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OBESITY AS A CHRONIC LOW-GRADE INFLAMMATORY DISEASE - PATHOPHYSIOLOGICAL MECHANISMS AND CLINICAL IMPLICATIONS. A REVIEW OF THE LITERATURE

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ABSTRACT

Obesity is currently recognized as one of the greatest global public health challenges and is increasingly referred to as the pandemic of the 21st century[1,2]. The results of recent analyses confirm that one of the main mechanisms responsible for the development and persistence of obesity and its metabolic and organ-related complications is chronic inflammation in the body[3]. In obesity, one observes immunological remodeling of adipose tissue, increased activation of inflammatory pathways[4], disturbances in adipokine secretion[5], as well as gut dysbiosis and increased intestinal barrier permeability, which exacerbate metabolic endotoxemia and systemic inflammation[6]. These mechanisms contribute to the development of insulin resistance, endothelial dysfunction, and numerous comorbidities, such as type 2 diabetes, cardiovascular diseases, MASLD, neurodegenerative diseases, and cancer[7,8]. Adipose tissue thus functions as an active endocrine-immunological organ that, through the production of inflammatory mediators, influences the metabolic homeostasis of the entire body[9,10]. Recognizing obesity as an inflammatory disease is changing the current treatment paradigm - the goal of therapy is not only weight reduction but also the restoration of immunological and metabolic balance and the mitigation of the long-term consequences of chronic inflammation[11,12]. The development of targeted therapies, modulation of the gut microbiota, and the use of epigenetic mechanisms may represent important avenues for future research and treatment of obesity[13–15]. GLP-1 receptor agonists and multireceptor drugs, which, in addition to their metabolic effects, also exhibit anti-inflammatory properties, are currently showing particularly promising results[7]. The aim of this study is to analyze and summarize the current state of knowledge regarding the role of low-grade chronic inflammation (LGCI) in the pathogenesis of obesity, with particular emphasis on inflammatory mechanisms, the role of adipokines and immune cells, as well as clinical consequences and potential therapeutic strategies.

KEYWORDS

Obesity, Chronic Low-Grade Inflammation, Adipose Tissue, Insulin Resistance, Adipokines, Metabolic Syndrome, Adipocyte Hypertrophy

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1. Introduction

According to a report published on the WHO website on December 8, 2025, in 2022, 1 in 8 people worldwide were obese (890 million, including 160 million children and adolescents aged 5 to 19). The number of obese adults doubled compared to 1990, and the number of obese adolescents quadrupled. In 2022, 2.5 billion adults were overweight[1,2] and in 2024, an estimated 35 million children under the age of 5[16].

In 2021, a higher-than-optimal BMI was responsible for approximately 3.7 million deaths from noncommunicable diseases (NCDs), such as cardiovascular and chronic respiratory diseases, diabetes, cancer, neurological or digestive disorders[17]. Furthermore, the global prevalence of obesity is projected to rise from 14% to 24%, affecting approximately 2 billion adults by 2035[7]. Obesity is widely considered a multifactorial disease caused by environmental and psychosocial factors as well as genetic variants[2]. But is that all there is to it? What makes this disease so difficult to cure? Why does it seem to be self-perpetuating, with its effects becoming increasingly profound and complex over time, leading to metabolic disorders and the development of a wide range of comorbidities[18]? An explanation may lie in the concept that views obesity as an inflammatory disease - a state of chronic immune system activation induced by dysfunctional adipose tissue[7]. This marks a paradigm shift: obesity is not merely an aesthetic issue or the result of poor choices[19]. It is a chronic inflammatory disease with an immunometabolic basis, in which chronic inflammation is an integral part of the pathogenesis[20]. This acts as a vicious cycle in which adipocytes begin to produce inflammatory mediators, thereby inducing low-grade chronic inflammation (LGCI), leading, among other things, to the development of insulin resistance, type 2 diabetes, and cardiovascular diseases, as well as causing further fat

accumulation, which closes the cycle and leads to the perpetuation of obesity[18,21]. Obesity, therefore, is not merely an excess of adipose tissue - it is an inflammatory disease at the molecular level[22]. Adipose tissue is not a passive "calorie store"; it is an active endocrine-immunological organ that generates inflammation on its own, and this inflammation drives the further progression of the disease[9,10,23]. Chronic inflammation thus turns out to be one of the key mechanisms driving the development and persistence of obesity and its complications[3,7].

2. Molecular mechanisms of chronic inflammation in obesity

The low-grade chronic inflammation associated with obesity (often referred to as meta-inflammation) is a multidimensional process involving numerous molecular mechanisms in adipose tissue and other organs involved in metabolic processes[3,24].

