders occur in patients of various ages and sexes, although they are more frequently observed in women than in men. According to Y.V. Karulina [4], such disorders are present in over 30% of paediatric patients with digestive system pathologies. These findings highlight the relevance of investigating the population-level consumption of medicines used to treat gastrointestinal peristalsis disorders.

Propulsives are the treatment of choice for GI motility disorders. Through various mechanisms of action, they enhance GI motor activity, prevent antiperistaltic contractions of the intestinal smooth muscle, and are used as part of first-line therapy for functional GI disorders. According to V.V. Chernyavskyi & L.L. Pavlovskyi [5], medicines from this group are considered a cornerstone of pharmacotherapy and are prioritised in the treatment of functional dyspepsia with predominant postprandial distress syndrome. In a study on approaches to prokinetic therapy for gastric motility disorders conducted by M. Camilleri *et al.* [6], it was found that propulsives are prescribed as the first pharmacological option following dietary advice, due to their ability to improve gastric emptying and alleviate symptoms of gastroparesis. An expert review by the European Society of Neurogastroenterology and Motility and the American Neurogastroenterology and Motility Society, as presented by S. Bor *et al.* [7], emphasised that medicines in this group improve GI motility both regionally and throughout the intestine. Each agent has specific advantages and limitations, as well as a distinct safety profile. These findings are supported by research conducted by Y.V. Nikiforova [8], which explored the clinical use of propulsives. In particular, the study highlighted the role of domperidone in the treatment of functional dyspepsia and gastro-oesophageal reflux disease, as well as its potential use following gastric resection, during cytostatic therapy, and in diabetic gastroparesis.

Available literature provides limited data on the consumption of medicines from the A03F group, propulsives. The existing data, obtained using the ATC/DDD methodology, are primarily the results of previous studies conducted on outpatient consumption of medicines from this group in Ukraine and selected other countries during 2016-2018 [9]. Comparable studies on the consumption of propulsives, expressed in DDDs per 1,000 inhabitants per day, conducted outside Ukraine are not found in the currently accessible literature. Only hospital consumption data for the broader A03 group, Drugs for functional gastrointestinal disorders, are available – specifically for Romania (1998-2018), as reported by M. Pană *et al.* [10], and for Moldova (2009-2013), as documented by E.P. Bernaz [11].

Given the growing global relevance of gastrointestinal motility disorders, continued investigation into the consumption of A03F group medicines in Ukraine is warranted, along with a comparative analysis of their use in other countries. This study aimed to assess the outpatient consumption of A03F propulsives in Ukraine between 2020 and 2022, in comparison with published data on the same group of medicines in Norway, Estonia, Lithuania, and Latvia.

Materials and Methods

The study period (2020-2022) was selected based on the most recent available statistical data on outpatient consumption of A03F group medicines, propulsives, in the countries chosen for comparison. Data from the pharmaceutical market research system "Proxima Research"/"Morion" provided by Morion Ltd were used to analyse the range and volume of these medicines. This included information on the number of international non-proprietary names (INNs), trade names (TNs), and units of medicine sold.

To assess outpatient medicine consumption, the ATC/DDD methodology was employed. This method is recognised by the World Health Organization (WHO) as the international standard in this field. The ATC/DDD methodology is based on the Anatomical Therapeutic Chemical (ATC) classification system and the assumed average maintenance dose per day for a medicine used for its main indication in adults (Defined Daily Dose – DDD) [12, 13]. Compared to other approaches that measure consumption in physical units (e.g. number of packages), the ATC/DDD methodology calculates a relative indicator and is considered the most reliable for evaluating whether the structure of medicine use aligns with the needs of the healthcare system. It also allows for meaningful cross-country comparisons.

The DDD values for the INNs of the medicines were obtained from the WHO website [14]. Where DDDs were not available, the Prescribed Daily Dose (PDD) was calculated using the official instructions for medical use. To determine the volume of A03F propulsives consumed in Ukraine, the number of DDDs for each medicine was calculated for each study year, followed by the calculation of DDDs per 1,000 inhabitants per day (DIDs). This relative indicator made it possible to estimate the number of DDDs consumed daily by every 1,000 people in the population over the study period. For the calculation of DIDs, population data from the State Statistics Service of Ukraine [15] were used, reflecting the available population as of 1 January for each respective year: 2020 – 41,902.4 thousand; 2021 – 41,588.4 thousand; 2022 – 41,167.3 thousand. The formula applied for the calculation was:

$$DIDs = DDDs \times 1{,}000 / Population\ of\ Ukraine \times 365\ days, \quad (1)$$

where *DDDs* is the number of defined daily doses consumed in Ukraine in a given year.

To compare the volume, structure, and dynamics of outpatient consumption of A03F group medicines in Ukraine during 2020-2022 with other countries, Norway

and the Baltic states (Lithuania, Latvia, and Estonia) were selected. The selection criterion for these countries was the availability of statistical data on outpatient consumption of A03F medicines during the same period, calculated using the ATC/DDD methodology, as published for Norway [16], Estonia [17], Lithuania [18], and Latvia [19].

Results and Discussion

At the first stage of the study, the range of A03F propulsives available on the Ukrainian pharmaceutical market during 2020-2022 was analysed, and the number of INNs and TNs recorded within the study period was determined. The findings are presented in Table 1. Analysis of the Ukrainian pharmaceutical market revealed that medicines in the A03F group were represented by four INNs between 2020 and 2022: domperidone, metoclopramide, itopride hydrochloride, and mosapride. The number of TNs for prokinetic agents varied slightly over the years, ranging from 33 to 34. Domperidone products accounted for the majority (18-20 TNs), while mosapride was represented by only one TN. Throughout the study period, the market was predominantly composed of Ukrainian-produced A03F medicines. Notably, no Ukrainian-manufactured trade names of mosapride were present during this time. The price range per pack for TNs of metoclopramide, domperidone, and itopride hydrochloride was broad, providing options suitable for patients with varying levels of purchasing power.

Table 1. Range of A03F propulsives on the Ukrainian pharmaceutical market in 2020-2022

ATC code, INN of medicines	Number of TN of medicines			Number of Ukrainian/ imported TNof medicines			Price range per package of medicine, UAH		
	2020	2021	2022	2020	2021	2022	2020	2021	2022
A03FA01 Metoclopramide	7	7	7	5/2	5/2	5/2	38.24-533.16	40.91-576.59	48.89-620.87
A03FA03 Domperidone	20	18	18	14/6	12/6	12/6	11.67-189.77	21.68-199.70	26.87-245.35
A03FA07 Itopride hydrochloride	6	7	8	1/5	2/5	2/6	111.59-641.80	115.39-656.51	133.39-855.36
A03FA09 Mosapride	1	1	1	0/1	0/1	0/1	158.68	173.73	217.81
Total	34	33	34	20/14	19/14	19/15	11.67-641.80	21.68-656.51	26.87-855.36

Source: compiled by the authors based on original research

In Ukraine, the use of prokinetic agents is regulated by current unified clinical protocols for the medical management of patients with gastro-oesophageal reflux disease and dyspepsia [20, 21], as well as the new clinical protocol "Guidelines 00172. Nausea and Vomiting", developed by international experts [22]. Trade names of metoclopramide, a representative of this pharmacological group, are included in the Affordable Medicines programme, according to the List of Medicinal Products subject to reimbursement under the state-guaranteed healthcare scheme [23]. The next stage of the study involved calculating DDDs per 1,000 inhabitants per day (DIDs) for A03F propulsives available on the Ukrainian pharmaceutical market during the study period, with the aim of assessing the volume, structure and trends in their outpatient use. The results showed that consumption levels of A03F propulsives in Ukraine over 2020-2022 were as follows: 2020 – 1.08 DIDs; 2021 – 1.21 DIDs; 2022 – 0.98 DIDs. Consumption figures for this medicine group varied annually, with the lowest value recorded in 2022 compared to previous years. Based on these findings, calculated per 1,000 Ukrainian inhabitants, it can be concluded that approximately 0.10%-0.12% of the Ukrainian population consumed one Defined Daily Dose (DDD) of a propulsives each day throughout the respective years. The consumption volumes of the INN of medicines belonging to the A03F group in Ukraine during 2020-2022 are shown in Figure 1.

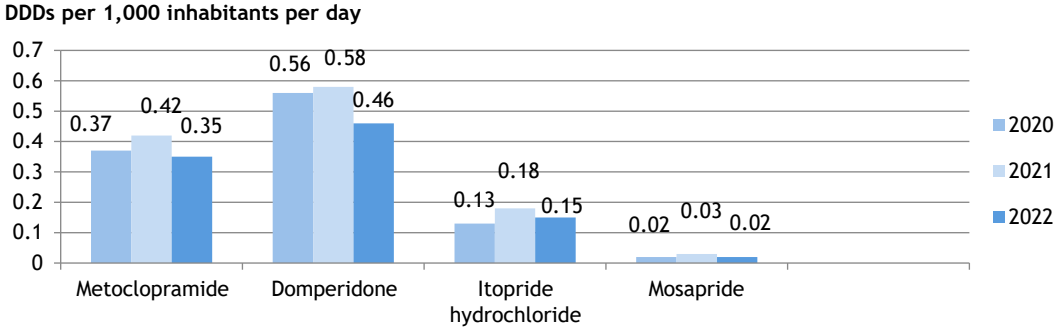

Figure 1. Outpatient consumption of A03F propulsives in Ukraine by INN, 2020-2022

Source: compiled by the authors based on original research

The highest consumption volumes in 2020-2022 were recorded for domperidone, which accounted on average for 49% of the total consumption of A03F medicines. This can be attributed to the wide availability of low-cost generics in the Ukrainian pharmaceutical market. These findings are consistent with data from the "PharmXplorer" market research system by Proxima Research, which listed domperidone among the top 10 most frequently prescribed INNs by gastroenterologists for digestive disorders in 2022 [24]. The lowest consumption volumes were observed for mosapride. During 2020-2021, the consumption of all A03F propulsives increased, but in 2022, there was a decline, coinciding with the onset of russia's full-scale invasion of Ukraine. This decrease may be linked to the significant migration of the Ukrainian population to other countries.

The next stage of the study involved comparing the results of outpatient consumption of A03F propulsives in Ukraine with published statistical data for 2020-2022 from Norway, Estonia, Lithuania and Latvia. The results are presented in Table 2.

Table 2. Volume and structure of consumption (DDDs per 1,000 inhabitants per day) of A03F propulsives in Ukraine, Norway, Estonia, Lithuania, Latvia in 2020-2022

No.	ATC code,INN of medicines	Indicator (DDDs per 1,000 inhabitants per day - DIDs)/country/years														
		Ukraine			Norway			Estonia			Lithuania			Latvia		
		2020	2021	2022	2020	2021	2022	2020	2021	2022	2020	2021	2022	2020	2021	2022
1	A03FA01 Metoclopramide	0.37	0.42	0.35	1.13	1.20	1.26	0.80	0.84	0.89	0.87	0.85	0.96	0.70	0.74	0.76
2	A03FA03 Domperidone	0.56	0.58	0.46	0.01	0.01	0.01	0.01	0.02	0.02	0.17	0.19	0.22	0.31	0.31	0.31
3	A03FA07 Itopride hydrochloride	0.13	0.18	0.15	-	-	-	-	-	-	-	-	0.24	-	-	-
4	A03FA09 Mosapride	0.02	0.03	0.02	-	-	-	-	-	-	-	-	-	-	-	-
	Total	1.08	1.21	0.98	1.14	1.21	1.27	0.81	0.86	0.91	1.04	1.04	1.42	1.01	1.05	1.07

Source: compiled by the authors based on original research and data [16-19]

During the study period, a nearly identical proportion of the population in each of the countries examined consumed 1 DDD of one of the prokinetic agents daily: Norway – between 0.11% and 0.13%, Lithuania – between 0.10% and 0.14%, Latvia – between 0.10% and 0.11%, and Estonia – between 0.08% and 0.09%. Leadership in the volume of A03F propulsives consumption shifted across countries during the period: in 2020, Norway ranked highest; in 2021, Ukraine and Norway shared the lead; and in 2022, Lithuania recorded the highest levels. Estonia consistently reported the lowest consumption volumes throughout the entire study period. Across all countries, the consumption of A03F propulsives fluctuated over time. In 2022, a decrease in consumption was observed in Ukraine, while Norway, Estonia, Latvia, and Lithuania recorded increases. Notably, Lithuania experienced a 1.3-fold increase in 2022 compared with 2020 and 2021, possibly due to an expansion in the range of available INNs of prokinetic agents in that year.

An analysis of the consumption structure of this group of medicinal products revealed that four substances were used in Ukraine (metoclopramide, domperidone, itopride hydrochloride, and mosapride). According to published statistical data from Norway [16], Estonia [17], and Latvia [19], only two INNs (domperidone and metoclopramide) were recorded over the three-year study period. In Lithuania, only two INNs (domperidone and metoclopramide) were used during 2020-2021, while in 2022, data on the consumption of three INNs (domperidone, metoclopramide, and itopride hydrochloride) were reported [18]. In Ukraine, domperidone was the clear leader in terms of consumption volume, whereas in the other four European countries studied, metoclopramide was most frequently used. This indicates differing national approaches to the use of A03F propulsives.

Ambulatory consumption of A03F group medicinal products has been the subject of relatively limited academic investigation. Available literature includes data only from a previous study by the authors on the use of this group of medicinal products in 2016-2018 in Ukraine and selected European countries (Norway, Estonia, Lithuania, and Latvia) [9], with no additional research findings reported by other scholars.

A comparison of the results of propulsives consumption in Ukraine during 2020-2022, as presented in the current study, with those from the earlier analogous study [9], indicates that there were no significant changes in consumption levels of this group of medicinal products over the six-year observation period: 1.03 in 2016, 1.15 in 2017, 1.27 in 2018 [9], 1.08 in 2020, 1.21 in 2021, and 0.98 in 2022. While Ukraine led in the consumption of these medicines among the studied European countries in 2018, it held lower positions in the rankings in 2016-2017 and 2020-2022. However, the overall differences in consumption volumes across the countries were relatively minor. Estonia consistently recorded the lowest values for DDDs per 1,000 inhabitants per day for this group of medicines across both study periods (2016-2018 and 2020-2022). Over time, the proportion of the population taking 1 DDD of a propulsives daily remained largely unchanged in Ukraine, Norway, and the Baltic states, ranging from 0.10% to 0.12% in Ukraine during both the 2016-2018 and 2020-2022 periods. Norway recorded a daily consumption rate of 0.11% during 2016-2018, increasing slightly to between 0.11% and 0.13% in 2020-2022. In Lithuania, the proportion ranged from 0.12% to 0.14% in 2016-2018, and from 0.10% to 0.14% in 2020-2022. In Latvia, it varied between 0.11% and 0.13% during 2016-2018 and between 0.10% and 0.11% in 2020-2022.

Estonia consistently showed the lowest values, from 0.08% to 0.09%, across both periods. Notably, changes in the approach to the use of A03F propulsives were observed only in Lithuania. In 2022, the use of itopride hydrochloride was introduced in the country, which may be attributed to its favourable safety profile compared with other propulsives. This advantage was explicitly highlighted in the Rome IV criteria for functional gastrointestinal disorders [25]. The leading substances by the number of consumed DDDs remained unchanged in 2020-2022: in Ukraine, domperidone was predominant, while in Norway and the Baltic states, metoclopramide maintained its leading position. These two medicines are the most widely known and well-researched representatives of the propulsives [5, 6].

Metoclopramide and domperidone are both dopamine receptor antagonists; however, they differ in chemical structure, and consequently in their safety profiles and clinical applications [26-28]. Metoclopramide inhibits central dopamine D2 and serotonin 5-HT3 receptors, blocks intestinal D2 and muscarinic receptors, and acts as an agonist at peripheral 5-HT4 serotonin receptors. According to V.V. Chernyavskyi & L.L. Pavlovskyi [5], who examined the use of propulsives in the management of functional gastroduodenal disorders, metoclopramide is primarily employed as an anti-nausea and antiemetic agent. In the opinion of S.M. Tkach & A.E. Dorofieiev [26], who conducted a comparative analysis of the efficacy and safety of dopamine receptor antagonists in gastrointestinal disorders, metoclopramide is considered a weak stimulant of intestinal peristalsis and is most frequently prescribed for gastroparesis of various origins. According to M.A. Kalas *et al.* [27], who investigated the mechanism of action and safety profile of metoclopramide, it is regarded as the only medicine approved by the FDA in the past 40 years specifically for the treatment of gastroparesis.

