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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.

References

[1] Klymenko MO. Low-grade diffuse chronic inflammation. Actual Probl Transport Med. 2022;3(69):7–19. DOI: 10.5281/zenodo.7188166
[2] Chavda VP, Feehan J, Apostolopoulos V. Inflammation: The cause of all diseases. Cells. 2024;13(22):1906. DOI: 10.3390/cells13221906
[3] Cifuentes M, Verdejo HE, Castro PF, Corvalan AH, Ferreccio C, Quest AF, et al. Low-grade chronic inflammation: A shared mechanism for chronic diseases. Physiol. 2025; 40(1):4–25. DOI: 10.1152/physiol.00021.2024
[4] Surma S, Sahebkar A, Banach M. Nutrition, nutraceuticals and bioactive compounds in the prevention and fight against inflammation. Nutrients. 2023;15(11):2629. DOI: 10.3390/nu15112629
[5] Balderas-Peña LMaA, Sat-Muñoz D, Mireles-Ramírez MA, Martínez-Herrera BE, Nava-Zavala AH, Cervantes-González LM, et al. Influence of chronic low-grade inflammation (obesity) on the systemic inflammatory response. In: Padilla-Raygoza N, editor. Multisystem inflammatory syndrome – natural history [Internet]. London: IntechOpen; 2023. [cited 2024 Dec 28]. DOI: 10.5772/intechopen.1002764
[6] Nogueira Silva Lima MT, Howsam M, Anton PM, Delayre-Orthez C, Tessier FJ. Effect of advanced glycation end-products and excessive calorie intake on diet-induced chronic low-grade inflammation biomarkers in murine models. Nutrients. 2021;13(9):3091. DOI: 10.3390/nu13093091
[7] Tristan Asensi M, Napoletano A, Sofi F, Dinu M. Low-grade inflammation and ultra-processed foods consumption: A review. Nutrients. 2023;15(6):1546. DOI: 10.3390/nu15061546
[8] Mello RN, Gois BP, Kravchychyn ACP, Dâmaso AR, Horst MA, Lima GC, et al. Dietary inflammatory index and its relation to the pathophysiological aspects of obesity: A narrative review. Arch Endocrinol Metab. 2023;67(6):e000631. DOI: 10.20945/2359-3997000000631
[9] Vetrani C, Di Nisio A, Paschou SA, Barrea L, Muscogiuri G, Graziadio C, et al. On behalf of the Obesity Programs of Nutrition, Education, Research and Assessment (OPERA) group. From gut microbiota through low-grade inflammation to obesity: Key players and potential targets. Nutrients. 2022;14(10):2103. DOI: 10.3390/nu14102103
[10] Parisi F, Milazzo R, Savasi VM, Cetin I. Maternal low-grade chronic inflammation and intrauterine programming of health and disease. Int J Mol Sci. 2021;22(4):1732. DOI: 10.3390/ijms22041732
[11] Mebratu YA, Jones JT, Liu C, Negasi ZH, Rahman M, Rojas-Quintero J, et al. Bik promotes proteasomal degradation to control low-grade inflammation. J Clin Invest. 2024;134(4):e170594. DOI: 10.1172/JCI170594
[12] Chen E, Yu T, Brody GH, Lam PH, Goosby BJ, Miller GE. Discrimination and inflammation in adolescents of color. Biol Psychiatry Glob Open Sci. 2023;3(2):204–12. DOI: 10.1016/j.bpsgos.2022.02.008
[13] Kaltenegger HC, Weigl M, Becker L, Rohleder N, Nowak D, Quartucci C. Psychosocial working conditions and chronic low-grade inflammation in geriatric care professionals: A cross-sectional study. PLoS One. 2022;17(9):e0274202. DOI: 10.1371/journal.pone.0274202.
[14] La Grotta R, de Candia P, Olivieri F, Matacchione G, Giuliani A, Rippo MR, et al. Anti-inflammatory effect of SGLT-2 inhibitors via uric acid and insulin. Cell Mol Life Sci. 2022;79:273. DOI: 10.1007/s00018-022-04289-z
[15] Hauta-alus HH, Rosendahl J, Holmlund-Suila EM, Valkama SM, Enlund-Cerullo M, Nurhonen M, et al. Low-grade inflammation from prenatal period to age 6–8 years in a Vitamin D trial. Pediatr Res. 2024;95:1578–86. DOI: 10.1038/s41390-024-03019-4
[16] Polak-Szczybyło E. Low-grade inflammation and role of anti-inflammatory diet in childhood obesity. Int J Environ Res Public Health. 2023;20(3):1682. DOI: 10.3390/ijerph20031682
[17] Fang B, Zheng C, Ma Y, Wu F, Cheng L, Lie Y, at al. Inhibited adipogenesis and low-grade inflammation enhance adipocyte hypertrophy in aging adipose tissue. Food Nutr Health. 2024;1:2. DOI: 10.1007/s44403-024-00006-9