2.1. Initiation of Inflammation: Adipocyte Hypertrophy and Hypoxia

The first characteristic feature of obesity is, of course, excessive adipose tissue growth - this is an objective, visible symptom that is easily measured through body weight, BMI, or body composition analysis. At the molecular level, we are dealing with adipose tissue hypertrophy (i.e., an increase in the size of adipocytes) and its hyperplasia (an increase in the number of adipocytes)[19]. It is worth noting, however, that this is not merely a quantitative process but is accompanied by profound qualitative changes that determine metabolic outcomes. What do these changes lead to? In the early stages of adipose tissue growth, adaptive remodeling and compensatory angiogenesis may occur, allowing the tissue to maintain metabolic homeostasis. However, after some time, the adaptive capacity of blood vessels becomes insufficient, and the rapid enlargement of adipocytes leads to impaired oxygen diffusion and the development of local hypoxia. Reduced oxygen availability triggers stress responses in adipocytes, including endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and increased production of reactive oxygen species (ROS). These processes stimulate the release of pro-inflammatory mediators and chemokines, which in turn recruit immune cells, particularly macrophages, to the adipose tissue microenvironment[25]. Hypertrophic adipocytes secrete, among other things, the chemotactic protein MCP-1 (monocyte chemoattractant protein-1), which plays a key role in the recruitment of monocytes to adipose tissue. Chronic exposure to hypoxic conditions further promotes extracellular matrix remodeling and fibrosis. Fibrotic adipose tissue exhibits a reduced capacity for lipid storage, altered adipokine secretion - notably, the synthesis of anti-inflammatory adipokines such as adiponectin is inhibited[18,21], as well as increased mechanical stiffness, which contributes to systemic insulin resistance. Importantly, the shift in the differentiation of progenitor cells toward pro-inflammatory and profibrotic phenotypes reinforces this abnormal cycle, exacerbating persistent low-grade inflammation. Dysfunctional adipose tissue then acts as an active immunometabolic organ rather than a passive energy reservoir[25]. The phenomena described above lead to mechanical stress and ultimately to adipocyte death, which further stimulates the recruitment of pro-inflammatory macrophages to adipose tissue[20].

2.2. Recruitment and Infiltration of Immune Cells

In adipose tissue with excessive volume, there is a significant change in the immune cell population - macrophages can account for as much as 40-60% of all cells, making them the dominant source of inflammatory mediators[19], whereas in lean individuals their number is only about 10%, at which point they perform homeostatic functions[26]. The traditional model classifies macrophages into two main phenotypes: classically activated M1 macrophages (pro-inflammatory) and alternately activated M2 macrophages (anti-inflammatory). In obesity, a phenotypic shift occurs from the M2 to the M1 profile[27]. M2 macrophages dominate in the adipose tissue of lean individuals and support insulin sensitivity and tissue repair processes[21,28]. They are activated by type 2 cytokines, such as IL-4 and IL-13, via the STAT6 signaling pathway[29]. They secrete anti-inflammatory molecules such as IL-10, IL-1Ra, and TGF-β1, and also exhibit arginase-1 activity, which inhibits nitric oxide production[20]. M1 macrophages are activated by saturated fatty acids (SFAs), lipopolysaccharide (LPS), and type γ interferon (IFN-γ)[26,30,31]. Their primary role in pathological conditions is the massive production of pro-inflammatory cytokines: TNF-α, IL-6, IL-1β, and the chemokine MCP-1[21,32]. These mediators drive a chronic, low-grade inflammatory state known as meta-inflammation[3,7]. The recruitment of macrophages is initiated by metabolically stressed, hypoxic, and dying adipocytes[19,20]. The key mechanism is the MCP-1 (CCL2)-CCR2 axis. Hypertrophic adipocytes secrete the MCP-1 protein, which attracts monocytes from the blood to adipose tissue, where they differentiate into pro-inflammatory macrophages[22]. They surround dying adipocytes to phagocytose their remnants and free lipid droplets, forming crown-like structures (CLS) - a histological hallmark of adipose tissue inflammation[21]. CLS structures often contain so-called lipid-associated macrophages (LAMs), characterized by the expression of the TREM2 protein, which act as a buffer for excess lipids[26,27].