According to a study by Y.V. Nikiforova [8] on the role and place of domperidone in contemporary clinical practice, domperidone is considered the treatment of choice for managing peristaltic disorders and is included in combination therapy regimens for GI disease. Domperidone belongs to the benzimidazole class and acts as a peripheral D2-receptor antagonist. These receptors mediate dopamine's predominantly inhibitory effect on smooth muscle by interacting with the cholinergic system [26]. As reported by H.V. Osiodlo & O.O. Fedorova [25], domperidone does not cross the blood-brain barrier and therefore does not cause many of the central adverse effects associated with metoclopramide, such as extrapyramidal disorders, headache, dizziness or drowsiness. According to V.V. Chernyavskyi & L.L. Pavlovskyi [5], the most clinically significant adverse reactions associated with domperidone involve the cardiovascular system. These include sudden cardiac death, QT interval prolongation, severe ventricular arrhythmias and torsade de pointes tachycardia. As a result, the use of domperidone has been restricted in many countries [26], prompting numerous clinical studies on its cardiovascular safety. These studies have supported its continued use with strict precautions. A cohort study by A. Cowan *et al.* [28] found a low risk of hospitalisation due to ventricular arrhythmia following a 30-day course of outpatient treatment with domperidone. No significant difference in risk levels was identified between domperidone and metoclopramide. According to other researchers [25], significant adverse effects associated with domperidone include elevated serum prolactin levels and the development of gynaecomastia, galactorrhoea and amenorrhoea. It is recommended that domperidone be used at the lowest effective dose for the shortest duration necessary to control symptoms. This approach helps minimise the risk of adverse effects, as demonstrated in the study by S. Alkhowaiter *et al.* [29], which investigated the treatment of chronic GI motility disorders in patients with systemic sclerosis. These adverse effects may have influenced the level of domperidone consumption observed in Norway, Estonia, Lithuania and Latvia, as established in the present study. In Ukraine, the use of domperidone is regulated by the current unified clinical protocols for the management of patients with gastro-oesophageal reflux disease and dyspepsia [20, 21].

The differences identified in the use of propulsives between Ukraine and the studied European countries highlight the need for further investigation into the medical, social, economic and political factors that affect the consumption and therapeutic use of this group of medicines across different countries. Relevant areas for exploration include clinical prescribing practices, the structure and policies of national healthcare systems, regulatory frameworks for medical care, medicine availability, patient awareness of treatment, and adherence to prescribed therapies. The findings from such studies could be valuable for healthcare policymakers and may contribute to improving medical and pharmaceutical care for patients with GI motility disorders.

Conclusions

Using the ATC/DDD methodology, an assessment was conducted of outpatient consumption of medicines in the A03F group, propulsives, in Ukraine during 2020-2022. The results were compared with published data on the consumption of this group of medicines in Norway and the Baltic countries. During the study period, four INNs from this group (metoclopramide, domperidone, itopride hydrochloride, and mosapride) were available on the Ukrainian pharmaceutical market, represented by 33 to 34 TN of medicines, mostly produced by Ukrainian manufacturers. Outpatient consumption volumes of propulsives, measured by the number of DDDs consumed, varied in Ukraine during the study period, with a 19% decrease recorded in 2022 compared to 2021. This decline may be attributed to the mass migration of the population abroad following the outbreak of full-scale war in the country.

The level of outpatient consumption of propulsives in Ukraine during 2020-2022 differed only slightly from that in Norway and the Baltic countries. Throughout the study period, the consumption of medicines in this group

fluctuated across all these countries, with the highest levels recorded in different countries in different years – Norway, Ukraine, and Lithuania. The lowest level of consumption during 2020-2022 was observed in Estonia. In contrast to Ukraine, a general upward trend in outpatient consumption of propulsives was noted in Norway and the Baltic countries, possibly reflecting gradual improvements in the diagnosis of functional bowel disorders and increased attention to patients' quality of life.

In terms of structure, outpatient consumption of medicines in the A03F propulsives in Ukraine differed significantly from that in Norway and the Baltic countries. In Ukraine, domperidone was the most commonly prescribed, whereas metoclopramide predominated in Norway and the Baltic states. Unlike Ukraine, clinical practice in Norway, Estonia, and Latvia was limited to TNs based on only two INNs (domperidone and metoclopramide), while in Lithuania, three INNs (domperidone, metoclopramide, and itopride hydrochloride) were used. These differences reflect varying approaches to the treatment of conditions associated with gastrointestinal motility disorders and the use of this group of medicines across the studied countries, which are shaped by national clinical guidelines, medical traditions, and medicine availability.

The study findings may contribute to the development of pharmaceutical policy and reimbursement systems for A03F group medicines in Ukraine within the framework of outpatient care for gastrointestinal motility disorders. Given the widespread prevalence of such conditions among the population of Ukraine and other countries, as well as the observed variation in the use of propulsives across different nations, further research into the volume of A03F medicine consumption in Ukraine, and comparisons with other countries in terms of consumption volume and structure, would be beneficial.

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Аналіз амбулаторного споживання стимуляторів перистальтики в Україні у порівнянні з Норвегією та країнами Балтії

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Анотація. Захворювання з розладами перистальтики шлунково-кишкового тракту значно поширені серед населення як в світі, так і в Україні. При їх лікуванні застосовують препарати стимуляторів перистальтики, які посилюють моторну активність шлунково-кишкового тракту і запобігають антиперистальтичним скороченням гладкої мускулатури в кишечнику. Метою роботи була оцінка амбулаторного споживання лікарських засобів групи A03F «Стимулятори перистальтики» у 2020-2022 роках в Україні у порівнянні з аналогічними опублікованими даними щодо споживання лікарських засобів цієї ж групи в таких країнах, як Норвегія, Естонія, Литва та Латвія. Обсяги споживання препаратів визначали за ATC/DDD-методологією у показниках «DDDs/1000 жителів/день» (або DIDs). Отримані дані порівнювали з аналогічними опублікованими статистичними даними Норвегії та країн Балтії. Основні результати дослідження показали, що обсяги споживання лікарських засобів групи A03F «Стимулятори перистальтики» протягом досліджуваного періоду становили 0,98-1,21 DIDs та в 2022 році зменшились. Україна незначно відрізнялась від Норвегії та країн Балтії за рівнем споживання цих препаратів. Позицію лідера за обсягами споживання лікарських засобів досліджуваної групи A03F обіймали різні країни: 2020 рік – Норвегія, 2021 рік – Україна та Норвегія, 2022 рік – Литва. Найменші обсяги споживання встановлені в Естонії. Лідером за обсягами споживання у досліджуваний період в Україні був домперидон, в Норвегії та країнах Балтії – метоклопрамід. Проведена порівняльна оцінка підходів до використання стимуляторів перистальтики в цих країнах. Отримані дані можуть бути використані для встановлення рівня забезпеченості в Україні пацієнтів з захворюваннями, які супроводжуються порушеннями перистальтики шлунково-кишкового тракту, базовими препаратами для їх корекції, і для прийняття відповідних регуляторних рішень організаторами охорони здоров'я

Ключові слова: фармацевтичний ринок; ATC/DDD-методологія; споживання лікарських засобів; порушення перистальтики шлунково-кишкового тракту; метоклопрамід; домперидон; ітоприду гідрохлорид; мозаприд

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Progress and prospects in research on low-grade diffuse chronic inflammation: A literature review

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Abstract. Low-grade inflammation (LGI) underlies numerous chronic diseases, including today's major non-communicable pandemics such as cardiovascular diseases, metabolic syndrome, type 2 diabetes, obesity, chronic obstructive pulmonary disease, chronic inflammatory bowel diseases, non-alcoholic fatty liver disease, chronic kidney disease, neurodegenerative disorders, and certain types of cancer. This review aimed to analyse recent findings from scientific and medical publications concerning LGI, which remains a pressing issue. Considerable progress has been made in understanding key aspects of this condition, including the concept of LGI, its aetiology and pathogenesis, its role in the onset and progression of chronic non-communicable diseases, as well as in approaches to diagnosis, treatment, and prevention. Research in this area primarily focused on the aetiology and pathogenesis of LGI, its association with chronic non-communicable diseases – especially metabolic disorders – and strategies for its modulation. The scope of this research covered the concept and prevalence of LGI; the significance of unhealthy dietary patterns, gut microbiota, social and psychosocial factors, sex and age in the aetiology and pathogenesis of LGI; certain molecular mechanisms involved in LGI; and its role in the development and progression of various chronic conditions and syndromes, including chronic pain, depression, Alzheimer's disease, post traumatic stress disorder, irritable bowel syndrome, osteoarthritis, polycystic ovary syndrome, metabolic disorders and their complications – metabolic syndrome, obesity, diabetes, atherosclerosis, stroke, and cancer. Further attention is given to selected immune and humoral mechanisms linking LGI with metabolic diseases, as well as to the application of diet and physical activity in the treatment and prevention of LGI. Research into the biological and clinical aspects of LGI offered insight into its underlying causes and mechanisms, as well as those of related chronic diseases. Understanding these factors contributes to the development of innovative strategies for the prevention and treatment of LGI and associated chronic conditions

Keywords: inflammation; chronic non-communicable diseases; contemporary non communicable pandemics; aetiology; pathogenesis; diagnosis; treatment; prevention

Introduction

From an evolutionary perspective, inflammation is a non-specific protective and adaptive response of the body to any local injury caused by infectious or non-infectious, exogenous or endogenous factors. Its primary purpose is to eliminate the harmful agent and the damaged tissue, promoting the integrity of the affected organ. This response represents the body's first line of defence and is triggered immediately following injury. Its effector systems include connective tissue, the microcirculatory bed, and the blood system. Key effectors of inflammation involve non-specific immune cellular and humoral components within these systems. At the same time, inflammation triggers activation of the immune system as a whole, including the adaptive (specific) immune response. This activation enhances the local inflammatory response through immune system effectors and initiates systemic immune reactions and targeted defence mechanisms. In this way, inflammation serves as a means of both deploying innate immunity and

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activating adaptive immunity. However, this model applies primarily to acute inflammation. In contrast, chronic inflammation becomes pathogenic in itself, forming the basis of numerous chronic diseases. It contributes to fibrosis and functional impairment of the affected organ, ultimately increasing the risk of premature death.

Of particular relevance today is the phenomenon of so-called low-grade inflammation (LGI), also referred to as low-level, low-intensity, low-gradient, or low-differentiation inflammation. It is widely considered to be a key underlying factor in a range of chronic non-communicable diseases. A previous review [1] summarised the existing knowledge on the concept of LGI, its causes, its significance in pathology as a foundation for chronic non-communicable diseases, and its mechanisms. It also addressed the consequences of LGI and outlined principles of its diagnosis, treatment, and prevention. A general framework was proposed to situate LGI within the broader pathological process of inflammation, including an overview of its general pathogenesis. Low-grade inflammation is a diffuse, chronic inflammatory process that is morphologically and clinically inconspicuous – often described as "microinflammation". It progresses slowly but steadily, contributing to the advancement of the chronic disease with which it is associated. LGI is linked to serious health complications, reduced quality of life, and ultimately death. For this reason, it is often referred to as a "silent" or "hidden" killer. LGI is driven by various lifestyle-related factors that disrupt physiological balance, such as prolonged emotional or physical stress, unhealthy dietary patterns, physical inactivity, weight gain, obesity, and disturbances in circadian rhythms. It is characterised by a sustained moderate increase in the production of inflammatory mediators – such as reactive oxygen species (ROS) and cytokines – as well as acute-phase proteins, and tissue infiltration by macrophages. LGI can result in chronic fatigue, reduced activity and concentration, weight gain, decreased resistance to adverse factors, accelerated ageing, and is a risk factor for mortality.

As noted by V.P. Chavda *et al.* [2], low-grade inflammation is implicated in a wide range of chronic non-communicable diseases, including cardiovascular diseases, type 2 diabetes (T2D), other metabolic disorders, cancer, autoimmune conditions, gastrointestinal disturbances, respiratory diseases, neurodegenerative processes, reproductive system dysfunctions, allergies, skin conditions, joint problems, headaches, food sensitivities, hormonal imbalances, and sleep disorders. Even prior to the emergence of the LGI concept, inflammation was believed to underlie more than 70% of known human diseases. With the recognition of the inflammatory basis of many chronic non-communicable diseases, this figure has increased substantially, and it is now often suggested that inflammation may be at the root of virtually all diseases. M. Cifuentes *et al.* [3] particularly emphasise the role of LGI in the development of today's non-infectious pandemics – such as obesity, cancer, and cardiovascular diseases – which contribute to rising global morbidity and mortality. LGI represents a shared mechanism in the pathogenesis of these conditions. Accordingly, there is a pressing need to study its pathogenic processes and to address the issue of LGI itself, in order to develop effective strategies for its prevention and the prevention of associated chronic diseases.

In the review by S. Surma *et al.* [4], it is summarised that LGI plays a particularly significant role in the pathophysiology of atherosclerotic cardiovascular disease, which remains the leading cause of death worldwide. Elevated levels of the inflammatory marker high-sensitivity C-reactive protein (hs-CRP) are associated with a markedly increased risk of all-cause mortality, as well as mortality from cardiovascular diseases and cancer. Anti-inflammatory agents such as canakinumab and colchicine have been shown to significantly reduce the risk of cardiovascular events, reinforcing the central role of LGI in the pathogenesis of these conditions. However, given that LGI represents a substantial residual risk factor for atherosclerosis and numerous other diseases and that the antiinflammatory effects of currently available treatments remain limited, further research into therapeutic approaches is essential.

L.Ma.A. Balderas-Peña *et al.* [5] also report that LGI is associated with the majority of human diseases – including cancer, autoimmune disorders, metabolic syndrome, cardiovascular diseases, and neurodegenerative conditions. The authors analyse the link between LGI in obesity and the development of T2D, and cardiovascular diseases (hypertension, ischaemic heart disease, stroke), as well as chronic kidney disease, and cancer. They highlight the importance of continued investigation into the relationship between LGI and chronic disease. Thus, LGI may act not only as a cause but also as a consequence and a key pathogenic mechanism of chronic illness. This is particularly evident in the case of excess weight and obesity, which affect over 50% of the population.

According to the summary by M.T. Nogueira Silva Lima *et al.* [6], the primary biomarkers of LGI include CRP, cytokines such as interleukin (IL)-6 and tumour necrosis factor (TNF)-α, adhesion molecules like VCAM-1 and ICAM-1, and the chemokine MCP-1. Elevated blood levels of CRP, for instance, have long been used as an indicator of cardiovascular disease risk, with thresholds for moderate or high risk now well established at > 1.5 mg/L. However, a consensus has yet to be reached regarding the most reliable biomarkers for assessing the pathogenic and prognostic significance of LGI.

In summary, LGI is both a cause and a key pathogenic mechanism in the development of a wide range of chronic non-communicable diseases. Despite its clinical significance, LGI often presents covertly, lacks clear morphological features, and frequently goes undiagnosed, leading to the development of complications. This underscores the increasing need for deeper investigation into the mechanisms underlying LGI, its role in the pathogenesis of systemic diseases, the identification of key mediators and markers, and the refinement of approaches to early diagnosis, prevention, and treatment. Accordingly, this study aimed to review contemporary literature on the aetiology and pathogenesis, diagnostic criteria, mechanisms of action,

and clinical consequences of LGI, and to evaluate its significance as a universal underlying inflammatory process in a wide array of chronic noncommunicable diseases.

This study was conducted in the format of a narrative literature review. To compile the source base, a structured search for scientific publications was carried out in open-access databases and academic online resources using the Google search engine with the query "Low-grade inflammation". Fifty consecutive articles on LGI published between 2021 and early 2025 were selected for analysis. Only peer-reviewed publications from academic journals meeting scholarly standards were included. Research from non-academic or non-specialist sources, as well as relevant academic articles published prior to 2021, were excluded. The selected sources were categorised according to the main areas of LGI research: concept, aetiology, pathogenesis, diagnostics, treatment, and prevention. Additionally, two further categories were created based on the analysis of the literature, reflecting particularly relevant themes: the role of age-related changes in the pathogenesis of LGI, and the impact of LGI on the development of metabolic disorders (including type 2 diabetes, obesity, and metabolic syndrome). A brief analytical abstract was prepared for each source, outlining the main points of the article and its approach to interpreting LGI. These materials formed the basis for the conclusions of the present review.

Concept and prevalence of low-grade inflammation

It is important to note that ongoing research into LGI has significantly expanded and deepened the understanding of this phenomenon. According to S. Surma *et al.* [4], LGI is characterised by the following features: 1) its trigger is a damage-associated molecular pattern (DAMP), the exposome, metabolic dysfunction, and tissue damage; 2) it is persistent and unresolved in nature; 3) it involves inflammation of low intensity; 4) its course is influenced by collateral tissue damage; 5) age is a key contributing factor; 6) it is a "silent" form of inflammation – lacking the typical clinical signs and biomarker levels observed in canonical inflammation. At the same time, LGI, like classical inflammation, is closely linked to oxidative stress: stimulation of Toll-like receptors (TLRs) by DAMPs leads to increased production of ROS and pro-inflammatory cytokines, including interleukins 1β, 6, and 18, resulting in an inflammatory response. LGI acts both as a cause and a pathogenetic mechanism within the "vicious cycle" of chronic disease, making its control crucial both prior to and following the onset of chronic conditions.