[18] Muscogiuri G, Bettini S, Boschetti M, Barrea L, Savastano S, Colao A. Low-grade inflammation, CoVID-19, and obesity: Clinical aspect and molecular insights in childhood and adulthood. Int J Obes. 2022;46:1254–61. DOI: 10.1038/s41366-022-01111-5
[19] Suárez-Reyes A, Villegas-Valverde CA. Implications of low-grade inflammation in SARS-CoV-2 immunopathology. MEDICC Rev. 2021;23(2):42–52. DOI: 10.37757/MR2021.V23.N2.4
[20] Salminen A. Increased immunosuppression impairs tissue homeostasis with aging and age-related diseases. J Mol Med. 2021; 99:1–20. DOI: 10.1007/s00109-020-01988-7
[21] Carvalho GB, Brandão-Lima PN, Payolla TB, Lucena SE, Sarti FM, Fisberget RM, et al. Circulating MiRNAs Are associated with low-grade systemic inflammation and leptin levels in older adults. Inflammation. 2023;46:2132–46. DOI: 10.1007/s10753-023-01867-6
[22] Bao Y, Chen X, Li Y, Yuan S, Han L, Deng X, Ran J. Chronic low-grade inflammation and brain structure in the middle-aged and elderly adults. Nutrients. 2024;16(14):2313. DOI: 10.3390/nu16142313
[23] Zhou WBS, Meng J, Zhang J. Does low grade systemic inflammation have a role in chronic pain? Front Mol Neurosci. 2021;14:785214. DOI: 10.3389/fnmol.2021.785214
[24] Chu K, Cadar D, Iob E, Frank P. Excess body weight and specific types of depressive symptoms: Is there a mediating role of systemic low-grade inflammation? Brain Behav Immun. 2023;108:233–44. DOI: 10.1016/j.bbi.2022.11.016
[25] Zhai W, Zhao M, Wei C, Meng L, Zhao A, Zhang Y, et al. Obesity-induced chronic low-grade inflammation in adipose tissue: A pathway to Alzheimer's disease. Ageing Res Rev. 2024;99:102402. DOI: 10.1016/j.arr.2024.102402
[26] Xie J, Gorlé N, Vandendriessche C, van Imschoot G, van Wonterghem E, van Cauwenbergheet C, et al. Low-grade peripheral inflammation affects brain pathology in the $App^{NL\text{-}G\text{-}F}$ mouse model of Alzheimer's disease. Acta Neuropathol Commun. 2021;9:163. DOI: 10.1186/s40478-021-01253-z
[27] Patas K, Baker DG, Chrousos GP, Agorastos A. Inflammation in posttraumatic stress disorder: Dysregulation or recalibration? Curr Neuropharmacol. 2024;22(4):e070823219478. DOI: 10.2174/1570159X21666230807152051
[28] Yuan Y, Wang X, Huang S, Wang H, Shen G. Low-level inflammation, immunity, and brain-gut axis in IBS: Unraveling the complex relationships. Gut Microbes. 2023;15(2): 2263209. DOI: 10.1080/19490976.2023.2263209
[29] Terkawi MA, Ebata T, Yokota S, Endo T, Matsumae G, Shimizu Te, et al. Low-grade inflammation in the pathogenesis of osteoarthritis: Cellular and molecular mechanisms and strategies for future therapeutic intervention. Biomedicines. 2022;10(5):1109. DOI: 10.3390/biomedicines10051109
[30] Orisaka M, Mizutani T, Miyazaki Y, Shirafuji A, Tamamura C, Fujita M, et al. Chronic low-grade inflammation and ovarian dysfunction in women with polycystic ovarian syndrome, endometriosis, and aging. Front Endocrinol. 2023;14:1324429. DOI: 10.3389/fendo.2023.1324429
[31] Dey R, Bhattacharya K, Basak AK, Paul N, Bandyopadhyay R, Chaudhuri GR, et al. Inflammatory perspectives of polycystic ovary syndrome: Role of specific mediators and markers. Middle East Fertil Soc J. 2023;28:33. DOI: 10.1186/s43043-023-00158-2
[32] Rodríguez-Vera D, Vergara-Castañeda A, Lazcano-Orozco DK, Ramírez-Vélez G, Vivar-Sierra A, Araiza-Macías MJ, et al. Inflammation parameters associated with metabolic disorders: Relationship between diet and microbiota. Metab Syndr Relat Disord. 2021;19(9):469–82. DOI: 10.1089/met.2021.0022
[33] Varra F, Varras M, Varra V, Theodosis-Nobelos P. Molecular and pathophysiological relationship between obesity and chronic inflammation in the manifestation of metabolic dysfunctions and their inflammationmediating treatment options (Review). Mol Med Rep. 2024;29:95. DOI: 10.3892/mmr.2024.13219
[34] Coppo M, Bandinelli M, Chiostri M, Modesti PA, Poggesi L, Boddi M. T Cell-based RAS activity and insulin levels in obese subjects with low grade inflammation. Am J Med Sci. 2022;363(5):428–34. DOI: 10.1016/j.amjms.2021.09.003
[35] Sharif S, Van der Graaf Y, Cramer MJ, Kapelle LJ, de Borst GJ, Visseren FL, et al. Low-grade inflammation as a risk factor for cardiovascular events and all-cause mortality in patients with type 2 diabetes. Cardiovasc Diabetol. 2021;20:220. DOI: 10.1186/s12933-021-01409-0
[36] Zhou Y, Luo Y, Liang H, Zhong P, Wu D. Applicability of the low-grade inflammation score in predicting 90-day functional outcomes after acute ischemic stroke. BMC Neurol. 2023;23:320. DOI: 10.1186/s12883-023-03365-6
[37] Wu M, Zhang X, Chen J, Zha M, Yuan K, Huang K, et al. A score of low-grade inflammation for predicting stroke recurrence in patients with ischemic stroke. J Inflamm Res. 2021;14:4605–14. DOI: 10.2147/JIR.S328383
[38] Cheng W, Du Z, Lu B. Chronic low-grade inflammation associated with higher risk and earlier onset of cardiometabolic multimorbidity in middle-aged and older adults: A population-based cohort study. Sci Rep. 2024;14:22635. DOI: 10.1038/s41598-024-72988-7
[39] Peng Y, Wang P, Gong J, Liu F, Qiao Y, Si C, et al. Association between the finnish diabetes risk score and cancer in middle-aged and older adults: Involvement of inflammation. Metabolism. 2023;144:155586. DOI: 10.1016/j.metabol.2023.155586
[40] Fedulovs A, Pahirko L, Jekabsons K, Kunrade L, Valeinis J, Riekstina U, et al. Association of endotoxemia with low-grade inflammation, metabolic syndrome and distinct response to lipopolysaccharide in type 1 diabetes. Biomedicines. 2023;11(12):3269. DOI: 10.3390/biomedicines11123269