The infiltration is sustained by a "vicious cycle": free fatty acids activate macrophages, which secrete TNF-α, which in turn stimulates adipocytes to produce further chemokines that attract macrophages[21,28]. The molecular consequences are insulin signaling blockade and insulin resistance. This is because M1 macrophages activate intracellular stress kinase cascades, such as JNK and IKKβ[3,29]. The activity of these kinases leads to inhibitory serine phosphorylation of the IRS-1 protein, which is a substrate of the insulin receptor, directly blocking insulin signaling[18,21,30]. The cytokine IL-1β, secreted by macrophages, further inhibits glucose transport by blocking the translocation of the GLUT4 transporter to the cell membrane of adipocytes[9]. In addition to macrophages, obesity is associated with an increase in the number of T lymphocytes (Th1, Th17, and cytotoxic CD8+ cells) and B lymphocytes, accompanied by a decrease in the number of anti-inflammatory Treg and Th2 cells[7,21]. Cytotoxic CD8+ lymphocytes infiltrate adipose tissue even before macrophages, actively promoting their recruitment[20,32]. In turn, B lymphocytes accumulate in visceral tissue and promote insulin resistance through the production of pathogenic IgG antibodies and the activation of pro-inflammatory T lymphocytes[26]. The sum of these immune interactions leads to systemic metabolic and mitochondrial dysfunction[9,24].

2.3. Activation of Receptors and Signaling Pathways

Dying adipocytes release excess saturated fatty acids (SFAs), which in turn act as endogenous ligands for the TLR4 receptor[7,33]. Toll-like receptors (TLRs) are a group of key proteins belonging to the innate immune system that act as "sensors" of danger - they recognize characteristic elements of pathogens and initiate an immediate defensive response by the body. Upon recognizing a pathogen, TLRs activate signaling pathways that lead to the production of cytokines (signaling molecules), triggering inflammation and mobilizing the immune system to fight[34,35]. In this case, TLR4 recognizes saturated fatty acids derived from excessive lipolysis. As a result of these processes, pro-inflammatory cascades are activated[7,33]. The activation of TLR4 and cytokine receptors (e.g., TNFR) leads to the activation of IKKβ kinase, which causes the degradation of the IκB inhibitor, allowing the NF-κB factor to translocate to the nucleus and stimulate the transcription of pro-inflammatory genes[21,29]. At the same time, NLRP3 is activated. This is a cytoplasmic protein receptor that, upon detection of danger signals (e.g., reactive oxygen species - ROS, ceramides, cholesterol crystals), becomes activated and forms a complex with other proteins. The NLRP3 inflammasome activates the enzyme caspase-1, which converts inactive forms of cytokines into their active forms: IL-1β and IL-18[9,36]. In addition, NLRP3 triggers pyroptosis, an inflammatory form of cell death that helps remove infected or damaged cells[37].

At the same time, stimulated by cytokines and cellular stress, the JNK (c-Jun N-terminal kinase) pathway is activated, also known as stress-activated protein kinase (SAPK). This pathway is also responsible for transmitting signals from the cell surface to the nucleus, leading to changes in gene expression in response to stressors and pro-inflammatory cytokines[38,39]. JNK phosphorylates specific proteins, including the c-Jun transcription factor (part of the AP-1 complex), which alters the activity of genes involved in the response to stress or cell death[40]. In this case, it leads to inhibitory serine phosphorylation in the IRS-1 protein (an insulin receptor substrate). This process involves the attachment of phosphate groups to serine residues (rather than tyrosine) in the IRS-1 molecule, which blocks signal transmission from the insulin receptor into the cell - directly blocking the insulin signal and inducing insulin resistance[7,20,41].

2.4. Organelle Stress and Lipotoxicity

When food intake exceeds energy requirements, the endoplasmic reticulum in adipocytes becomes overloaded with the synthesis of lipids and proteins (e.g., hormones such as adiponectin). This leads to chronic ER stress, the accumulation of unfolded or misfolded proteins, and, as a result, the activation of the unfolded protein response (UPR)[33,42]. This is a cellular defense mechanism - the UPR temporarily halts the production of new proteins, increases the production of chaperones and activates the degradation of damaged molecules to restore balance. The UPR then promotes the synthesis of cytokines (TNF-α, IL-6) by activating the PERK, IRE-1, and ATF6 pathways[29]. If the stress is too great and the cell cannot regain balance, the UPR triggers apoptosis, or programmed cell death, to prevent the cell from harming the entire organism[43]. Another organelle whose function is disrupted in obesity is the mitochondrion. Cellular stress, excess nutrients, and hypoxia result in increased ROS production and damage to mitochondrial DNA (mtDNA), which further exacerbates inflammation by activating the NLRP3 inflammasome[24]. Under conditions of nutrient excess (high levels of fatty acids and glucose), intracellular lipid accumulation occurs. Free fatty acids (FFA) are converted into diacylglycerols (DAG), which activate isoforms of protein kinase C (PKC), leading to disruptions in the PI3K/Akt pathway (which is key for glucose uptake and induces insulin resistance), increased production of reactive oxygen species (ROS), and activation of pro-inflammatory pathways (e.g., NF-κB, JNK)[7,21].