According to M. Cifuentes *et al.* [3], the general patterns of LGI, also referred to as parainflammation, are as follows:

- LGI is a manifestation of tissue stress in response to local or systemic damage that remains below the threshold required to trigger classical inflammation or a pronounced systemic inflammatory response (SIR);
- the principal triggers of LGI are metabolic in nature. These include modified proteins (denatured, oxidised, or glycated), elevated levels of saturated fatty acids, oxidised low-density lipoproteins (LDL), homocysteine, and numerous others. The development of LGI is also promoted by the progressive accumulation of genomic, proteomic, and metabolomic damage during ageing. Of particular importance are scavenger receptors found on stromal macrophages, endothelial cells, and other cells involved in metabolism, immunity, and inflammation;
- LGI is marked by moderate features of SIR: blood CRP concentrations typically range between 3 and 10 mg/L, while levels of pro-inflammatory cytokines are elevated by no more than two- to fourfold; significant tissue damage and hypercoagulation are not characteristic; organ dysfunction develops slowly within the bounds of allostasis;
- when local clinical manifestations are present, it is possible to differentiate between local and systemic LGI, as seen, for example, in diabetic kidney disease;
- LGI involves parenchymal and stromal cells of various organs, with relatively minor involvement of leukocytes. Consequently, LGI lacks both a barrier function and the visible features of classical inflammation;
- a key and integrative pathogenic feature of LGI is systemic endotheliosis – pathological activation and dysfunction of endothelial cells, characterised by disruption of the integrity of the endothelial glycocalyx;
- LGI is associated with interrelated changes in key facultatively glycated tissues – namely adipose, hepatic, and muscle tissues – leading to the development of insulin resistance (IR) and further metabolic disturbances. Clinically, LGI is therefore linked with obesity, metabolic syndrome (MetS), T2D, and sarcopenia. It is also associated with atherosclerosis, hypertension, chronic heart failure, neurodegeneration, osteoarthritis, and other conditions.

L.Ma.A. Balderas-Peña *et al.* [5] define LGI as para-inflammation, or quasi-inflammation – a non-classical type of inflammation marked by the long-term presence of damage-associated factors, the absence of a distinct inflammatory focus, delocalisation of the process, compromised mechanical barriers (linked to tissue ageing), damage-associated metabolic mediators, and endotheliosis. These features are observed in obesity, MetS, T2D, and sarcopenia The authors also argue that the combination of LGI with acute inflammation may give rise to a "perfect" cytokine storm, whereby chronic diseases associated with LGI exacerbate the acute inflammatory response to a current injury, resulting in hyperinflammation – as was seen in cases of COVID-19.

M.T. Nogueira Silva Lima *et al.* [6] suggest that LGI may be formally defined as a pathological condition without overt inflammation but characterised by sustained and unresolved production of inflammatory mediators, macrophage infiltration, adipocyte imbalance, or vascular injury. These effects are associated with metabolically active tissues such as adipose tissue, skeletal muscle, and the liver, highlighting LGI's involvement in metabolic diseases. In older individuals, the progression of LGI is also linked to age-related immunosenescence and the accumulation of cellular debris.

Thus, LGI is understood as a non-classical form of inflammation – para-inflammation. Its key mechanisms, including systemic endotheliosis, have been identified, and its molecular and metabolic triggers explored in greater depth. Future efforts should focus on further refining the conceptual framework of LGI and clarifying the role of its components in the aetiology and pathogenesis of related chronic non-communicable diseases.

Aetiology and pathogenesis of low-grade inflammation

As previously noted, the causes of LGI include a range of factors associated with disruptions to a healthy lifestyle, particularly poor dietary habits. M.T. Nogueira Silva Lima *et al.* [6] demonstrated that excessive intake of advanced glycation end products and macronutrients leads to increased production of both local and systemic pro-inflammatory biomarkers – thereby contributing to the development of LGI – in both human and animal models. Further research is needed to identify optimal biomarkers for the prediction and diagnosis of LGI resulting from dietary imbalances. M. Tristan Asensi *et al.* [7] found that the consumption of ultra-processed foods (UPFs) plays a role in the onset of LGI and, consequently, in the development of chronic non-communicable diseases. UPFs exert harmful effects not only due to their nutritional profile but also through non-nutritional components and their impact on gut health. The authors conclude that public policy should aim to limit UPF consumption and promote healthy eating in order to modulate LGI and, in turn, improve population health outcomes.

R.N. Mello *et al.* [8] identified a strong association between the Dietary Inflammatory Index (DII) – which assesses the combined impact of dietary elements (whole foods, nutrients, and food components) on inflammatory markers such as cytokines and CRP – and obesity-associated LGI. A pro-inflammatory diet was linked to elevated levels of CRP, IL-1β, IL-6, and TNF-α. These findings suggest that the DII may serve as a useful tool for establishing the relationship between dietary patterns and obesity-related LGI.

C. Vetrani *et al.* [9] presented new insights into the role of gut microbiota in the aetiology and pathogenesis of LGI. The microbiota plays a key role as a contributing factor to LGI in obesity and its complications. Dysbiosis results in increased intestinal permeability and diffusion of bacterial lipopolysaccharide (LPS) and other antigens, which activate pro-inflammatory pathways such as the NLRP3 inflammasome and promote the transformation of M1 to M2 macrophages – producers of TNF-α, IL-6, and other mediators – leading to LGI. This, in turn, may cause insulin resistance, impaired secretion of gut hormones, and dysregulation of the gut-brain-adipose axis, thereby contributing to obesity. Obesity further exacerbates dysbiosis. Additionally, both dysbiosis and LGI may trigger inflammation in adipose tissue, which strongly promotes the development of obesity. In turn, obesity may intensify LGI and jointly influence the composition of the gut microbiome. Thus, LGI functions as a trigger of obesity and participates in multiple "vicious cycles". It is therefore necessary to identify effective strategies for modulating microbiota composition and reducing dysbiosis to mitigate LGI in obesity and its associated complications.

Concerning hereditary and congenital factors, the findings of F. Parisi *et al.* [10] are of particular interest. These indicate that excessive maternal weight and obesity are associated with increased birth weight, childhood obesity, and a heightened risk of chronic non-communicable diseases in offspring, resulting in a "vicious perpetuation" of metabolic disorders. In cases of maternal obesity, LGI may potentially extend to the placenta, leading to intrauterine disturbances. It may also affect the oocyte during the early stages of embryonic and placental development. Animal models of LGI have demonstrated an increased incidence of metabolic dysfunction and obesity in offspring. This metabolic imprinting may be mediated by cytokines transferred from the maternal to the foetal circulation, which are capable of modulating nutrient transfer across the placenta. Further research is needed to examine the impact of LGI on the maternal reproductive system and pregnancy outcomes, as well as to inform the development of appropriate preventive measures.

Regarding the role of biological sex in the aetiology and pathogenesis of LGI, Y.A. Mebratu *et al.* [11] found that a deficiency in Bik (Bcl-2-interacting killer – a protein that facilitates the proteasomal degradation of nuclear proteins) induces LGI and the development of spontaneous pulmonary emphysema in female, but not male, mice. This is attributed to lower levels of Bcl-2 and Bik in the lung tissue and airway cells of females compared with males. Consequently, targeting Bik and Bcl-2 to modulate LGI may be crucial in the treatment of age-related chronic diseases. These findings also highlight the significance of biological sex in the aetiology and pathogenesis of LGI and related chronic conditions. Clinically, they are relevant in light of the increased susceptibility of women to chronic obstructive pulmonary disease (COPD).

The influence of social and psychosocial factors on LGI warrants close examination. In a study by E. Chen *et al.* [12], involving African American adolescents, the relationship between experiences of discrimination and inflammation – considered a key biological pathway in mental and physical illnesses – was explored, with a focus on sex differences. Male adolescents who reported higher levels of discrimination exhibited a more pro-inflammatory phenotype, characterised by stronger cytokine responses to stimuli, reduced sensitivity to anti-inflammatory agents, higher monocyte counts, and increased LGI. These associations were not observed in female adolescents. This suggests that male adolescents of colour may be particularly vulnerable to LGI driven by psychosocial stress and its potential impact on mental health. In a separate study, H.C. Kaltenegger *et al.* [13] investigated the relationship between psychosocial working conditions and LGI among professionals caring for geriatric patients. A direct correlation was found between work autonomy and CRP levels, indicating a link between workplace stress, LGI,

and the subsequent development of chronic diseases. Prospective studies are needed to further elucidate the connections between psychosocial work environments, LGI, and long-term health outcomes among healthcare professionals.

In terms of the pathogenesis of LGI, R. La Grotta *et al.* [14] demonstrated that sodium-glucose cotransporter 2 inhibitors (SGLT-2i) reduce cardiovascular and renal complications in patients with T2D. Given that LGI is a key driver of vascular complications, the effect of SGLT-2i on LGI in T2D was investigated. Patients treated with SGLT-2i exhibited lower circulating levels of IL-6, as well as reduced levels of uric acid and insulin. Further *in vitro* studies using two LGI models – LPS-treated monocytes and endothelial cells exposed to hyperglycaemia – confirmed the pro-inflammatory role of uric acid and insulin. These findings suggest that SGLT-2i exert significant anti-inflammatory effects against LGI, likely mediated through their capacity to lower uric acid and insulin concentrations.

In summary, new and important insights have been gained into the role of detrimental dietary patterns (including excessive intake of advanced glycation end-products, macronutrients, ultraprocessed foods, and pro-inflammatory diets in general), gut microbiota, social and psychosocial factors, and biological sex in the aetiology and pathogenesis of LGI and related chronic non-communicable diseases. Mechanisms involving Bik, Bcl-2, and SGLT-2 have also been identified. Further research is required to deepen understanding of the aetiology and pathogenesis of LGI and its associated conditions and to develop novel aetiotropic and pathogenetic therapeutic strategies.

The role of age in the aetiology and pathogenesis of low-grade inflammation

Age is one of the endogenous aetiological factors contributing to disease. As noted above, it is a critical determinant in the development of LGI. With increasing age, the likelihood of LGI and chronic diseases rises. Conversely, LGI plays a significant role in the ageing process and age-related conditions. It is also implicated in premature ageing. The concept of LGI as a key factor in ageing and age-associated diseases has been termed "inflammaging". However, LGI and chronic conditions may also arise during childhood. H.H. Hauta-alus *et al.* [15] demonstrated that in children, LGI – as assessed by hs-CRP – can persist from birth up to the age of 6-8 years. This suggests a sustained pro-inflammatory phenotype during early life and indicates that the risk of LGI-related chronic diseases may originate in the intrauterine period or early childhood. According to E. Polak-Szczybyło [16], children with obesity are at particularly high risk of developing LGI, which may have a profound impact on their long-term health. LGI can increase the likelihood of several diseases emerging at an early age. A raised body mass index (BMI) in childhood is a known predictor of MetS in adulthood. In children with obesity, assessing the extent of LGI may assist in predicting conditions such as cardiovascular disease and T2D. Such assessment would also support the development of anti-inflammatory dietary interventions aimed at reducing obesity and its adverse health consequences in both childhood and later life.

B. Fang *et al.* [17] identified factors influencing adipogenesis, lipogenesis and the inflammatory microenvironment of adipose tissue during ageing. Cellular senescence and the depletion of adiposederived stem cells (ASCs) hinder the renewal of adipocytes, leading to their hypertrophy and the development of LGI. Moreover, different ASC subtypes may either promote or inhibit adipogenesis. Future studies should investigate how changes in ASC subtypes and immune cell populations affect the ageing of adipose tissue, which may offer promising avenues for anti-ageing therapies.

In research related to the COVID-19 pandemic, G. Muscogiuri *et al.* [18] proposed that LGI associated with obesity may represent a critical vulnerability – an "Achilles' heel" – contributing to more severe outcomes of COVID-19 in individuals with obesity. The authors summarised evidence on the role of LGI in the clinical manifestations of COVID-19 among obese patients in both childhood and adulthood, along with the molecular mechanisms underlying this association. Most children appear to be protected against the acute hyperinflammatory response to SARS-CoV-2. Among the comorbidities that impair an effective immune response and increase susceptibility to and severity of COVID-19, obesity stands out as a major factor. Identifying LGI associated with obesity is important in guiding decisions regarding hospitalisation, early respiratory support, and the use of immunosuppressive therapy to mitigate the severity of COVID-19.

A. Suárez-Reyes & C.A. Villegas-Valverde [19] characterised the immunopathogenic changes observed in COVID-19 among elderly patients or those with chronic non-communicable diseases. These changes include the development of LGI accompanied by endothelial dysfunction and activation of the immune system – primarily the innate branch – with increased production of proinflammatory mediators. These mediators trigger an unregulated immune response, creating pathogenic conditions and impeding viral clearance. LGI functions as both an aetiological and pathogenetic factor in diseases such as obesity, T2D, hypertension, COPD, and cancer – all of which are risk factors for severe forms of COVID-19. The risk is significantly elevated in individuals over the age of 60 with these conditions. Further research is needed to elucidate the connections between LGI, chronic diseases, and alterations in the immune response to COVID-19. A deeper understanding of the role of LGI in COVID-19 pathogenesis may aid in developing strategies to prevent and mitigate complications during treatment. According to A. Salminen [20], LGI contributes to compensatory immunosuppression associated with ageing and age-related diseases, increasing the number of immunosuppressive cells in the body. While age-related immunosuppression may protect against inflammatory damage, it also promotes tissue degeneration linked to ageing and associated diseases. Clarifying the mechanisms by which age-related immunosuppression adversely affects tissue homeostasis remains a key research priority.

As age-related inflammation refers to LGI that develops with advancing age in the context of chronic non-communicable diseases, and microRNAs (miRNAs) have been proposed as potential biomarkers of these conditions in older adults, G.B. Carvalho *et al.* [21] characterised the expression of circulating miRNAs and their associations with inflammatory biomarkers in this population. The expression of circulating miRNAs was found to be negatively correlated with leptin concentrations. Negative associations were observed between miRNAs, leptin, and/or LGI, suggesting a potential role for miRNAs as biomarkers of cardiometabolic risk.

Y. Bao *et al.* [22] provided new insights into the effects of LGI on brain structure, which are relevant to the understanding of accelerated ageing and the association between LGI and neuropsychiatric disorders. Using an aggregated LGI index – the inflammation score (INFLA score), which includes CRP, leukocyte count, platelet count, and the granulocyte-to-lymphocyte ratio – together with neuroimaging techniques, the study demonstrated that LGI is associated with reduced volumes in both subcortical and cortical brain regions. Notable reductions were observed in areas such as the globus pallidus, thalamus, insula, superior temporal gyrus, and lateral orbitofrontal cortex. The most pronounced effects were seen among urban residents, males, and individuals with physical impairments. It has been concluded that LGI may contribute to subclinical cognitive decline or neuropsychiatric disorders through structural neural pathways. These findings support the advancement of clinical diagnostics and treatments for neuropsychiatric conditions and suggest that anti-inflammatory dietary interventions could serve as an early preventive strategy in cases of subclinical brain involvement.

Thus, one of the major contemporary areas of research into the aetiology and pathogenesis of LGI is the investigation of age-related factors. New data have been obtained regarding the proinflammatory phenotype in early childhood, the consequences of LGI in children with obesity, age-related changes in adipose tissue and their role in inflammation, LGI in individuals of various ages with obesity and COVID-19, immunopathogenic alterations in elderly patients or those with age-related diseases during COVID-19, compensatory immunosuppression associated with ageing and age-related conditions, the role of miRNAs in the pathogenesis of LGI in older adults, and the impact of LGI on brain structure, accelerated ageing, and neuropsychiatric disorders. These findings, along with further studies into the age-related aspects of LGI, are of significant importance for the development of therapies targeting LGI, its associated conditions, and ageing itself.

Association of low-grade inflammation with chronic non-infectious diseases

Systematic research continues to shed light on the role of LGI in the aetiology and pathogenesis of chronic non-communicable diseases, as well as their complications and outcomes. W.B.S. Zhou *et al.* [23] have suggested that LGI may act as a predisposing and/or triggering factor in the development of chronic pain (CP), one of the main clinical manifestations of peripheral neuropathy arising from injury or disease. Individuals with LGI often exhibit a higher prevalence of chronic pain and psychological disorders. Several hypotheses have been proposed to explain these associations. Further studies are required to clarify the relationship between LGI and CP.

Given that obesity is associated with an increased risk of depression, and that LGI – commonly present in individuals with obesity – is also linked to depression, K. Chu *et al.* [24] investigated whether LGI mediates the relationship between overweight and obesity and the development of general, cognitive-affective, and somatic depressive symptoms. The findings indicate that excess body weight is associated with elevated somatic depressive symptoms, but not with cognitiveaffective or general depressive symptoms. A similar pattern was observed with blood CRP levels. These results suggest that LGI may mediate the relationship between overweight and somatic depressive symptoms.

W. Zhai *et al.* [25] examined the role of LGI in the mechanisms by which adipose tissue contributes to the onset and progression of Alzheimer's disease (AD) in the context of obesity. AD is a leading cause of cognitive decline. Excess body weight and obesity are closely associated with comorbidities such as hypertension, T2D, and IR, which significantly contribute to the development of AD and the associated morbidity and mortality. Obesity induces LGI in adipose tissue, which in turn promotes AD. LGI leads to neurodegeneration, apoptosis, and disruption of brain homeostasis. Adipokines and resident immune cells within adipose tissue mediate both the initiation and progression of AD.