[41] Van de Vyver M. Immunology of chronic low-grade inflammation: relationship with metabolic function. J Endocrinol. 2023;257(1):e220271. DOI: 10.1530/JOE-22-0271
[42] Geng S, Zhang Y, Yi Z, Lu R, Li L. Resolving monocytes generated through TRAM deletion attenuate atherosclerosis. JCI Insight. 2021;6(20):e149651. DOI: 10.1172/jci.insight.149651
[43] Lautenbach A, Stoll F, Mann O, Busch P, Huber TB, Kielstein H, et al. Long-term improvement of chronic low-grade inflammation after bariatric surgery. OBES SURG. 2021;31:2913–20. DOI: 10.1007/s11695-021-05315-y
[44] Hofseth LJ, Hébert JR. Chapter 3 – Diet and acute and chronic, systemic, low-grade inflammation. In: Hébert JR, Hofseth LJ, editors. Diet inflammation health. New York: Academic Press; 2022. P. 85–111. DOI: 10.1016/B978-0-12-822130-3.00011-9
[45] Barrea L, Caprio M, Watanabe M, Cammarata G, Feraco A, Muscogiuri G, et al. Could very low-calorie ketogenic diets turn off low grade inflammation in obesity? Emerging evidence. Crit Rev Food Sci Nutr. 2022;63(26):8320–36. DOI: 10.1080/10408398.2022.2054935
[46] Ayyadurai VAS, Deonikar P, Bannuru RR. Attenuation of low-grade chronic inflammation by phytonutrients: A computational systems biology analysis. Clin Nutr ESPEN. 2022;49:425–35. DOI: 10.1016/j.clnesp.2022.03.010
[47] Zhang Y, Capanoglu E, Jiao L, Yin L, Liu X, Wang R, et al. Coarse cereals modulating chronic low-grade inflammation: Review. Crit Rev Food Sci Nutr. 2022;63(29):9694–715. DOI: 10.1080/10408398.2022.2070596
[48] Fioranelli M, Roccia MG, Przybylek B, Sconci FR, Garo ML. Low-grade chronic inflammation and transcriptomics: How molecular pharmacognosy can help find new natural treatment alternatives – a narrative review. Beni-Suef Univ J Basic Appl Sci. 2024;13:48. DOI: 10.1186/s43088-024-00506-9
[49] Divella R, Marino G, Infusino S, Lanotte L, Gadaleta-Caldarola G, Gadaleta-Caldarola G. The mediterranean lifestyle to contrast low-grade inflammation behavior in cancer. Nutrients. 2023;15(7):1667. DOI: 10.3390/nu15071667
[50] Bishop NC, Wadley AJ, Hamrouni M, Roberts MJ. Inactivity and obesity: Consequences for macrophage-mediated inflammation and the development of cardiometabolic disease. Proc Nutr Soc. 2023;82(1):13–21. DOI: 10.1017/S0029665122002671
[51] Agbaje AO. Longitudinal mediating effect of fat mass and lipids on sedentary time, light PA, and MVPA with inflammation in youth. J Clin Endocrinol Metab. 2023;108(12):3250–9. DOI: 10.1210/clinem/dgad354

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