3. The Role of Adipokines and Circulating Mediators

In obesity, particularly visceral obesity, and in cases of chronic low-grade inflammation, the secretory profile of adipose tissue changes: the concentration of pro-inflammatory adipokines (leptin, resistin, visfatin) increases, while levels of the anti-inflammatory adiponectin decrease[9,29]. Leptin plays a central role in regulating appetite and energy balance by suppressing food intake and stimulating energy expenditure, and it also influences mood regulation - its deficiency is associated with depression. An increase in its concentration might therefore seem beneficial. However, obese individuals often develop leptin resistance. Additionally, leptin acts as a pro-inflammatory cytokine, increasing the production of, among others, IL-6 and TNF-α. Resistin, whose levels also rise in obesity, is directly involved in the development of insulin resistance and other metabolic disorders. It promotes the activation of the NF-κB factor, which leads to the secretion of further inflammatory mediators, and contributes to the progression of atherosclerosis and endothelial dysfunction. Visfatin (also known as NAMPT), secreted by white adipose tissue, particularly visceral fat, and macrophages, exhibits a unique insulin-mimetic effect, which helps lower blood glucose levels. It participates in the biosynthesis of NAD+, an important cofactor in energy metabolism, but excess levels are associated with obesity and may also promote inflammatory processes. Adiponectin is the most desirable - it is an adipokine with strong anti-inflammatory and insulin-sensitizing effects. It plays a key role in glucose homeostasis and lipid metabolism. It has a protective effect on blood vessels and may act as a tumor suppressor. However, unlike other adipokines, its levels decrease in obese individuals, which increases the risk of insulin resistance and cardiovascular diseases. Another adipokine whose serum concentration unfortunately increases significantly in the course of obesity is retinol-binding protein 4 (RBP4), secreted by both the liver and adipose tissue. It acts as a key mediator that transmits signals of adipose tissue dysfunction to other metabolic organs, directly contributing to the development of insulin resistance[44]. In muscle tissue, RBP4 exerts a negative effect on the early stages of insulin signaling, ultimately impairing glucose transport into myocytes. In the liver, it enhances gluconeogenesis, leading to persistently high blood sugar levels (hyperglycemia)[45]. It also has a reciprocal effect on adipose tissue itself - it inhibits GLUT4 mRNA expression, which drastically reduces the ability of adipocytes to uptake glucose, thereby exacerbating local insulin resistance. RBP4 also exhibits strong pro-inflammatory properties: it acts via Toll-like receptor 4 (TLR4) on immune cells, which initiates inflammatory cascades. It can stimulate antigen-presenting cells in adipose tissue, which promotes the formation of pro-inflammatory Th1 lymphocytes, exacerbates vascular inflammation (via the JAK2/STAT3 pathway), and promotes the transformation of macrophages into foam cells, accelerating atherosclerotic plaque formation[44].

SOCS (Suppressors of Cytokine Signaling) proteins are also mediators involved in the inflammatory response. Inflammatory cytokines (e.g., TNF-alpha or IL-6) produced by adipose tissue in overweight individuals are responsible for the increased production of SOCS proteins. These act as negative regulators (inhibitors) of intracellular signaling, functioning through negative feedback. They inhibit the JAK/STAT signaling pathway activated by cytokines (molecules associated with inflammation and immunity) - that is, SOCS protein production is stimulated by the very same cytokines that are subsequently inhibited by SOCS proteins, thereby preventing an excessive and harmful immune response. Under physiological conditions. However, their deficiency or, as in this case, excess can lead to chronic inflammation, insulin resistance, and the development of type 2 diabetes. High levels of SOCS (primarily SOCS-3) cause, for example, the proteolytic degradation of IRS proteins, thereby promoting insulin resistance[20,21,46].

4. The Role of the Gut Microbiota

The gut microbiota has a multifaceted influence on the development of chronic inflammation in obesity. A key factor is the imbalance between gut microorganisms and the host's intestinal barrier[47].

4.1. Dysbiosis, Inflammation, and Intestinal Permeability

Obesity and a high-fat diet cause dysbiosis - that is, profound quantitative and qualitative changes in the composition of the gut microbiota - leading to an imbalance in the microbiota and a complete alteration of the gut's metabolic profile[19]. These changes primarily include a reduction in the population of anti-inflammatory bacterial species, such as Faecalibacterium prausnitzii, accompanied by an increase in the abundance of "pro-inflammatory" strains, so-called pathobionts, e.g. from the genus Bacteroides or Ruminococcus gnavus[44]. Protective bacteria, such as Faecalibacterium prausnitzii, ferment dietary fiber, producing short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate, which strengthen the intestinal barrier and exert anti-inflammatory effects via GPR41/43 receptors[7,47]. Butyrate is the primary energy source for enterocytes and