The impact of peripheral LGI was explored in a mouse model of AD with amyloid precursor protein (APP) overexpression – AppNL-G-F – by J. Xie *et al.* [26]. They demonstrated that peripheral LGI affects microglial characteristics, the integrity of the blood-spinal cord barrier, infiltration of peripheral immune cells, and deposition of β-amyloid (Aβ) in the brain. Mechanisms identified include impaired Aβ clearance, persistent microglial activation, neural dysfunction, Aβ efflux disturbances, and promotion of Aβ aggregation. These findings indicate that even peripheral LGI – not solely central neuroinflammation – contributes to AD progression, supporting the modulation of peripheral LGI as a potential therapeutic strategy in the management of AD.

K. Patas *et al.* [27] investigated the causal relationship between systemic LGI and central nervous system (CNS) inflammatory processes in patients with post-traumatic stress disorder (PTSD). Pro-inflammatory activity may play an ambiguous role in the pathogenesis of PTSD. In fact, timely and targeted enhancement – rather than suppression – of inflammatory responses may be beneficial in individuals with LGI, particularly those exhibiting suppressed microglial function. The authors concluded that the detrimental impact of stress-related systemic LGI should be considered alongside its often-overlooked adaptive effects at the tissue level.

In their study, Y. Yuan *et al.* [28] demonstrated that inflammatory, immune, and hypothalamicpituitary-adrenal (HPA) axis processes interact in irritable bowel syndrome (IBS). A triad comprising altered immune cell activation in the gut environment, changes in the intestinal microbiota, and disrupted neuroimmune interactions contributes to the development of LGI. IBS is a multifactorial condition involving immunological, microbiotic, and brain-gut axis signalling alterations. To advance understanding of the disorder, the authors propose conceptualising IBS as a microbial disease of the immune-brain-gut axis.

M.A. Terkawi *et al.* [29] provided evidence that LGI plays a central role in the development of osteoarthritis (OA), sustaining synovial inflammation triggered by DAMPs arising from extracellular matrix injury or necrotic cells, and promoting catabolic responses in chondrocytes that lead to cartilage degeneration. Attenuation of joint inflammation and subsequent OA progression may be achieved by modulating interactions between synovial macrophages and chondrocytes, aiming to limit DAMP activity. Additionally, the use of probiotics, prebiotics, dietary antioxidant supplements, and physical activity has been shown to reduce LGI. Further research is needed to improve understanding of the pathological roles of DAMPs and LGI in OA, which may offer new opportunities for identifying therapeutic targets.

According to M. Orisaka *et al.* [30], LGI may induce oxidative stress and fibrosis in ovarian tissue. Elevated levels of pro-inflammatory cytokines in follicular fluid are frequently observed in polycystic ovary syndrome (PCOS), endometriosis, and ageing. In women with PCOS and obesity, LGI is driven by hyperandrogenism and IR, which in turn exacerbate oxidative stress and impair follicular development. In ovarian endometrioma, LGI is triggered by iron overload, resulting in oxidative stress, ferroptosis, and ovarian fibrosis. During ageing, LGI is initiated by inflammatory ageing factors secreted by senescent cells, which promote oxidative stress in the ovary. Therefore, controlling LGI may represent a novel therapeutic strategy for preventing pro-inflammatory microenvironments, dysfunction, and fibrosis in ovarian tissue.

R. Dey *et al.* [31] demonstrated that the progression of PCOS is associated with increased leukocyte counts and elevated CRP levels in peripheral blood. The CRP-to-albumin ratio may serve as a reliable biomarker for PCOS. An early indicator of the condition could be a rise in neutrophil and lymphocyte counts. Another inflammatory marker useful in diagnosing PCOS is the neutrophilto-lymphocyte ratio (NLR), while the platelet-to-lymphocyte ratio (PLR) can help assess disease prognosis. The TNF-α levels show a positive correlation with IR. The IL-6 may also be elevated in IR, posing a cardiovascular risk factor for women. Elevated levels of interleukins 17, 1, and 8 have been found to correlate with the severity of PCOS. It is hypothesised that the hyperandrogenic state characteristic of PCOS may activate resident macrophages, resulting in LGI and a pro-inflammatory microenvironment. The use of these inflammatory biomarkers is crucial for the early detection and management of PCOS.

In summary, numerous recent studies have produced new insights into the role of LGI in the aetiology and pathogenesis of chronic non-communicable disorders, particularly conditions such as CP, depression, AD, PTSD, IBS, OA, and PCOS. In addition to well-established LGI-associated conditions such as CP, depression, AD, and OA, newly recognised associations now include PTSD, IBS, and PCOS. These findings, along with continued research in this area, are of critical importance for the development of novel strategies for the prevention and treatment of a wide range of chronic conditions.

The role of low-grade inflammation in the aetiology and pathogenesis of metabolic diseases

LGI plays a significant role in the development of metabolic conditions such as dyslipidaemia, atherogenesis, obesity, T2D, and systemic arterial hypertension. For this reason, it is often referred to as "metaflammation" [1]. LGI is particularly characterised by metabolic stress associated with elevated levels of circulating inflammatory mediators, and by a sustained moderate imbalance in adipocyte function or endothelial activity – effects linked to metabolically active tissues such as adipose tissue, the liver, and skeletal muscle. This highlights the involvement of LGI in the aetiology and pathogenesis of metabolic diseases. LGI not only contributes to the onset of obesity, T2D, and atherosclerosis, but the participation of metabolic tissues also defines and intensifies the progression of LGI [6].

A comprehensive review by D. Rodríguez-Vera *et al.* [32] focuses on the association between LGI and MetS. LGI is identified as a central mechanism underlying the aetiology and clinical manifestations of MetS, contributing to its adverse outcomes. Changes in gut microbiota are observed both in the presence of MetS and in cases of LGI independently of MetS. Furthermore, microbiota composition is influenced by diet. Dietary patterns modulate LGI and the microbiome and play a crucial role in the treatment of MetS. The review demonstrates a link between metabolic disturbances in MetS, LGI parameters, the state of the gut microbiota, and dietary interventions applied to treat MetS and regulate inflammation and microbiota composition.

F. Varra *et al.* [33] summarised evidence concerning the association between LGI and the consequences of obesity. Obesity contributes to the development of MetS, IR, T2D, hypertension, atherosclerosis, dyslipidaemia, cardiovascular disease, respiratory disorders, and various types of cancer. The molecular and pathophysiological mechanisms linking obesity with its outcomes are primarily driven by LGI and oxidative stress. Obesity induces a pro-inflammatory state within adipocytes, characterised by the release of pro-inflammatory adipokines – such as plasminogen activator inhibitor-1, visfatin, resistin, and leptin – and infiltration of adipose tissue by M1 macrophages, which produce inflammatory cytokines including IL-1β, IL-6, and TNF-α. Obesityrelated factors such as high-calorie diets, sedentary behaviour, the adipose tissue microenvironment, and

dysregulation of the gut microbiota further exacerbate LGI. Clinical studies have demonstrated the efficacy of molecular therapies targeting obesity-associated LGI, particularly in enhancing insulin sensitivity and improving metabolic function. The authors conclude that there is a need to identify novel, effective, and safe molecularly targeted agents.

The renin-angiotensin system (RAS) may represent a key pathogenic link between obesity and IR. M. Coppo *et al*. [34] investigated RAS activity in circulating T cells from individuals with obesity, both with and without IR and LGI, in the presence or absence of angiotensin II stimulation. Their findings revealed that LGI amplifies the T-cell RAS response to angiotensin II stimulation. Moreover, RAS gene expression in T cells and serum levels of inflammatory cytokines were inversely related to insulin concentration, suggesting a protective role of insulin against the development of LGI. S. Sharif *et al*. [35] demonstrated that LGI, measured via hs-CRP, is an independent risk factor for both vascular mortality and all-cause mortality among high-risk patients with T2D. No association was found between log(hs-CRP) and either myocardial infarction or stroke. LGI may therefore represent a therapeutic target for reducing residual cardiovascular risk in patients with T2D.

The LGI indicator known as the INFLA score has been shown to closely correlate with the severity of acute ischaemic stroke, as assessed by the National Institutes of Health Stroke Scale (NIHSS), throughout the course of the illness. Furthermore, LGI has been identified as a potential predictor of poor outcomes at 90 days in patients with acute ischaemic stroke [36]. The association between LGI and stroke recurrence in individuals with ischaemic stroke has also been analysed. Patients who experienced a recurrent stroke had higher LGI scores, as measured by the INFLA score than those without recurrence. Therefore, an elevated LGI score was associated with an increased risk of stroke recurrence, independent of other vascular risk factors [37]. LGI has also been linked to higher risk and earlier onset of cardiometabolic multimorbidity – the co-occurrence of two or more cardiometabolic conditions, such as coronary heart disease, T2D, hypertension, and stroke – in middle-aged and older adults. Monitoring and screening for the INFLA score in adults without cardiometabolic diseases may improve early prevention of cardiometabolic multimorbidity [38].

In a prospective study, Y. Peng *et al*. [39] assessed the association between the Finnish Diabetes Risk Score (FINDRISC) and the risks of cancer incidence and mortality, as well as the mediating role of LGI in this relationship. It was found that dose-dependent increases in FINDRISC were associated with higher overall cancer incidence and mortality, including for most site-specific cancers. This association was primarily mediated by LGI. Therefore, individuals at increased risk of developing T2D should also be targeted for cancer prevention strategies.

A. Fedulovs *et al*. [40] investigated the relationship between endotoxaemia, MetS, and LGI in type 1 diabetes (T1D). Higher levels of endotoxaemia were observed in patients with both T1D and MetS, along with statistically significant associations between markers of endotoxaemia, hsCRP, and MetS. These findings are clinically relevant, highlighting the potential value of screening for and managing MetS with consideration of endotoxaemia severity. Further research into the inflammatory response mechanisms in T1D is also warranted, as it may lead to new approaches for treating LGI and MetS to slow the progression and complications of T1D.

Immune mechanisms play a significant role in the pathogenesis of metaflammation. According to M. van de Vyver [41], these mechanisms involve abnormal metabolic activation of innate immune cells – such as neutrophils, macrophages, dendritic cells, and mast cells – which, in turn, contribute substantially to disease progression. A prominent example of this is the obesity-diabetes link. As a result, the treatment of patients with T2D should focus not only on weight reduction and glycaemic control but also on anti-inflammatory therapy. Early introduction of such therapy is recommended – during the obesity stage preceding the onset of T2D.

Monocyte polarisation in the context of LGI facilitates the pathogenesis of atherosclerosis. S. Geng *et al*. [42] demonstrated that the adaptor molecule TRAM (TRIF-related adaptor molecule), associated with the TIR-domain-containing adaptor inducing interferon-β (TRIF), mediates monocyte polarisation both *in vivo* and *in vitro*. Mice deficient in TRAM were resistant to high-fat diet-induced atherosclerosis. Intravenous administration of TRAM-deficient monocytes to mice with atherosclerosis significantly reduced disease progression. These findings suggest that targeting TRAM may support the efficient generation of therapeutic monocytes suitable for the treatment of atherosclerosis.

A. Lautenbach *et al*. [43] found that bariatric surgery (including gastric bypass and other weight-loss procedures) can reduce markers of obesity-related LGI – such as levels of CRP, hs-CRP, ferritin and leukocytes – for up to four years post-surgery. Improvements in metaflammation were associated with reductions in BMI and long-term remission of T2D.

Thus, an important area of research into the role of LGI in the aetiology and pathogenesis of chronic non-communicable diseases is its function as metaflammation in the development of metabolic disorders. Numerous recent studies have produced new findings on LGI as both a cause and mechanism underpinning metabolic diseases, their complications and outcomes – such as MetS, obesity, diabetes, atherosclerosis, stroke and cancer. The importance of immune mechanisms in the pathogenesis of LGI has been demonstrated, including the immune-mediated effects of LGI, its role in the activation of the RAS, and the association between LGI and endotoxaemia in metabolic conditions. These findings support the rationale and importance of incorporating anti-inflammatory therapy into the comprehensive treatment of metabolic disorders.

Diagnosis, treatment and prevention of low-grade inflammation

As LGI is associated with nutritional status, S. Surma *et al.* [4] argued that the prognostic inflammatory and nutritional index (PINI), which assesses levels of CRP, α1-acid glycoprotein, albumin and transthyretin, serves as a valuable diagnostic tool. PINI is designed to evaluate nutritional status and LGI in patients with inflammatory conditions, with or without impaired enteral nutrition. The authors concluded that dietary interventions based on natural food sources are crucial for reducing LGI, thereby improving overall health, lowering the risk of chronic diseases, delaying and/or preventing cardiovascular disease, and improving clinical outcomes.

Dietary strategies are essential for regulating LGI and, consequently, for enhancing quality of life and preventing a broad range of chronic conditions [44]. L. Barrea *et al.* [45] demonstrated that ketogenic diets (KDs) may serve as a dietary intervention capable of reducing LGI and oxidative stress in individuals with obesity. KDs exert anti-inflammatory effects through several mechanisms, including the suppression of nuclear NF-κB activation, inhibition of the NLRP3 inflammasome, and the blocking of histone deacetylases. Further research is required to explore the potential of KDs in the treatment of obesity and its associated complications.

The potential to mitigate LGI through phytonutrients – particularly plant-derived flavonoids – is well documented [1]. V.A.S. Ayyadurai *et al.* [46] investigated the effectiveness of a fruit, berry and vegetable (FBV) juice blend containing bioactive compounds such as luteolin, epicatechin, epigallocatechin gallate, lycopene, quercetin, and vitamins A, C, and E. Consumption of FBV significantly reduced the production of TNF-α, IL-1β, the chemokine CCL2, and ROS. Thus, FBV provides a combination of bioactive substances that act synergistically to reduce LGI in the context of chronic disease.

Y. Zhang *et al.* [47] reported that whole grains hold considerable promise as dietary resources for preventing LGI in individuals with existing health conditions. Their active ingredients – including β-glucan, resistant starch, arabinoxylan, phenolic acids, flavonoids, phytosterols and lignans – combat LGI through a range of intracellular signalling pathways and immunomodulatory mechanisms. Further research is needed to assess the potential application of whole grains for LGI modulation.

Recent transcriptomic studies have led to the development of multicomponent medicinal products for treating LGI of various origins. These include plant- and organ-based extracts targeting the skin and musculoskeletal system (Traumeel: Tr14), liver (Lycopodium compositum: HC-24), and joints (Zeel-T: Ze-14). Molecular pharmacognosy may offer an effective approach for identifying and validating plant-derived agents capable of adequately controlling LGI [48].

R. Divella *et al.* [49] emphasised that the Mediterranean diet and physical activity activate biological mechanisms capable of counteracting LGI, which is present in cancer patients. This suggests that maintaining a healthy lifestyle during cancer treatment may alleviate the adverse effects of both the disease and its treatment, thereby improving patients' quality of life. As a result, cancer treatment programmes should always incorporate additional interventions such as dietary modifications and physical exercise.

N.C. Bishop *et al.* [50] demonstrated that reducing sedentary behaviour and increasing physical activity helps to lower LGI in individuals with obesity, thereby decreasing the risk of cardiometabolic diseases. This effect was observed independently of any changes in body weight. Moreover, even an increase in light physical activity was sufficient to reduce LGI. This provides a more accessible strategy for overweight and obese individuals to manage LGI and improve their cardiometabolic health.

In a study examining LGI prevention in children through enhanced physical activity, A.O. Agbaje [51] found that increased total sedentary time was associated with heightened inflammation, as indicated by hs-CRP levels. However, greater engagement in light physical activity produced a twofold reduction in inflammation, and this effect was more resilient to the influence of body fat than that of moderate or vigorous physical activity. Therefore, efforts to prevent and manage LGI should focus on promoting light physical activity.

A substantial body of research on LGI has been devoted to its management. Notably, both the treatment and prevention of LGI can be achieved through natural interventions such as dietary modification and increased physical activity. This aligns with the understanding that LGI often results from disruptions to a healthy lifestyle, particularly poor dietary habits and physical inactivity. It also supports the notion that the prevention and mitigation of chronic non-communicable diseases may be possible by addressing these contributing factors.

A review of the literature reveals significant progress in LGI research in recent years. The LGI is now regarded as an atypical form of inflammation – para-inflammation. There has been a deeper investigation into its initiating mechanisms, particularly molecular and metabolic factors, and key processes such as systemic endothelial dysfunction have been identified. New insights have been gained into the aetiology and pathogenesis of LGI and its associated chronic non-communicable diseases, including the role of unhealthy diets, gut microbiota, social and psychosocial influences, and biological sex. Mechanisms implicated in LGI, such as Bik, Bcl-2, and SGLT-2, have also been explored. Among the aetiological factors, age has received the greatest research attention. New findings have been obtained regarding the pro-inflammatory phenotype in early childhood, the consequences of LGI in children with obesity, age-related changes in adipose tissue and their role in the onset of inflammation, LGI in patients of various ages with obesity and COVID-19, immunopathogenic changes in COVID-19 among older individuals or those with age-related diseases, compensatory immunosuppression associated with ageing and age-related conditions, the role

of miRNAs in the pathogenesis of LGI in the elderly, and the impact of LGI on brain structure, accelerated ageing, and neuropsychiatric disorders. The largest area of LGI research concerns its role in the aetiology and pathogenesis of chronic non-communicable diseases. The conditions and syndromes studied include CP, depression, AD, PTSD, IBS, OA, and PCOS. Thus, to the previously recognised conditions associated with LGI – such as CP, depression, AD, and OA, newly recognised associations now include PTSD, IBS, and PCOS. A significant proportion of research in this area focuses on metaflammation, i.e. the role of LGI in the aetiology and pathogenesis of metabolic diseases, their complications and consequences, including MetS, obesity, T2D, atherosclerosis, stroke, and cancer. The importance of immune mechanisms in the pathogenesis of LGI has been highlighted, along with the immunological pathways through which LGI acts, the role of LGI in activating the RAS, and its link with endotoxaemia in metabolic diseases. A substantial part of LGI research is also devoted to its treatment and prevention, particularly through the use of natural factors such as diet and increased physical activity.