is essential for maintaining their integrity and mucus production. Without sufficient SCFAs (when the population of beneficial bacteria declines), intestinal cells become "malnourished," regenerate more slowly, and their ability to maintain a tight barrier diminishes. Their deficiency thus promotes inflammation, and pro-inflammatory bacteria actively destroy the intestinal barrier. A healthy microbiota also stimulates the epithelium to produce antimicrobial peptides (AMPs), natural antibiotics such as REG3γ, which control the number of bacteria at the intestinal wall. The altered microbiota ceases to send signals (via PRR receptors, such as NOD2) that prompt the body to produce these peptides. This allows harmful bacteria to freely colonize the intestinal surface and damage its structure[24]. The first line of defense separating the bacteria living inside the intestines from the epithelial cells is the mucus layer. When the diet is low in fiber (which is common in obesity), bacteria seeking alternative energy sources destroy the intestinal mucus, using the glycans that make it up as food. This leads to a drastic reduction in the thickness of the mucus layer, allowing bacteria to come into direct contact with epithelial cells and triggering inflammation. Furthermore, local immune cells are stimulated to produce pro-inflammatory cytokines, such as TNF-α[21]. TNF-α, in turn, activates the NF-κB pathway, which directly increases the permeability of tight junctions formed by proteins such as zonulin, occludin, and claudin-1, whose role is to bind the membranes of adjacent cells by forming a tight, waterproof barrier on the apical surfaces of epithelial cells[44,47]. The destruction of these junctions causes the intestinal barrier to become leaky. Consequently, substances that should be excreted - toxins, undigested food residues or bacterial components, particularly lipopolysaccharide (LPS) - an endotoxin from the membranes of Gram-negative bacteria - can be absorbed into the portal and systemic circulations[3]. In obese individuals, hyperglycemia (high glucose levels) can directly reprogram intestinal cells, leading to the disruption of tight junctions independently of the bacteria themselves. In the presence of dietary fats, LPS can be transported across the intestinal barrier inside chylomicrons (fat-carrying particles), which further facilitates the entry of toxins into the bloodstream[7,19]. The lack of protection from "good" bacteria allows for the overgrowth of LPS-producing species, and LPS further damages protein-based tight junctions[47]. Even a slight, 2- to 3-fold increase in blood LPS levels (known as metabolic endotoxemia) is sufficient to trigger chronic low-grade inflammation[24]. Circulating LPS reaches metabolic tissues, such as adipose tissue, the liver, and skeletal muscle, where it binds to TLR4 (Toll-like receptor 4) receptors and the CD14 protein. Activation of TLR4 triggers intracellular signaling cascades, including the NF-κB and JNK kinase pathways, which stimulate the production and release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, which then circulate systemically and exacerbate inflammation[3,21,29,33]. The loss of bacterial balance and diversity therefore leads to impaired intestinal barrier function and, consequently, promotes the initiation and maintenance of inflammation[7].

4.2. Direct Inhibition of Insulin Signaling

A key link between inflammation and insulin resistance is the effect of activated kinases (JNK and IKKβ) on insulin receptor substrate (IRS) proteins, which are present in most cells, particularly in insulin-sensitive tissues such as adipose tissue, the liver, and muscle[33,47]. The IRS-1 (Insulin Receptor Substrate 1) protein is a key intracellular adaptor protein that plays a major role in transmitting the signal from the insulin receptor to downstream cellular components - after insulin binds to the insulin receptor on the cell surface, IRS-1 is activated (phosphorylated) and "informs" the cell that it is time to take up glucose from the blood. It is therefore essential for proper carbohydrate metabolism and the functioning of the body's energy balance. In contrast, kinases activated by intestinal stimuli (LPS) cause inhibitory phosphorylation of serine residues in the IRS-1 protein[21]. This blocks glucose transport - the altered IRS-1 protein cannot properly transmit the signal from the insulin receptor to the PI3K kinase, resulting in impaired translocation of the GLUT4 transporter to the cell membrane and a failure of cells to uptake glucose[7]. This ultimately leads to insulin resistance and the development of type II diabetes[3,33]. Gut dysbiosis also affects the population of immune cells residing in the gut and adipose tissue. Changes in the microbiome promote the differentiation of lymphocytes into pro-inflammatory Th1 and Th17 subtypes, accompanied by a decrease in the number of regulatory Treg cells. Signals from the gut (LPS, metabolites) stimulate the infiltration of adipose tissue by pro-inflammatory M1-type macrophages, which are the primary source of inflammatory mediators that block insulin action[21,29]. A microbiota with low diversity is often enriched in genes responsible for the transport of branched-chain amino acids (BCAAs), elevated levels of which in the blood also strongly correlate with insulin resistance[19]. Additionally, certain bacterial strains dominant in dysbiosis produce metabolites that directly disrupt metabolism, such as imidazole propionate, which inhibits insulin signaling via the mTORC1 pathway. In summary, the gut microbiota in obesity ceases to play a protective role and becomes a source of signaling