Current research on LGI primarily focuses on its aetiology and pathogenesis – particularly age-related aspects – its association with chronic non-communicable diseases (especially metabolic disorders), and its potential for therapeutic correction. An analysis of 50 articles on LGI revealed that 17 addressed its aetiology and pathogenesis, including eight focused specifically on the role of age; 21 explored its links to chronic non-communicable diseases, of which 12 examined metabolic conditions; and 9 dealt with diagnosis, treatment, and prevention – mainly correction (8). The remaining three papers focused on the prevalence of LGI and the conceptual understanding of this type of inflammation.

Overall, the problem of LGI undeniably remains highly relevant. A growing body of evidence suggests that it plays a significant role in the aetiology and pathogenesis of chronic diseases, acting as a cause and/or key pathogenetic mechanism. The range of conditions associated with LGI continues to expand. Based on recent findings, there is increasing interest in assessing the effectiveness and potential of anti-inflammatory therapies as part of comprehensive treatment strategies for various chronic non-communicable diseases. Further research into the biological and clinical aspects of LGI is required to deepen understanding of its underlying causes and mechanisms, as well as its connections to chronic illness, and to support the development of innovative strategies for prevention and treatment.

Conclusions

A review of the literature confirms that LGI remains a pressing issue. LGI is recognised as a cause and/or a key pathogenetic mechanism underlying many chronic diseases. Between 2021 and early 2025, significant new findings have emerged concerning various aspects of LGI, including its definition, aetiology and pathogenesis, its role in the development of chronic non-communicable diseases, as well as its diagnosis, treatment, and prevention. Particular attention has been given to the influence of age in LGI pathogenesis, its association with metabolic disorders, and strategies for its correction. Of the 50 reviewed publications on LGI, 17 addressed its aetiology and pathogenesis – 8 of which focused on age-related factors; 21 examined its links to chronic non-communicable diseases, including 12 that specifically dealt with metabolic conditions; and 8 were devoted to its correction. LGI research has explored a wide range of relevant topics, such as its definition and prevalence; the role of harmful dietary patterns, gut microbiota, psychosocial and social determinants, biological sex, and age in its development; mechanisms including Bik, Bcl-2, and SGLT-2; and the involvement of LGI in the aetiology and pathogenesis of chronic diseases and syndromes, including chronic pain, depression, Alzheimer's disease, post-traumatic stress disorder, irritable bowel syndrome, osteoarthritis, polycystic ovary syndrome, metabolic disorders, and their complications and consequences – namely, metabolic syndrome, obesity, diabetes mellitus, atherosclerosis, stroke, and cancer; the significance of immune mechanisms in the pathogenesis of LGI, the immunological mode of action of LGI, its role in the activation of the RAS, and its association with endotoxaemia in metabolic diseases have also been highlighted. Additionally, the use of dietary interventions and physical activity in the treatment and prevention of LGI has received growing attention. Research into the role of age in the aetiology and pathogenesis of LGI has explored the pro-inflammatory phenotype in early childhood, the consequences of LGI in children with obesity, age-related changes in adipose tissue and their role in inflammation onset, LGI in individuals of different ages with obesity and COVID-19, immunopathogenic changes in older adults or those with age-related diseases during COVID-19, compensatory immunosuppression associated with ageing and age-related conditions, the role of microRNAs in the pathogenesis of LGI in the elderly, and the impact of LGI on brain structure, accelerated ageing, and neuropsychiatric disorders. Studies focused on the diagnosis, treatment, and prevention of LGI have examined the diagnostic value of the PINI, the efficacy of ketogenic diets, fruit and vegetable juice, whole grain products, and multi-component herbal and organ-based medicinal preparations in LGI management. Further research has addressed the use of diet and exercise to counteract LGI in cancer, the reduction of sedentary behaviour and increase in physical activity to mitigate LGI in obesity, and the effectiveness of light physical activity in lowering LGI levels in children.

Future efforts should focus on expanding the understanding of the conceptual components of LGI and their relevance in the aetiology and pathogenesis of associated chronic non-communicable diseases. Research into the causes and mechanisms of LGI and its related pathologies should be directed towards the development of novel strategies for aetiotropic and pathogenetic therapy. Continued investigation into the age-related aspects of LGI is of particular importance for informing therapeutic

approaches to LGI, its associated conditions, and the ageing process. Further studies are also essential to clarify the role of LGI in the aetiology and pathogenesis of chronic non-communicable diseases, including metabolic disorders, which is of critical importance for the justification of new methods for the prevention and treatment of a wide range of chronic conditions. Additionally, the development of new approaches to the diagnosis, treatment, and prevention of LGI and its associated diseases remains a key research priority.

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Conflict of Interest
None.

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Прогрес та перспективи дослідження низькоступеневого дифузного хронічного запалення: огляд літератури

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Анотація. Низькоступеневе дифузне хронічне запалення (low-grade inflammation – LGI) є причиною численних хронічних захворювань, у тому числі сучасних неінфекційних пандемій – серцево-судинних захворювань, метаболічного синдрому, цукрового діабету 2 типу, ожиріння, хронічного обструктивного захворювання легень, хронічних запальних захворювань кишечника, неалкогольної жирової хвороби печінки, хронічної хвороби нирок, нейродегенеративних захворювань, деяких форм раку тощо. Мета роботи – проаналізувати останні дані наукових медичних публікацій про LGI, проблема якого залишається актуальною. Досягнутий значний прогрес у розробці таких питань цієї проблеми, як поняття про LGI, його етіологія та патогенез, роль LGI у виникненні та розвитку хронічних неінфекційних захворювань, діагностика, лікування та профілактика LGI. Переважними напрямами досліджень цього запалення є його етіологія та патогенез, зв'язок з хронічними неінфекційними, особливо з метаболічними, захворюваннями та його корекція. За тематикою дослідження стосуються поняття та поширеності LGI; значення шкідливого типу харчування, кишкової мікробіоти, соціальних та психосоціальних чинників, статі та віку в етіології та патогенезі LGI; деяких молекулярних механізмів LGI; ролі у виникненні та розвитку таких хронічних захворювань та синдромів, як хронічний біль, депресія, хвороба Альцгеймера, посттравматичний стресовий розлад, синдром подразненого кишечника, остеоартрит, синдром полікистозних яєчників, метаболічні захворювання, їх ускладнення та наслідки – метаболічний синдром, ожиріння, цукровий діабет, атеросклероз, інсульт, рак; деяких імунних та гуморальних механізмів взаємозв'язку між LGI та метаболічними захворюваннями; використання дієти та фізичної активності у лікуванні та профілактиці LGI. Дослідження біологічних та клінічних аспектів LGI дозволяє з'ясувати причини та механізми його самого та взаємопов'язаних з ним хронічних захворювань, а розуміння цих причин та механізмів сприяє розробці інноваційних стратегій профілактики та лікування LGI та асоційованих хронічних захворювань

Ключові слова: запалення; хронічні неінфекційні захворювання; сучасні неінфекційні пандемії; етіологія; патогенез; діагностика; лікування; профілактика

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Application of the dry needle method in the correction of myofascial pain in women after caesarean section and myomectomy

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Abstract. Myofascial pain after uterine surgery, in particular caesarean section and myomectomy, is a common problem that significantly reduces the quality of life of women in the postoperative period. Traditional methods of treatment do not always demonstrate high efficiency, which necessitates the search for alternative approaches to pain relief, one of which is the dry needle method. The aim of the study was to evaluate the effectiveness of the dry needle method in the correction of myofascial pain in women after caesarean section and myomectomy in comparison with standard methods of treatment. The prospective randomised controlled trial involved 12 women (aged 25-45 years) who underwent caesarean section (n = 8) or myomectomy (n = 4). The patients were divided into a treatment group (n = 6), which received dry needling in addition to standard therapy, and a control group (n = 6), which received standard therapy alone. The pain intensity was assessed using a visual analogue scale, McGill questionnaire, quality of life (sf-36), anxiety and depression levels using the HADS scale were studied before treatment, 7, 14, 30 and 90 days after treatment. Patients in the main group showed a significant decrease in pain intensity by 45.8% after 7 days and 78.3% after 30 days of treatment, compared to the control group – 23.2% and 56.1%, respectively ($p < 0.01$). The sf-36 quality of life scores in the intervention group were 32.5% higher after 30 days and 41.2% higher after 90 days compared to the control group ($p < 0.01$). The level of anxiety and depression according to the HADS scale decreased by 38.7% and 42.3%, respectively, in the main group compared to the control group ($p < 0.05$). The use of the dry needle method in the complex treatment of myofascial pain in women after cesarean section and myomectomy demonstrates high efficiency in reducing pain intensity, improving the quality of life and psycho-emotional state of patients compared to standard methods of treatment. The method can be recommended as an additional therapeutic approach in such patients

Keywords: myofascial trigger points; rehabilitation; postoperative period; physical therapy; pain relief

Introduction

Myofascial pain syndrome (MPS) is a common issue for women following pelvic organ surgeries, especially after Caesarean sections and myomectomies. Current research indicates that the incidence of post-operative pain syndrome is around 60%, significantly exceeding other complications [1]. This highlights the urgent need for effective

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treatment and rehabilitation methods for these patients, as traditional approaches don't always provide adequate pain relief. Persistent pain substantially lowers quality of life, hinders social integration, and can lead to the pain syndrome becoming chronic.

Analysis of recent scientific publications reveals a growing interest in alternative MPS treatments, with dry needling holding a particularly important place. In their research, C. Fernández-de-Las-Peñas & J. Nijs [2] presented a contemporary neurophysiological model of how dry needling affects myofascial trigger points. They demonstrated that mechanical irritation from the needle triggers a cascade of tissue reactions, helping to reduce pain and muscle spasm. The authors noted that the method's effectiveness depends on accurately identifying trigger points and the correct technique for the manipulation.

An updated systematic review and meta-analysis by M.J. Navarro-Santana *et al.* [3] showed the effectiveness of dry needling for myofascial trigger points associated with neck pain symptoms. The researchers found a statistically significant reduction in pain intensity and improved functional status in patients compared to control groups, with the treatment effect lasting for an extended observation period.

I.C. Lara-Palomo *et al.* [4] systematically compiled data on dry needling's effectiveness for chronic lower back pain in their systematic review and meta-analysis of randomised controlled trials. The authors confirmed a significant reduction in pain intensity and improved functional status in the active treatment group compared to the control group, finding a correlation between the number of procedures and the degree of clinical effect.

In their systematic review, F. Dach & K.S. Ferreira [5] investigated the best evidence-based practices for treating myofascial lower back pain with dry needling. The researchers determined optimal procedure parameters (needle insertion depth, session duration, frequency of procedures) for achieving maximum therapeutic effect and developed recommendations for applying the method in various clinical situations.

Researchers M. Chys *et al.* [6] conducted an umbrella review on the clinical effectiveness of dry needling in patients with musculoskeletal pain. They systematised data on the mechanisms of dry needling for myofascial pain in different locations, identifying local, segmental, and central components of its analgesic effect. The researchers also demonstrated improved microcirculation in the area of myofascial trigger points after the procedure, which aids in flushing out inflammatory and pain mediators and is a key mechanism of the method's therapeutic action.

A significant contribution to understanding the effectiveness of myofascial trigger point therapy was made by M. Olesiejuk *et al.* [7] in their 2023 study. The authors demonstrated that myofascial trigger point therapy significantly reduces the myotonometric tone and stiffness of the trapezius muscle, leading to a notable improvement in headaches and muscle pain in patients with migraines. The study confirmed not only the local effects of trigger point therapy but also its systemic impact on pain sensitivity and neuromuscular function, which is particularly important for understanding the mechanisms of action in chronic pain syndromes.

A comprehensive review of the treatment and management of myofascial pain syndrome within the best practices of clinical anaesthesiology was presented by I. Urits *et al.* [8]. The researchers determined the optimal parameters for the dry needling procedure (needle insertion depth, session duration, frequency of procedures) to achieve maximum therapeutic effect and developed clinical recommendations for applying the method in various clinical situations, including the post-operative period.

Of particular interest is the randomised controlled clinical trial by N. Sedighimehr *et al.* [9], conducted in 2024 and dedicated to the effectiveness of dry needling for chronic pelvic pain in women. The authors demonstrated that myofascial trigger points play a key role in the development of central sensitisation in pelvic pain, and that dry needling can effectively modulate pain responses at the spinal cord level and in higher parts of the nervous system. This study is especially valuable for understanding the mechanisms of dry needling in pain syndromes in women after pelvic organ surgeries, demonstrating the potential to influence central pain mechanisms that often complicate the post-operative course.

Despite the considerable amount of scientific research on the effectiveness of dry needling for myofascial pain of various origins, there is still a lack of sufficient attention in contemporary literature to its specific application in women following gynaecological and obstetric surgeries. Most existing studies focus on musculoskeletal pathology, and the characteristics of myofascial pain syndrome after uterine interventions and the effectiveness of dry needling in this category of patients remain under-researched. The study's aim was to evaluate the clinical effectiveness of dry needling in the complex treatment of myofascial pain in women after Caesarean sections and myomectomies by determining changes in pain intensity, quality of life, and psycho-emotional state of patients compared to standard therapy methods.

Materials and Methods

This prospective, randomised controlled study was conducted at the Department of Biosafety and Human Health at the National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute" and the "Spina+" rehabilitation centre. Data was collected between December 2024 and April 2025. The study adhered to the principles of the World Medical Association's Declaration of Helsinki, specifically "Ethical Principles for Medical Research Involving Human Subjects" [10]. All participants were fully informed of the potential risks associated with consenting to the use of their data in scientific research, as well as the assurance of anonymity and confidentiality. Following this, they provided signed consent to participate.

The study included 12 women aged 25 to 45 years (mean age 34.2 ± 5.7 years). All participants had undergone

either a Caesarean section (n = 8) or a myomectomy (n = 4) and had been diagnosed with myofascial pain syndrome according to the diagnostic criteria of J.G. Travell *et al.* [11]. Criteria for inclusion of patients in the study:

1. Women aged 25-45 years after caesarean section or myomectomy;
2. The presence of myofascial pain of moderate to high intensity (> 4 points on the visual analogue scale (VAS);
3. Postoperative period – from 4 weeks to 6 months;
4. Signing an informed consent to participate in the study.

Exclusion criteria:

1. Presence of acute infectious diseases;
2. Blood clotting disorders and anticoagulant use;
3. Allergic reactions to metals (for dry needle method);
4. Mental disorders;
5. Oncological diseases;
6. Pregnancy;
7. Decompensated somatic diseases;
8. Patient refusal to participate in the study.

The patients were divided into two groups: the main group (n = 6) – patients who received treatment with the dry needle method in addition to standard therapy; the control group (n = 6) – patients who received only standard therapy. Each group included 4 patients after caesarean section and 2 patients after myomectomy. The groups were comparable in terms of age, social status, parity, body mass index, postoperative period, and pain nature and intensity ($p > 0.05$).

Standard therapy in both groups included:

- non-steroidal anti-inflammatory drugs (meloxicam 15 mg/day) for 7 days;
- muscle relaxants (tizanidine 4 mg twice daily) for 14 days;
- physiotherapy procedures (low-intensity laser therapy, 10 sessions);
- a complex of therapeutic physical culture (daily throughout the observation period).

In the main group, dry needling was additionally performed. The procedures were performed by a certified specialist with at least 5 years of experience. Disposable sterile acupuncture needles with a size of 0.25 × 40 mm were used. The treatments were performed twice a week for the first two weeks, then once a week for the next two weeks (6 sessions in total).

During the dry needling procedure, active myofascial trigger points were targeted, which were detected by palpation in the muscles of the anterior abdominal wall (rectus abdominis, external and internal obliques), lumbosacral muscles and pelvic floor muscles. When myofascial trigger points (MTPs) were identified, the needle was inserted perpendicular to the skin and advanced until it reached the muscle (Fig. 1). After that, rapid reciprocating movements of the needle in different directions were performed to obtain a local twitch response. The needle was left in the tissue for 10-15 minutes, and periodic manipulations (scrolling, deepening, surface movements) were performed to maintain the feeling of deqi (a specific sensation in acupuncture).