molecules (LPS, specific metabolites) that carry inflammation from the gastrointestinal tract to key metabolic organs via the bloodstream[47]. Reduced bacterial diversity "compromises" the intestinal barrier, allowing toxins (LPS) to flood the body. These toxins activate "brakes" (stress kinases) in cells, which physically block the pathway through which insulin signals sugar uptake. The molecular basis of inflammation in obesity is a "vicious cycle" in which metabolic stress in adipocytes activates immune cells, which in turn secrete cytokines that exacerbate cellular stress and block metabolic pathways[18,21]. Additionally, released free fatty acids and cytokines can further disrupt the composition of the gut microbiota and the integrity of the barrier[7,30]. Inflammatory mediators and circulating LPS stimulate the proliferation of pre-adipocytes and their hypertrophy, which exacerbates adipose tissue dysfunction[47]. Disrupted microbiota may also inhibit the "browning" of white adipose tissue, which reduces the body's energy expenditure and promotes further fat storage[44].

5. Discussion of the Clinical Consequences of Chronic Inflammation in Obese Individuals.

5.1 Progression to Type 2 Diabetes (T2DM)

Long-term insulin resistance caused by inflammation leads to the exhaustion of the pancreas's compensatory mechanisms. The action of pro-inflammatory cytokines, such as IL-1β, leads to direct damage to pancreatic islet beta cells. This occurs, because as a result of the chronic stress to which the endoplasmic reticulum is exposed, these cells ultimately trigger apoptosis or programmed cell death. This results in impaired insulin secretion[48]. Insulin resistance intensifies lipolysis in adipose tissue, which increases serum FFA levels, which in turn further promote inflammation and tissue resistance to insulin[7,49]. An excess of fatty acids is also present inside beta cells that remain active. This condition, known as lipotoxicity, leads to the formation of toxic intermediate metabolites such as ceramides, which activate inflammatory pathways and generate free radicals further damaging the structure of the islets[21,50]. The pancreas cannot keep up with insulin production, leading to persistently elevated glucose levels (hyperglycemia). This condition - chronically elevated blood glucose levels resulting from insulin resistance and a relative insulin deficiency caused by pancreatic beta cell dysfunction - is type 2 diabetes. Diabetes is a more serious condition than insulin resistance alone. It is a chronic metabolic disease that cannot be cured in the sense of permanently eliminating the cause - it does not disappear forever - but remission can be achieved through weight loss, dietary changes, and increased physical activity[51–53].

5.2 Effects on the Liver (MASLD)

The most significant consequence of chronic inflammation in the liver is the development of MASLD (non-alcoholic steatohepatitis). It occurs as a result of the so-called "multiple hit hypothesis" - the disease does not result from a single factor, but rather from the synergy of several factors occurring simultaneously[54,55]. First and foremost, insulin resistance in the liver paradoxically promotes increased de novo lipogenesis (DNL) - that is the synthesis of new fats - while simultaneously impairing the process of β-oxidation (burning) of fatty acids, which enter the liver in greater quantities[7,49]. The accumulation of triglycerides leads to hepatic steatosis - initially, simple steatosis of the liver (MASL) develops. This mechanism is driven, among other things, by the synergy of IL-6 and TNF-α, which impair insulin sensitivity in the liver, increase glucose production, enhance fat storage, and activate inflammatory pathways (NF-κB, inflammasome)[56–58]. Excess FFA in hepatocytes leads to mitochondrial dysfunction and excessive production of reactive oxygen species (ROS), which generates oxidative stress[7,59]. Ultimately, this leads to progression from simple steatosis (MASL) to steatohepatitis (MASH). A key element is the recruitment of macrophages and Th17 lymphocytes by chemokines (e.g., CXCL9, CXCL10), which promotes hepatocyte damage, activation of hepatostatic cells (HSCs) and consequently, liver fibrosis[49]. Non-alcoholic fatty liver disease can lead to cirrhosis and even the development of hepatocellular carcinoma (HCC)[60].