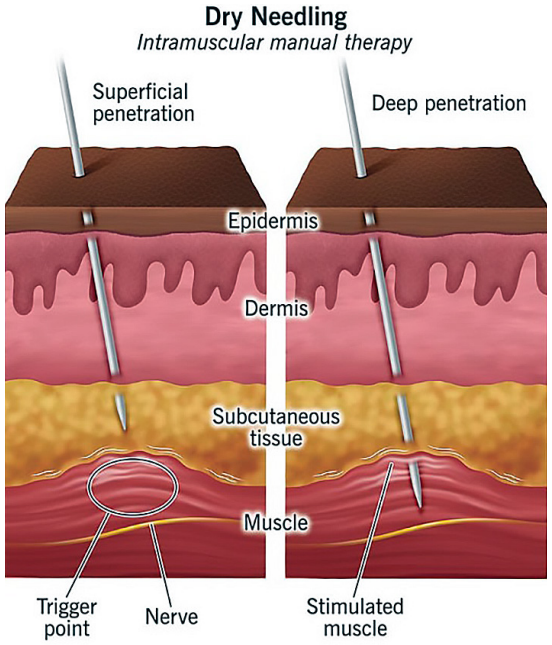

Figure 1. Schematic representation of the dry needle insertion technique
Source: [12]

The effectiveness of the treatment was assessed by the following parameters:

- Pain intensity on the Visual Analogue Scale (VAS) from 0 to 10 points;
- Qualitative pain characteristics using the McGill Pain Questionnaire;
- Quality of life using the SF-36 questionnaire;
- Anxiety and depression levels using the Hospital Anxiety and Depression Scale (HADS);
- Number of active myofascial trigger points (MTP);
- Need for additional use of analgesic medications;
- Presence of side effects and complications.

Statistical data processing was performed using SPSS Statistics v.25.0 software. For quantitative data, the mean and standard deviation (M ± SD) were calculated. Student's t-test for independent samples and χ^2 test for categorical variables were used to assess the reliability of differences between groups. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion

A comprehensive study of the effectiveness of the dry needle method in 12 women after uterine surgery demonstrated statistically significant advantages of this method compared to standard therapy in all evaluated parameters. The obtained results revealed not only the analgesic effect of the method, but also its positive impact on the quality of life and psycho-emotional state of patients, which is of great clinical importance for this category of patients.

The average age of patients in the main group was 33.8 ± 5.4 years, in the control group – 34.6 ± 6.0 years ($p = 0.47$). Body mass index in the main group was

26.4±4.2 kg/m², in the control group – 25.9 ± 3.8 kg/m² (p = 0.56). The average postoperative period at the time of inclusion in the study was 8.4 ± 2.1 weeks in the main group and 8.2 ± 1.9 weeks in the control group (p = 0.63). The groups were comparable in terms of socio-demographic characteristics, obstetric and gynaecological history and the nature of the operations (p > 0.05).

The initial VAS pain intensity in patients of the main group was 6.8 ± 1.2 points, in the control group – 6.7 ± 1.3 points (p = 0.78). The most frequent MTPs were detected in the rectus abdominis muscles (83.3%), lumbar muscles (76.7%), lumboiliac muscles (65.0%) and pelvic floor muscles (58.3%). The average number of active MTPs in the main group was 5.4 ± 1.8, in the control group – 5.2 ± 1.6 (p = 0.68).

In patients of the main group treated with the dry needle method, a progressive decrease in pain intensity was observed throughout the observation period. In particular, the VAS scores decreased by 45.8% after 7 days, 61.5% after 14 days, 78.3% after 30 days and 85.2% after 90 days of treatment compared to the baseline. In the control group, the reduction in pain was less pronounced, with the corresponding figures being 23.2%, 40.3%, 56.1% and 65.3% (p < 0.01 between groups at all stages). This result demonstrates not only a more significant analgesic effect of complex treatment with the inclusion of the dry needle method, but also a faster achievement of the therapeutic effect, which is especially important for patients in the early postoperative period.

A clinically significant reduction in pain (defined as a ≥ 50% decrease from baseline) was observed in 78.3% of patients in the main group and in 43.3% of those in the control group after 14 days (p < 0.001), and in 91.7% and 66.7%, respectively, after 30 days (p < 0.01). These indicators indicate a significantly higher effectiveness of the integrated approach using the dry needle method and are of great practical importance for predicting treatment outcomes.

Analysis of the qualitative characteristics of pain according to the McGill questionnaire showed that before treatment, patients in both groups were dominated by sensory descriptors of pain: "aching", "burning", "pulling", "sharp", "tense". After treatment, a more pronounced decrease in both sensory and affective components of pain was observed in patients of the main group compared to the control group. Such dynamics indicates a complex effect of the dry needling method not only on the intensity of pain, but also on its qualitative characteristics, which corresponds to modern ideas about the multicomponent nature of pain syndrome.

The index of the number of selected descriptors before treatment was 10.8 ± 2.4 in the main group and 10.5 ± 2.2 in the control group (p = 0.59). In 30 days after the start of treatment, this indicator decreased to 3.2 ± 1.1 in the main group and to 5.9 ± 1.6 in the control group (p < 0.001). The ranked pain index decreased from 27.3 ± 5.6 to 6.8 ± 2.3 in the main group and from 26.9 ± 5.4 to 14.2 ± 3.8 in the control group (p < 0.001) (Table 1).

Table 1. Dynamics of SF-36 quality of life indicators in the study groups

Scale SF-36	Before treatment		After 30 days		After 90 days	
	Main group	Control group	Main group	Control group	Main group	Control group
Physical functioning (PF)	57,2 ± 10,3	58,4 ± 11,2	78,6 ± 8,1*	65,2 ± 9,3*	85,3 ± 7,2*	72,1 ± 8,5*
Role functioning due to physical condition (RP)	34,5 ± 15,2	33,9 ± 16,1	72,8 ± 12,3*	51,4 ± 14,2*	80,5 ± 10,1*	62,7 ± 12,5*
Pain intensity (BP)	35,3 ± 8,4	36,1 ± 9,1	77,4 ± 7,2*	58,5 ± 8,4*	82,3 ± 6,5*	65,2 ± 7,8*
General health (GH)	58,7 ± 11,2	57,9 ± 10,8	75,2 ± 8,3*	65,3 ± 9,1*	80,1 ± 7,4*	70,2 ± 8,3*
Vital activity (VT)	45,2 ± 9,3	44,8 ± 9,7	72,5 ± 7,6*	59,4 ± 8,2*	78,6 ± 6,8*	67,3 ± 7,5*
Social functioning (SF)	53,1 ± 12,4	52,5 ± 11,9	82,3 ± 9,5*	68,2 ± 10,3*	87,4 ± 8,2*	74,5 ± 9,6*
Role functioning due to emotional state (RE)	42,3 ± 16,5	43,1 ± 15,8	76,5 ± 10,2*	60,4 ± 11,8*	83,2 ± 9,5*	68,7 ± 10,4*
Mental health (MH)	51,4 ± 10,5	50,8 ± 11,2	75,8 ± 8,3*	62,7 ± 9,5*	80,3 ± 7,6*	70,2 ± 8,9*

Notes: *p < 0.05 compared to pre-treatment values; all differences between groups after 30 and 90 days are statistically significant (p < 0.01)
Source: authors' data

The table analysis shows that the greatest increase was observed in the "Pain intensity" (BP), "Role functioning due to physical condition" (RP) and "Social functioning" (SF) scales. At 30 days after the start of treatment, the scores on these scales in the intervention group were 32.5%, 41.6% and 20.7% higher, respectively, compared to the control group (p < 0.01). After 90 days, the difference between the groups persisted, although it was less pronounced: 26.2%, 28.4% and 17.3%, respectively (p < 0.01). These results confirm the comprehensive positive effect of the dry needling method not only on the physical but also on the psychosocial component of patients' health, which is especially important for full rehabilitation and restoration of normal life. Prior to treatment, patients in both groups exhibited elevated levels of anxiety and subclinical symptoms of depression. In the main group, the average score on the anxiety scale was 11.2 ± 3.4, and on the depression scale – 9.8 ± 2.6; in the control group, the corresponding indicators were 11.5 ± 3.2 and 9.6 ± 2.8 (p > 0.05). 30 days after the start of treatment, the level of anxiety decreased to 5.4 ± 1.8 points in the main group and to 8.2 ± 2.3 points in the control group (p < 0.001). The level of depression decreased to 4.3 ± 1.5 points in the main group and to 7.1 ± 2.1 points in the control group (p < 0.001). 90 days after the start of

treatment, the main group showed normalisation of the psychoemotional state (anxiety – 3.2 ± 1.2 points, depression – 2.8 ± 1.0 points), while the control group maintained subclinical manifestations of anxiety (6.7 ± 1.8 points) and depression (5.4 ± 1.6 points) ($p < 0.001$ between groups). These data indicate a significant improvement in the psycho-emotional state of patients in the main group, which can be explained not only by a decrease in pain intensity but also by the psychological aspects of dry needling treatment.

An important criterion for the effectiveness of treatment was the reduction in the number of active MTPs. At the beginning of the study, the average number of active MTPs in the main group was 5.4 ± 1.8, in the control group – 5.2 ± 1.6 ($p = 0.68$). After 14 days of treatment, the average number of active MTPs decreased to 2.3 ± 0.9 in the main group and to 3.8 ± 1.2 in the control group ($p < 0.001$). After 30 days, the corresponding indicators were 1.2 ± 0.6 and 2.5 ± 0.9 ($p < 0.001$), and after 90 days – 0.7 ± 0.4 and 1.9 ± 0.7 ($p < 0.001$). Such dynamics confirms the pathogenetic effect of the dry needling method on myofascial trigger points, which is a key factor in the treatment of MPS.

During the first week of treatment, 23.3% of patients in the main group and 56.7% of the control group required additional painkillers (paracetamol) ($p < 0.001$). On the second week of treatment, these figures were 11.7% and 41.7%, respectively ($p < 0.001$), and on the third and fourth weeks – 5.0% and 30.0%, respectively ($p < 0.001$). The average total dose of additional paracetamol taken during the entire observation period was 1.2 ± 0.8 g in patients of the main group and 4.5 ± 1.6 g in the control group ($p < 0.001$). These data are of clinical importance, especially for women after caesarean section who often breastfeed, as a reduced need for analgesics reduces the risk of side effects and increases the safety of treatment.

The following side effects were observed in patients in the main group during the dry needling procedure: local pain at the needle insertion site (91.7%), local haemorrhage (15.0%), muscle spasm (23.3%), temporary increase in pain after the procedure (18.3%), and autonomic reactions (dizziness, sweating) (8.3%). All side effects were temporary and disappeared on their own within 24-48 hours after the procedure. No serious complications requiring medical intervention were observed in any patient. In the control group, side effects were mainly associated with the intake of non-steroidal anti-inflammatory drugs and muscle relaxants: dyspeptic symptoms (23.3%), drowsiness (31.7%), headache (15.0%), allergic reactions (5.0%).

When comparing the effectiveness of the dry needle method in patients after different types of surgery (caesarean section vs myomectomy), no statistically significant differences were found. In patients after caesarean section ($n = 4$), the reduction in VAS pain intensity after 30 days of treatment was 79.1%, in patients after myomectomy ($n = 2$) – 76.8% ($p = 0.42$). SF-36 quality of life scores, HADS anxiety and depression scores, and the dynamics of the number of active MTPs also did not differ significantly in patients after different types of surgery ($p > 0.05$). However, in patients after myomectomy, MTPs were more often detected in the pelvic floor muscles (75.0% vs 50.0% in patients after caesarean section, $p = 0.04$) and lumbosacral muscles (80.0% vs 57.5%, $p = 0.03$), which may be due to the peculiarities of surgical technique and postoperative rehabilitation.

The results of the study demonstrated the high efficacy of the dry needle method in the treatment of myofascial pain in women after caesarean section and myomectomy. Patients who received complex treatment with the dry needling method showed a more significant and rapid reduction in pain intensity, improvement in quality of life and psycho-emotional state compared to patients who received standard therapy alone. The mechanism of action of the dry needling method in myofascial pain is complex and includes several components.

L. Martín-Sacristán *et al.* [13] in their study described in detail the physiological basis of the dry needling method for active and latent trigger points in patients with neck pain. The authors demonstrated that mechanical irritation of the MTP with a needle causes a local twitch response, which helps to break the vicious circle of "pain – muscle spasm – pain". The researchers also noted that the effectiveness of the dry needling method depends on the accuracy of trigger points and the technique of performing the manipulation, which is consistent with the results of the current study, where all procedures were performed by an experienced specialist using a standardised methodology.

I. Yehoshua *et al.* [14] investigated the use of dry needling for the treatment of acute myofascial pain syndrome in primary care. The results showed that DN is a safe, easy-to-use and effective method of short-term pain relief that can be used in primary care settings without complex equipment. Dry needling can be integrated into the practice of a family doctor as an alternative to drug treatment of pain, especially in myofascial syndrome.

L.W. Chou *et al.* [15] studied the neurophysiological mechanisms of dry needling, noting that needle insertion stimulates the release of endogenous opioids and activates antinociceptive systems at the segmental and supra-segmental levels. This explains not only the local but also the systemic analgesic effect of the method, which is manifested in a decrease in the overall VAS pain intensity and an improvement in the quality of life of patients, which was also demonstrated in the current study.

A statistically significant decrease in muscle stiffness was found by J.A. Valera-Calero *et al.* [16] in a randomised controlled trial of changes in the stiffness of active myofascial trigger points of the upper trapezius muscle after dry needling in patients with chronic neck pain. The authors emphasised the importance of an individual approach to the choice of trigger points and procedure regimen depending on the location and severity of myofascial pain syndrome. In the current study, such an individualised approach was used, taking into account the location of active MTPs in each patient, which could contribute to the high effectiveness of treatment.

J. Sánchez-Infante *et al.* [17] studied changes in the electromyographic activity of latent trigger points after dry needling intervention. The authors defined the diagnostic criteria for myofascial trigger points and clinical aspects of their treatment, noting that dry needling is one of the most effective methods of influencing MTP, especially in combination with other therapeutic approaches, which is confirmed by the results of the current study, where the highest effectiveness was observed in complex treatment.

The effectiveness of the dry needling method for active myofascial trigger points and pain intensity in tension-type headache was confirmed by the study by S. Monti-Ballano *et al.* [18]. The researchers noted a significant reduction in pain intensity and improvement in functional status in the active treatment group compared to the control group. They also found that the most significant reduction in pain was observed during the first two weeks of treatment, which is in line with the results of the present study, where the most pronounced dynamics was also observed in the first two weeks.

N. Sedighimehr *et al.* [9] conducted a randomised parallel-group controlled clinical trial of the effect of dry needling on pain and central sensitisation in women with chronic pelvic pain. The authors noted that the dry needling method was more effective in reducing pain and improving quality of life compared to placebo, and also noted a reduced need for analgesics in the active treatment group, which is consistent with the results of this study, where the need for additional painkillers was significantly lower in the intervention group.

In a systematic review and meta-analysis conducted by G. Plaza-Manzano *et al.* [19] identified the diagnostic criteria for myofascial trigger points and clinical aspects of their treatment in the combined use of dry needling with other therapeutic methods for neck pain syndromes. The authors noted that dry needling is one of the most effective methods of influencing MTP, especially in combination with other therapeutic approaches, which is confirmed by the results of the current study, where the highest efficacy was observed in complex treatment.

T. Ghanavati *et al.* [20] conducted a single-blind randomised controlled trial comparing the long-term effects of dry needling and ischaemic pressure on pain intensity and myofascial trigger point threshold in women. The authors demonstrated that both methods have a significant therapeutic effect, but dry needling was more effective in reducing pain sensitivity and improving functional status. The study confirmed the importance of a gender-specific approach to the treatment of myofascial pain syndrome, as women have peculiarities of pain sensitisation and response to therapeutic interventions. The current study also took into account the gender-specific features of myofascial pain syndrome formation, which allowed achieving optimal treatment results.

D. Lucena-Anton *et al.* [21] conducted a systematic review of the effectiveness of dry needling of myofascial trigger points in the muscles of the trilateral calf. The authors analysed the results of several randomised controlled trials and found significant efficacy of the method in reducing pain and improving the functional status of the lower extremities. The study highlighted the importance of accurate identification of myofascial trigger points and the use of standardised treatment protocols to achieve maximum therapeutic effect. In the present study, a similar systematic approach to the diagnosis and treatment of myofascial trigger points of various localisations was used, which ensured high quality and reproducibility of the results of therapeutic intervention.

The study also confirmed the safety of the dry needle method when performed correctly. The side effects observed were mostly mild and temporary, which is consistent with the data of S. Brady *et al.* [22], who conducted a prospective study of dry needling side effects. The authors also noted that the most common side effects were local pain, haemorrhage, and temporary increase in symptoms that resolved on their own within a short time. Most previous studies have focused on the effectiveness of the dry needling method in myofascial pain associated with musculoskeletal pathology, while research in women after gynaecological and obstetric surgery is limited. In this context, the present study adds to the existing data on the use of the dry needling method in a new clinical population.

Conclusions

In a prospective randomised controlled trial involving 12 women after caesarean section and myomectomy, the effectiveness of the dry needle method in the complex treatment of myofascial pain syndrome was studied. The intensity of pain, quality of life, psycho-emotional state of patients, the number of active myofascial trigger points and the need for additional analgesics during treatment were assessed. The study demonstrated that the dry needle method is a highly effective component of the complex treatment of myofascial pain in women after caesarean section and myomectomy, as evidenced by a more significant reduction in VAS pain intensity by 45.8% after 7 days and 78.3% after 30 days of treatment compared to the control group (23.2% and 56.1%, respectively, $p < 0.01$). The use of the dry needle method improves the quality of life of patients on all scales of the SF-36 questionnaire, with the main group scoring 32.5% higher after 30 days and 41.2% higher after 90 days compared to the control group ($p < 0.01$).

Patients treated with the dry needle method showed a more significant reduction in anxiety and depression on the HADS scale compared to the control group ($p < 0.05$), and a reduced need for additional painkillers, which is of particular importance for breastfeeding women after caesarean section. The effectiveness of the dry needle method does not depend on the type of surgery performed (caesarean section or myomectomy), but patients after myomectomy are more likely to have MTP in the pelvic floor and lumbosacral muscles. The most significant predictors of the effectiveness of dry needle treatment are the time after surgery at the time of treatment ($\beta = -0.48$, $p < 0.001$) and the patient's age ($\beta = -0.39$, $p < 0.01$).

The dry needle technique is safe if the procedure is performed correctly and patients are properly selected, and side effects are mostly mild and temporary. Early detection and treatment of myofascial pain syndrome in women after

caesarean section and myomectomy using the dry needle technique can improve the effectiveness of rehabilitation and prevent chronic pain. The prospect of further research is to study the long-term effects of the dry needle method, optimise treatment protocols for different categories of patients, and investigate the combination of the dry needle method with other innovative approaches to the treatment of myofascial pain in women after gynaecological and obstetric surgeries.

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Conflict of Interest
None.

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Застосування методу сухої голки в корекції міофасціального болю у жінок після кесаревого розтину та міомектомії

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Анотація. Міофасціальний біль після хірургічних втручань на матці, зокрема кесаревого розтину та міомектомії, є поширеною проблемою, що суттєво знижує якість життя жінок у післяопераційному періоді. Традиційні методи лікування не завжди демонструють високу ефективність, що зумовлює необхідність пошуку альтернативних підходів до знеболення, одним з яких є метод сухої голки. Мета дослідження – оцінити ефективність застосування методу сухої голки в корекції міофасціального болю у жінок після кесаревого розтину та міомектомії порівняно зі стандартними методами лікування. У проспективному рандомізованому контрольованому дослідженні взяли участь 12 жінок (вік 25-45 років), яким було виконано кесарів розтин (n = 8) або міомектомію (n = 4). Пацієнтки були розподілені на основну групу (n = 6), яка отримувала лікування методом сухої голки додатково до стандартної терапії, та контрольну групу (n = 6), що отримувала лише стандартну терапію. Оцінка інтенсивності болю проводилась за візуальною аналоговою шкалою, опитувальником МакГілла, досліджувалась якість життя за sf-36, рівень тривожності та депресії за шкалою hads до лікування, через 7, 14, 30 та 90 днів після початку лікування. У пацієнток основної групи спостерігалось достовірне зниження інтенсивності болю на 45,8% через 7 днів і на 78,3% через 30 днів лікування, порівняно з контрольною групою – 23,2% та 56,1% відповідно ($p < 0,01$). Показники якості життя за sf-36 у основній групі були вищими на 32,5% через 30 днів та на 41,2% через 90 днів порівняно з контрольною групою ($p < 0,01$). Рівень тривожності та депресії за шкалою HADS знизився на 38,7% та 42,3% відповідно в основній групі у порівнянні з показниками контрольної групи ($p < 0,05$). Застосування методу сухої голки в комплексному лікуванні міофасціального болю у жінок після кесаревого розтину та міомектомії демонструє високу ефективність у зниженні інтенсивності болю, покращенні якості життя та психоемоційного стану пацієнток у порівнянні зі стандартними методами лікування. Метод може бути рекомендований як додатковий терапевтичний підхід у таких пацієнток

Ключові слова: міофасціальні тригерні точки; реабілітація; післяопераційний період; фізична терапія; знеболювання

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Effect of creatine on improving a person's physical performance: A literature review

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Abstract. Creatine is a popular dietary supplement that has a significant impact on physical performance, strength, and endurance, making it relevant for use in sports, rehabilitation, and performance improvement in different age groups. The purpose of the study was to evaluate the effectiveness of creatine use to improve athletic performance, physical endurance, muscle strength, muscle hypertrophy, and functional performance of athletes, people with physical disabilities, and the elderly. The results of numerous experimental studies were analysed, including controlled trials, systematic reviews, and meta-analyses that evaluated the effects of creatine on a person's physical performance using combined training protocols and various dosing strategies. The conducted studies indicated a high efficiency of creatine use by athletes and people of other professions related to both physical and mental work. It helps to reduce muscle damage and increase the overall performance of athletes, in particular, by increasing phosphocreatine reserves and stimulating anabolic processes. In athletes, creatine helped to increase muscle mass, reduce fatigue, and improve training intensity, regardless of gender. The combination of creatine with other substances has shown additional benefits in increasing strength and endurance. The use of creatine in combination with training contributed to regional muscle hypertrophy, increases their thickness and volume, especially in conditions of restricted blood flow. In older adults, the supplement reduced muscle loss, improved strength and functionality even with low levels of physical activity. Creatine reduced fatigue and improved functional performance in patients with chronic diseases and neurodegenerative conditions. The results poined to the universality of creatine as an effective tool for improving athletic performance, functional performance, and recovery after exercise in various population groups. Its use is recommended for professional athletes, the elderly, and people with special physical needs

Keywords: dietary supplements; sports performance; physical performance; functional efficiency; muscle strength; muscle hypertrophy

Introduction

Creatine is a naturally occurring nitrogen-containing organic compound that plays a key role in muscle energy production during exercise and is an important element of energy metabolism, as it allows rapid regeneration of

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adenosine triphosphate (ATP), supporting muscle performance and endurance. Such properties of creatine are physiologically determined, since the body itself produces and uses this compound for biochemical transformations. It is synthesised in the liver, kidneys, and pancreas from the amino acids arginine, glycine, and methionine, and also enters the body with protein products (meat, fish) or as food additives. Currently, creatine is the most common dietary supplement in the world of sports and modern medicine. The study of this compound opens up new opportunities in its use to increase physical performance, endurance, maintain cognitive health, recover from injuries and loads, and treat various diseases. In the modern world, this is very relevant, since the level of minimum sports standards has significantly increased. The intense rhythm of life and global changes cause stress, anxiety, and nervous disorders, which can be regulated with creatine supplements. In addition, they play an important role in the comprehensive treatment of diseases associated with physical disability and sedentary behaviour, especially among the elderly. Therefore, creatine as a mono-agent, or as part of a complex application, has not only a preventive and energy potential, but also a significant therapeutic effect.

Recent studies of creatine prove its relevance and steady interest of researchers from different countries. Special attention is paid to its application in sports, in particular in dynamic sports such as football, basketball, short-distance running, and weightlifting, where physical processes require a rapid release of energy, since creatine helps to increase the endurance, strength, and speed characteristics of athletes. In particular, the effect of creatine on improving the physical performance of basketball players was investigated by S. Vargas-Molina *et al*. [1], a similar study among weightlifters was conducted by D. Almeida *et al*. [2]. They proved that creatine supplements can increase muscle strength and endurance, without negative effects on health indicators and with minimal side effects. A positive effect was observed on both overall physical performance and strength of the lower and upper extremities. Blood and urine tests for basic biochemical parameters remained normal. Therefore, researchers recommended the use of creatine monohydrate in the sports under consideration.

D. Varillas-Delgado [3] studied the genetic effects on body mass index growth and muscle gain in professional soccer players during and after taking creatine supplements. The experiment involved 161 athletes, each of whom took 20 g/day of creatine for five days, then another seven weeks of 5 g/day. To evaluate the results, the overall genetic profile of the participants was calculated and their anthropometric parameters, in particular, body mass index, muscle and fat mass, were determined. The study found that the increase in muscle mass and body mass index in response to creatine supplementation was most pronounced in athletes who had a genotype associated with increased muscle performance.

A. Gordji-Nejad *et al.* [4] investigated the effect of a single creatine supplement on cognitive function in the brain, in particular, sleep deprivation. According to their research, in people suffering from insomnia or unable to sleep enough hours, a single dose of high-dose creatine orally helped restore metabolic processes in fatigue and cognitive decline. According to the researchers, no side effects were observed, and there were no complaints about the gastrointestinal tract either. Thus, they concluded that even a single dose of creatine can restore the main energy metabolic processes during sleep deprivation in four hours.

B.M. Kious *et al.* [5] studied the possibilities of using creatine in the treatment of neurophysiological disorders. They argued that new strategies for creating antidepressants need to be developed, especially targeting physiological processes that are different from those targeted by conventional treatments. According to current diagnostic and control methods, such as human neuroimaging, genetics, epidemiology, and animal studies, failure in the production, storage, and use of brain energy has been shown to be involved in the development and maintenance of depression. It is creatine, as a dietary supplement, according to their findings, that has prospects for relieving these disorders in patients in the early stages of depression and other diseases in the treatment of which antidepressants are used.

S.M. Ostojic *et al*. [6] studied the effect of creatine on women's reproductive health. Their results proved that supplements of this compound in the diet in the range of 13 mg per kg of body weight per day, throughout a woman's life cycle, provide many potential benefits, contributing to the regularity of the menstrual cycle, the normal functioning of the reproductive system, improving hormonal balance and the ability to ovulate. In particular, cases of oligomenorrhea, the risks of foetal macrosomia in pregnant women, pelvic infections, ovariectomy, and hysterectomy were reduced. The researchers emphasise the need for future studies of the effects of creatine on women at different stages of the menstrual cycle to determine the potential for its use throughout life. Thus, the use of creatine with food of 13 mg per kg of body weight per day significantly reduces the risk of irregular menstruation, pelvic pathologies, and obstetric diseases. However, more research is needed to fully confirm the effect of creatine supplementation on improving reproductive health in women. As a similar study by J. Antonio *et al*. [7] confirmed that an important aspect is that taking creatine does not cause serious side effects if the recommended doses are met.

Research on both the long-term and short-term effects of creatine on the human body opens up new horizons not only in sports, but also in medicine, rehabilitation practice, and preventive use. Improvements in many of the physical parameters that ensure optimal functioning of the human body can be adjusted with the correct use of creatine supplements. The description of positive changes and negative effects during creatine use, physical characteristics in healthy and sick people, athletes and workers, the elderly and people with cognitive disorders will allow understanding more clearly the scale of impact and effectiveness of its use. The purpose of the current study was to investigate the effectiveness of creatine-based

supplements for improving physical performance in various categories of the population, to analyse positive changes, manifestations of side effects, and prospects for use.

To achieve this goal, the most significant and representative scientific articles, meta-analyses, and literature reviews containing quantitative and qualitative data on the effects of creatine on the human body were selected. A comprehensive approach has been applied to search, select, and evaluate research papers. Electronic databases and online libraries were used to search for information: Google Scholar, PubMed, Web of Science, Scopus, Willey, MDPI. The criteria for inclusion in the analysis were: publications with effective conclusions and clear evidence of effectiveness, clear methodological approaches; studies no older than 2014; published in English or Ukrainian; availability of data on the effect of creatine on physical endurance, muscle strength, muscle hypertrophy, functional indicators of the respiratory, nervous, and cardiovascular systems. The exclusion criteria included: papers with unproven effectiveness, insufficiently clear conclusions; older than 10 years; non-compliance with the topic. 43 papers that met the selected criteria were selected. The analysis was carried out in several areas. In particular, the use of creatine to improve the physical capabilities of athletes, the use of this compound in medicine for the treatment of certain clinical conditions and diseases, and the effect of creatine on the physiological parameters of a person, including the elderly.

Use of creatine-based supplements during training and in sports

The efficacy and safety of creatine in the correct dosages explain its popularity as a supplement for optimising physical abilities, improving health, cognitive function, and recovery from hard work or training. More and more people, having learned about the positive properties of creatine, use it as a dietary supplement or include it in the diet of sports nutrition. It is important to understand exactly what physical indicators this supplement improves and whether the result really has such an unsurpassed effect.

The use of creatine-based supplements during intensive training, professional sports gives quite high positive reviews. C. Lanhers *et al.* [8] conducted a meta-analysis of 60 studies on the effects of creatine on the human body under short-term lower limb loads and proved that the use of this supplement improves strength performance during exercises lasting less than 3 minutes, regardless of the characteristics of participants, training protocols, and dosage. The effect of long-term creatine use during training in athletes of various sports was investigated by C.-C. Wang *et al.* [9]. The researchers conducted an experiment during which athletes used creatine supplements for 4 weeks in combination with complex training, which involved performing both anaerobic exercises – in the form of jumps and half-squats, and aerobic – running, complex training. After analysing the blood creatine kinase content and physical performance of athletes, the researchers concluded that the use of creatine supplements helps to reduce muscle damage and has a positive effect on overall athletic performance.

Furthermore, M. Kaviani *et al.* [10] found that creatine intake during strength training is an effective strategy for increasing muscle strength in physically active young adults. In their experiment, they divided 18 participants into two groups: one received creatine during exercise, the other – a placebo. The training programme lasted eight weeks (three days of training per week), with regular strength measurements every two weeks and blood counts 24 and 48 hours after training. The creatine group showed significant improvements in strength in four of the six exercises (triceps extension, leg press, shoulder press, bench press, but no improvements in biceps flexion and deadlift) compared to the placebo group. According to the findings, when creatine monohydrate is added, the increase in muscle strength increases markedly after two weeks of use. However, they note that there was no reduction in muscle damage. Researchers attribute this to excessive training intensity. Similar results for improving training performance and increasing muscle thickness were obtained by R. Sousa-Silva *et al.* [11] and V. Korotych [12]. These observations were also confirmed by a meta-analysis performed by R. Burke *et al.* [13], who claim that the combination of creatine with strength training contributes to regional muscle hypertrophy, which allows purposefully increasing the volume of individual muscle groups. According to the results of their study, the addition of creatine to strength training leads to a significant increase in muscle thickness (average difference of 0.90 mm) and muscle cross-sectional area (average difference of 0.17 cm^2) compared to training without creatine supplementation. The researchers concluded that creatine combined with strength training contributes to more pronounced muscle hypertrophy, especially in the upper extremities. Thus, the claim about the long-term use of creatine to improve physical performance during training of varying intensity is confirmed by a number of experiments and is quite proven.

Creatine use is also common among professional athletes. Researchers conducted experiments involving athletes of various sports to find out whether it is appropriate to use this substance at a professional level. A.P. da Silva Azevedo *et al.* [14] conducted a study of the effect of creatine supplementation on biomechanical parameters during high-intensity interval training (HIIT), accompanied by impact reduction. The experiment involved eight elite football players, who were divided into two groups: one took creatine, the other – placebo. Tests were conducted during HIIT, which included five sessions of exhaustion running. The results showed that creatine supplementation contributed to a higher time to reach the first peak of exhaustion than placebo. There were also significant changes in muscle activation in the initial and intermediate phases. It should be noted that when athletes consumed creatine, there was no effect on heart rate and lactate concentration. According to the results obtained, the researchers note that creatine supplementation can affect the control and strength of impact during high-intensity interval training in football players, and reduce shock and well-being in HIIT.

R. Ramírez-Campillo *et al*. [15] conducted a six-week study on the effects of creatine supplementation on endurance and recovery rate in female football players. Two groups were formed: control and experimental. Athletes were evaluated for maximum and repeated sprint running, speed of change of direction, jumping, and endurance before and after six weeks of training. As a result of research, no noticeable changes were observed in the control group, however in the experimental group, jumping, sprinting, and repeated sprint running improved. These studies support expectations for the positive effects of creatine supplementation on football athletes.

The effect of creatine compounds on the performance of rowers engaged in endurance sports was studied by J. Fernández-Landa *et al.* [16]. The study involved 28 male athletes from the best rowing club of the First Coaching League of Spain. They were divided into four groups: the placebo group, the creatine monohydrate-only group, the β-hydroxy β-methylbutyrate-only group, and the group taking a combination of the two drugs. For 10 weeks, participants took appropriate supplements after training with a chocolate smoothie for recovery, and their athletic performance was assessed using various tests before exhaustion. In addition, the level of lactate was measured, which indicated indicators of exhaustion of athletes. The results showed that combined administration of creatine monohydrate and β-hydroxy β-methylbutyrate resulted in a synergistic improvement in aerobic capacity associated with individual lactate thresholds, whereas individual administration of these supplements did not have such an effect. Researchers explain this by various physiological mechanisms of influence on the body's energy assets.

S.J. Brooks *et al.* [17] investigated changes in dry body weight (excluding fat) after 6 weeks of creatine use by female dancers. According to their research, creatine contributes to an increase in total body water levels and muscle mass, and the amount of visceral adipose tissue has significantly decreased over time. In addition, considering the mental load of female students, a study was conducted on the impact on their mental activity and cognitive functions, but no significant changes were found. According to researchers, such experiments should be conducted during the academic semester, since 6 weeks is a rather limited time to determine these indicators.