5.3 Cardiovascular Diseases

Chronic low-grade inflammation in adipose tissue is also a key factor in the development of cardiovascular diseases[58]. Insulin resistance in adipose tissue increases lipolysis and the release of free fatty acids (FFA), which reach the liver and enhance VLDL production, thereby exacerbating lipid abnormalities[56,61]. Atherogenic dyslipidemia, characterized by elevated triglyceride levels, small dense LDL, and reduced HDL, plays a significant role[62]. Small dense LDL (sdLDL) particles are particularly dangerous - because they are smaller and denser than standard LDL, they penetrate vascular walls more easily and

undergo oxidation, after which they are engulfed by macrophages, forming foam cells - this is how atherosclerotic plaques form[49,59]. The presence of sdLDL increases the risk of ischemic heart disease by up to 7-fold. Excess FFA and cytokines increase oxidative stress by stimulating the production of reactive oxygen species (ROS), which damage the vascular endothelium[50]. Damaged endothelium increases the expression of adhesion molecules (e.g., VCAM-1), which "trap" monocytes from the blood and draw them into the arterial wall, where they become a component of the atherosclerotic plaque[56]. Inflammatory cytokines and adipokines (e.g., leptin, resistin) further exacerbate the inflammatory process in the vascular wall, promoting atherosclerotic plaque instability and making it prone to rupture. Inflammation associated with obesity also promotes a procoagulant state in the blood (through increased platelet reactivity and elevated levels of clotting factors), which facilitates clot formation at the site of vascular damage[59]. Rupture of an unstable atherosclerotic plaque and the formation of a thrombus can cause occlusion of the coronary artery lumen, which directly triggers a heart attack[21]. Meta-inflammation and dyslipidemia also cause a decrease in the bioavailability of nitric oxide (NO), which further exacerbates endothelial dysfunction and leads to increased vascular tone and elevated peripheral resistance[49]. This and other mechanisms lead to the development of hypertension. Additionally, pro-inflammatory cytokines (leptin, TNF-α) stimulate the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). Angiotensin II causes direct vasoconstriction and sodium retention in the kidneys. Furthermore, excess retroperitoneal fat physically compresses the kidney, increasing intrarenal pressure, which also activates mechanisms that raise blood pressure[59]. It can therefore be concluded that the key element linking excess body weight to cardiovascular complications is chronic low-grade inflammation (so-called meta-inflammation), which initiates and drives a pathophysiological cascade leading to dyslipidemia, atherosclerosis, and hypertension, all of which directly increase the risk of cardiovascular events such as myocardial infarction[21,50].

5.4. Effects on the Central Nervous System (CNS)

The chronic, low-grade inflammation associated with obesity may also play a role in the development of certain mental and neurological disorders. Among other things, meta-inflammation impairs the blood-brain barrier (BBB) - weakening the integrity of tight junction proteins (e.g., occludin), which leads to the "leakage" of toxins into the brain parenchyma. In addition to toxins, excessive amounts of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, can also cross the blood-brain barrier[63,64]. Resident immune cells of the brain (microglia), under the influence of inflammatory signals from the periphery, enter a state of chronic activation, releasing neurotoxic substances that destroy neurons and inhibit neurogenesis (i.e., the process of forming new nerve cells)[65]. Additionally, inflammation increases the production of reactive oxygen species (ROS), inducing oxidative stress, which leads to mitochondrial dysfunction in neurons and impaired synaptic plasticity[63,66]. Neuroinflammation thus leads to widespread structural and functional changes in the brain. Structural changes are visible on MRI - obese individuals have been shown to have reduced gray matter volume (particularly in the hippocampus and prefrontal cortex) and changes in white matter, which correlate with deficits in memory, attention, and executive function[67].

5.4.1 Depression and Mood Disorders

Pathophysiological inflammatory mechanisms also link obesity to mood disorders. Neuroinflammation disrupts the synthesis and metabolism of neurotransmitters such as serotonin (5-HT), dopamine (DA), and gamma-aminobutyric acid (GABA), which forms the biological basis of anxiety and depressive states[65]. The tryptophan metabolic pathway is also redirected toward the production of toxic metabolites, such as quinolinic acid, which negatively affects CNS homeostasis and white matter integrity. Furthermore, there is a significant impact on the hypothalamic-pituitary-adrenal (HPA) axis - obesity intensifies the activity of the stress axis, leading to chronic hypercortisolism, which further promotes inflammation and depression. The relationship between obesity and depression is bidirectional and gut-brain axis dysfunction plays a significant role. In obese individuals, intestinal dysbiosis and increased intestinal permeability ("leaky gut") are common, allowing bacterial endotoxins (LPS) to enter the circulation and trigger inflammatory responses in the CNS. Additionally, a decrease in the production of short-chain fatty acids (SCFAs) such as butyrate, deprives the brain of anti-inflammatory protection, which promotes the development of depressive symptoms and chronic inflammation affects the brain's reward system, which can lead to emotional and compulsive eating, exacerbating the vicious cycle of obesity and depression[63,64].