S.C. Forbes *et al.* [18] considered the indisputable advantage of creatine to be the ability to reduce inflammatory processes, repair damaged muscle fibres in microtrauma, which allows athletes to recover faster after injuries or intense training. They investigated the effects of creatine in athletes involved in running and jumping, cycling, and skiing. Researchers have found that when exercising for more than three minutes, creatine has good restorative properties, delays the onset of exhaustion, and develops endurance. Researchers explain the positive results by the effect of creatine on such processes as reducing oxidative stress in cells, improving the transport of ATP from mitochondria to recycling sites, improving the kinetic parameters of oxygen, and increasing the buffering of hydrogen ions. In particular, C.R. Soares Freitas Sampaio *et al.* [19] conducted a study involving eight Brazilian paralympic powerlifting athletes aged 23 to 29 years. During the trial, athletes took a placebo for the first 7 days, then a 7-day break, and then 7 days of creatine intake. The results showed that fatigue levels were 16% lower when taking creatine than placebo. The results of maximum torque also improved, while the remaining indicators were similar for both placebo control and creatine. According to researchers, the use of creatine improves strength indicators and reduces the level of fatigue in professional athletes.

Considering the results of research, it is possible to summarise data on the positive effect of creatine supplementation on physical performance during training in professional athletes and people engaged in training in their spare time. It is important to note that no noticeable side effects were detected in the experiments under consideration, with the exception of isolated cases of nausea. All participants in the experiment adhered to the recommended doses of supplements, not exceeding the norm of 3-5 g per day. Also noteworthy is the fact that the effectiveness of creatine is observed with both short-term and long-term use, depending on the expected results.

Creatine use in medical practice

Creatine is widely used in medical practice to support cell energy metabolism, especially in diseases associated with mitochondrial dysfunction. Its use has shown effectiveness in the treatment of neurodegenerative diseases, in particular Parkinson's disease, ALS, and Huntington's disease, as it helps to protect nerve cells from degenerative changes. Creatine is also used in the treatment of a number of diseases of the cardiovascular, respiratory, and nervous systems. In addition, metabolic and cognitive disorders also respond better to treatment when using creatine, especially when combined with other drugs [20].

The effectiveness of creatine use in the treatment of respiratory diseases was studied by F. De Benedetto *et al.* [21]. They showed that patients with chronic obstructive pulmonary disease (COPD) experience improved functional performance when taking creatine together with the antioxidant coenzyme Q. A blind, randomised, placebo-controlled clinical trial involved 108 COPD patients in 9 Italian hospitals. Patients underwent spirometry, a 6-minute walk test (6MWT), bioelectric impedance analysis, and activities of daily living questionnaire (ADL) at the beginning and after 2 months of therapy. 90 patients completed the study in full. Some of them received QTer (coenzyme Q10) and creatine supplements, while others received a placebo. Patients taking the supplements showed improvements of 6MWT (51 ± 69 vs 15 ± 91 m, $p < 0.05$), body cell mass, sodium/potassium ratio, shortness of breath indices, and ADL compared to the placebo group. In the group taking the supplements, the concentration of coenzyme Q10 in plasma increased, while in the placebo group it did not change. Side effects were similar in both groups.

The results showed that in patients with COPD, dietary supplements with CoQ10 and creatine improved functional performance, body structure, and reduced shortness of breath. The systemic increase in some anti-inflammatory metabolites confirms the pathobiological mechanism as the reason for these benefits. Further research is needed to better understand the role of QTer and creatine in COPD patients, the researchers said.

Studies showed that people with type 2 diabetes have altered creatine metabolism and uptake in the body [22, 23]. Therefore, it remains important to determine the dose and duration of creatine supplementation to improve blood glucose control. A. Oskroba *et al.* [24] conducted an experiment on the therapeutic effect of creatine supplementation in patients with type II diabetes mellitus. It was found that the combination of creatine with physical activity significantly reduced glycemic indicators in these patients. Hypoglycemic effects are explained by creatine stimulation of the work of glucose-transmitting protein-4 (GLUT-4), which is insulin-dependent and is responsible for the translocation of glucose into muscle cells to the sarcolemma. Researchers insist on the feasibility of further long-term study, because positive changes in glucose control are very important in the treatment of diabetes.

Another potential therapeutic property of creatine is its ability to support brain function and protect neurons from degenerative changes in diseases such as Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis. Research conducted by C.J. Hass *et al.* [25] proves the positive effect of combining physical activity with creatine supplementation in patients suffering from mild to moderate Parkinson's disease. Participants in the experiment took creatine monohydrate at a dose of 20 g/day. Their exercise results were better compared to the placebo group. Thus, on average, the results improved from 12% to 16%. These studies prove the need to combine physical activity with the use of creatine monohydrate, but require more detailed research. A. Attia *et al.* [26] studied the effect of creatine supplementation on the development of treatment for neurodegenerative disorders. According to researchers, although there are a number of successful clinical experiments on the therapeutic effectiveness of creatine supplements in animals with Parkinson's disease, there are not enough evidence-based modern clinical trials with people with neurodegenerative diseases. Researchers conducted a meta-analysis of the effectiveness of creatine supplementation in people with Parkinson's disease. 1,935 randomised controlled trials were conducted comparing the effects of creatine and placebo on motor activity and quality of life in patients. Unified calculations were performed on the unified Parkinson's disease rating scale (UPDRS). According to their findings, there is no clinically significant evidence for the use of creatine for neuroprotective effects in the treatment of Parkinson's disease. Well-planned randomised controlled trials are needed in the future. Therefore, such studies remain open to determine the optimal protocol for creatine supplementation in the treatment of these diseases.

The effect of creatine supplementation in the complex treatment of cardiovascular diseases, in particular, coronary heart disease, heart failure, or myocardial infarction, is quite relevant, but not yet sufficiently studied. Group of researchers consisting of A. Del Franco *et al.* [27] conducted a meta-analysis and concluded that there was a direct relationship between the creatine content in the heart muscle and the development of heart failure. The researchers attribute this to the fact that creatine, as a component of the energy buffer system, is involved in the metabolism of cardiac activity, contributing to the transmission of a signal from the site of synthesis to the site of use. A decrease in ATP synthesis, the phosphorylation of which depends on the presence of creatine, leads to contractile dysfunction of the heart muscle. Therefore, future research should be aimed at creating protocols for the treatment of patients with heart failure with creatine preparations and determining the optimal doses of creatine.

A. Aron *et al.* [28] conducted a randomised controlled trial on the effect of short-term creatine supplementation on heart and vascular function in older men. For the experiment, men aged 55-80 years were divided into three groups taking creatine, placebo, and a control group. Creatine and placebo were taken for 7 days at a dose of 20 mg per day. Patients were tested on days 1 and 8. The operation of blood vessels was tested using equipment for measuring the pulse wave velocity, and the assessment of cardiac activity was determined by an impedance cardiography device. According to the results of the experiment, the cardio-vascular index had the best indicators in the group taking creatine (8.7 ± 0.5 to 8.2 ± 0.5, $p = 0.03$). There were no changes in the other two groups. The situation was similar with systolic blood pressure, and there was a slight improvement in the creatine group: from 144.0 ± 12.7 mm Hg. up to 136.1 ± 13.4 mm Hg., $p = 0.08$. Stroke volume, ejection fractions, and contractility index were similar in all three groups. Thus, according to the results of the study, the use of creatine for 7 days can have a positive effect on the cardiovascular system, in particular, in heart diseases and atherosclerosis in the elderly. The researchers note that adding creatine to a therapeutic treatment plan is quite effective and safe. Thus, creatine supplements are increasingly used in the complex therapy of rather complex diseases, which allows patients to have a milder course of the disease or recover faster, or have better physical performance.

Effect of creatine on human physiological parameters: general strengthening effects, preventive use

Researchers are actively studying the effect of creatine on human physiological parameters, in particular, its general strengthening effects and the possibility of preventive use. Although most attention is paid to its use in sports and medicine, studies also confirm the benefits of creatine for the elderly, people engaged in heavy physical labour, and patients in the rehabilitation and recovery phase [29-31]. Scientific evidence suggests a positive effect of this compound

on endurance, recovery rate after physical exertion and the body's resistance to stress factors, which makes it a promising tool for a wide range of applications.

K. Elstad *et al.* [32] investigated that in addition to sports achievements, creatine has a positive effect on performance in professions with increased physical activity, in particular in firefighters, which indicates its versatility. The experiment, which lasted 4 weeks, involved 30 male firefighters. The study used carbohydrate and protein supplements for both groups of the experiment, but one also added creatine. The training tests in this study were aimed at evaluating the physical skills needed to effectively perform firefighters' official duties. In particular, they included rescue and forced entry tests that simulated real-world rescue scenarios that required explosive strength, speed, and endurance. An improvement in these indicators in the creatine group indicates its positive effect on explosive power and muscle endurance during short-term but intense physical effort. However, the absence of significant differences between the groups in tests for climbing stairs, moving with a hose, and overall task completion time may indicate that these activities are more dependent on overall aerobic endurance, which is less affected by creatine. Thus, the study confirmed that the combined use of creatine with protein and carbohydrates can improve professional performance in tasks that require short-term maximum physical effort.

K. Prokopidis *et al.* [33] conducted a systematic review and meta-analysis of clinical studies on the effects of creatine on memory in healthy individuals. They summarised the data and concluded that people who consumed creatine as a dietary supplement to the main diet at doses of 2 to 20 g per day improved memory, compared with the placebo groups, by an average of 66%, and in older people (66-76 years) by 83%. Based on the analysed data, researchers claimed that creatine supplementation increases memory processes, especially in the elderly.

People over the age of 65 often have problems not only with memory but also with limited physical abilities. This problem was studied by T.W. Davies [34]. They investigated whether creatine has a positive effect on physical function and mental health in older adults. Because with age, certain physical disabilities can develop, such as muscle weakness, frequent falls, fatigue, limited mobility, which can lead to functional disability and reduced self-care levels. According to the results of the study, researchers found that the use of creatine in general can counteract bioenergetic muscle insufficiency, providing the ability to independently perform functional tasks. This is evidenced by the analysis of the average indicators of the conducted experiments. Thus, in the groups that took creatine supplements, the values of bench press, leg press, and average physical activity tests improved. This is another confirmation of the positive effect of this compound on physical characteristics in the elderly. Similar studies were conducted by V. Seper *et al.* [34]. They noted that creatine affects the physical performance of older adults, in particular, increases muscle strength and endurance. In a pilot project among older participants, it was found that guanidinoacetate-creatine supplements have a positive effect on functional efficiency and improve muscle and brain energy. Various creatine dosing strategies studied by M.J. Chrusch *et al.* [36] also showed a positive effect on physical function, in particular, contributed to slowing age-related loss of muscle mass. An important aspect is that even at an older age, it is possible to achieve significant improvements in physical condition due to the correct use of creatine in combination with physical training. Such studies once again confirmed the hypothesis that creatine can be a useful tool for maintaining an active lifestyle and improving physical function in the elderly, even in people with low fitness levels [37, 38].

The effectiveness of creatine supplements for restoring functional ability after a period of immobilisation of a certain part of the body was also studied. Thus, J.C. Fransen *et al.* [39] conducted an experiment on the rate of recovery of an immobilised limb with and without creatine use. 25 active young people between the ages of 20 and 28 were involved. They performed various exercises on the upper limbs, in the wrist area, after two weeks of immobilisation. In general, the recovery of limb performance in the experimental group had slightly better indicators, but additional research in this area is required. A similar study was conducted by A.P.W. Johnston *et al.* [40], only in their experiment the shoulder joint in young people was immobilised. According to their findings, creatine supplementation helped to maintain muscle mass, elbow flexion strength, and endurance in an immobilised limb.

These studies confirm the prospects of using creatine to stimulate muscle growth, improve physical endurance and strength in various settings, in particular, in people of certain professions, physically active people, people with disabilities and the elderly. Studies show that creatine is the natural energy compound that allows restoring bioenergetic potential in the shortest possible time, with minimal damage to the body. Therefore, when creatine is added as dietary supplements, there are almost no side effects or allergic reactions, with the correct dosage of the drug. Versatility in application, low manufacturing cost – these are other advantages of this compound. The possibility of using creatine compounds in patients and the elderly allows them to be more mobile and feel a surge of strength and the ability to think logically. This effect on the elderly and sick people has been proven experimentally, so this bioactive supplement is increasingly used in medical practice.

M. Balestrino & E. Adriano [41] analysed the results of a large number of studies, and provided evidence for the effectiveness of creatine use in improving the condition of patients with hereditary diseases associated with impaired synthesis of this compound by the body, muscular dystrophy, for the prevention of statin myopathy and certain types of depression in women, and increasing neuropsychic performance. Researchers have confirmed the safety of using creatine in doses up to 20 g per day, with some caveats for people with kidney disease. A similar conclusion was reached by M. Dahal *et al.* [42], who have shown that

creatine is safe and well tolerated by healthy people with both short-and long-term use. In particular, young people who train in gyms both at a professional level and for general strengthening of the body often take creatine supplements as a one-component composition or in combination with proteins, carbohydrates or some B vitamins. Most studies approve of such combinations and prove the effectiveness of their use, in particular, L.U. Schäfer *et al.* [43]. Thus, all the benefits of using creatine to improve physical performance in people of different ages and professional orientation are obvious and experimentally proven.

However, as the analysis of the processed papers has shown, there are still many questions that need to be considered in future research. Researchers explain some inaccuracies in the results or uninformative indicators by the insignificant duration of research or the coverage of a small number of people. The most studied was the effect of creatine on endurance, physical indicators of muscle strength in trained people who exercise in gyms.

Conclusions

The current study evaluated the effectiveness of creatine supplementation in improving athletic performance, physical endurance, muscle strength, muscle hypertrophy, and functional performance in athletes, people with disabilities, and the elderly. The results confirmed that creatine proved to be an effective and safe tool for improving physical performance and rapid recovery. The effect of creatine on muscle hypertrophy, strength, endurance, cognitive function, and recovery after intense physical exertion was analysed. Studies have shown a positive effect in various groups: professional athletes, the elderly, and patients with chronic diseases. Creatine, especially in combination with physical training and in combination with other substances, has been found to increase athletic performance, help maintain muscle mass and functionality, reduce inflammation, and support cognitive functions. Due to minimal side effects and good tolerance by the body, this compound is increasingly prescribed to people with sarcopenia, muscular dystrophy, and neurodegenerative disorders. An important point for good absorption of creatine-based drugs is a clear dosage and compliance with daily consumption standards.

The results obtained prove the universality of the use of creatine to improve physical performance, and the prevention of muscular dystrophy, certain neurophysiological conditions in different segments of the population. A wide range of applications allows restoring the energy potential of both athletes and the sick and elderly. The described results allow developing a clear picture of the effective effect of creatine on various systems and organs and the prospects for its use in various spheres of life. Promising areas of further research are the study of the long-term effects of creatine on the body and the development of optimal dosage protocols for different population groups. Research on its effects on metabolism, hormone balance, and long-term cognitive functionality is important. Experiments on the use of creatine in the treatment of cancer are both under-researched and promising.

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Conflict of Interest

None.

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Вплив креатину на покращення фізичних показників людини: огляд літератури

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Анотація. Креатин є популярною харчовою добавкою, яка демонструє значний вплив на фізичну продуктивність, силу та витривалість, що робить його актуальним для використання у спорті, реабілітації та підвищенні фізичних можливостей у різних вікових групах. Метою роботи було оцінити ефективність застосування креатину для покращення спортивної продуктивності, фізичної витривалості, м'язової сили, гіпертрофії м'язів та функціональних показників спортсменів, осіб з фізичними обмеженнями та літніх людей. Було проведено аналіз результатів численних експериментальних досліджень, зокрема контрольованих випробувань, систематичних оглядів та метааналізів, які оцінювали вплив креатину на фізичні показники людини, використовуючи комбіновані тренувальні протоколи та різні стратегії дозування. Проведені дослідження свідчать про високу ефективність використання креатину спортсменами і людьми інших професій, пов'язаних як з фізичною, так і розумовою роботою. Він сприяє зменшенню м'язових пошкоджень і підвищенню загальної продуктивності спортсменів, зокрема завдяки збільшенню запасів фосфокреатину та стимуляції анаболічних процесів. У спортсменів креатин сприяє зростанню маси м'язів, зниженню втоми та покращенню інтенсивності тренувань, незалежно від статі. Комбінація креатину з іншими речовинами показала додаткові переваги у збільшенні сили та витривалості. Використання креатину в поєднанні з тренуваннями сприяє регіональній гіпертрофії м'язів, збільшує їхню товщину та об'єм, особливо в умовах обмеження кровотоку. У літніх людей добавка зменшує втрату м'язової маси, покращує силу та функціональні можливості навіть за низького рівня фізичної активності. Креатин зменшує відчуття втоми та покращує функціональні показники у пацієнтів із хронічними захворюваннями та нейродегенеративними станами. Результати вказують на універсальність креатину як ефективного засобу для підвищення спортивних результатів, функціональних показників та відновлення після навантажень у різних групах населення. Його застосування рекомендоване для професійних спортсменів, літніх людей та осіб із підвищеними фізичними потребами

Ключові слова: харчові добавки; спортивна продуктивність; фізична працездатність; функціональна ефективність; м'язова сила; гіпертрофія м'язів

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