5.4.2. Alzheimer's Disease (AD)

The pathogenesis of Alzheimer's disease (AD) is primarily based on the accumulation of amyloid plaques (beta-amyloid) and neurofibrillary tangles (tau protein) in the brain, leading to neurodegeneration, neuronal death, and dementia[68]. Obesity in middle age is considered one of the most important risk factors for the development of dementia and Alzheimer's disease later in life, because chronic inflammation leads to the development of insulin and IGF-1 resistance in the central nervous system (sometimes referred to as "type 3 diabetes") - whereas under normal conditions insulin inhibits the formation of amyloid plaques and tau phosphorylation, in a state of insulin resistance these processes are intensified, accelerating the pathogenesis of AD. Additionally, inflammatory mediators activate microglia in the hippocampus and prefrontal cortex, resulting in the chronic release of neurotoxic substances and neuronal death[63,69].

5.5 Cancer

Chronic inflammation associated with obesity is also a recognized factor promoting carcinogenesis[63]. Adipose tissue in obese individuals serves as a source of excess estrogen, insulin, and cytokines (TNF-α, IL-6), which stimulate cell proliferation and inhibit apoptosis[65]. Leptin also plays a significant role - its high levels in obesity stimulate angiogenesis (the formation of blood vessels within a tumor) and the proliferation of cancer cells[7,61]. A strong association has been demonstrated between obesity and an increased risk of endometrial and breast cancers (especially after menopause), prostate cancer, colorectal cancer, and liver cancer[63,66,69]. The mechanisms are complex - damage to the intestinal barrier allows bacteria to penetrate the intestinal lamina propria, causing local inflammation that stimulates tumor growth and may lead to the development of colorectal cancer. Inflammatory cytokines play a significant role in the development of HCC by activating hepatocytes to divide excessively, which combined with DNA damage leads to the formation of cancerous mutations[61].

5.6 Hormonal and Reproductive Disorders

5.6.1 Polycystic Ovary Syndrome (PCOS) and Female Fertility

The link between obesity and PCOS is based on the so-called PCOS-insulin-inflammation triangle. Chronic inflammation impairs insulin signaling, leading to hyperinsulinemia. High insulin levels subsequently inhibit hepatic production of SHBG (sex hormone-binding globulin), which increases the bioavailability of free androgens - their excess disrupts the processes of folliculogenesis and ovulation, leading to infertility, hirsutism, and acne. Additionally, cytokines intrinsically associated with meta-inflammation, such as TNF-α, directly stimulate the cells of the ovarian theca to produce androgens, exacerbating hyperandrogenism[70,71].

5.6.2. Hypogonadism and Fertility Disorders in Men

In men, obesity leads to obesity-related secondary hypogonadism (MOSH), often referred to as functional hypogonadism. Meta-inflammation and excess leptin inhibit kisspeptin secretion in the hypothalamus, resulting in reduced release of GnRH and consequently of LH and FSH. Excess adipose tissue also increases aromatase activity, which converts testosterone into estradiol (E2), further inhibiting the hypothalamic-pituitary-testicular axis via negative feedback. Semen parameters also change -in obese men, reduced concentration, motility, and abnormal sperm morphology are observed - and the deterioration in semen quality is more pronounced the higher the BMI. Additionally, other factors associated with obesity, such as elevated scrotal temperature and oxidative stress caused by inflammation, lead to increased sperm DNA fragmentation (SDF), i.e. damage to the structure of the genetic material contained in the sperm heads - high levels of fragmentation reduce male fertility, hinder conception, and increase the risk of failure in assisted reproductive technologies and the risk of miscarriage[72–74].

5.7 Immune Disorders

Obesity and the associated systemic inflammation drastically alter the cellular and functional profile of the immune system. In adults, an increase in the number of pro-inflammatory Th1 and Th17 lymphocytes is observed, accompanied by a suppression of Treg (regulatory) lymphocyte function. Interestingly, in children, the number of Tregs in peripheral blood may initially be elevated as a compensatory mechanism aimed at suppressing inflammation. Most importantly, however, chronic activation of the immune system leads to metabolic exhaustion of CD8+ lymphocytes, which ultimately impairs immunity - susceptibility to infections increases and their course may be more severe due to an impaired immune system. Furthermore, the quality and durability of the immune response following vaccination are compromised[75–77].

6. Presentation of Current and Future Directions in Therapies Aimed at Modulating Inflammation - Intervention Strategies

6.1. Pharmacotherapy: Incretin Receptor Agonists and New Molecules

The greatest breakthrough in the pharmacological inhibition of inflammation in obesity is represented by glucagon-like peptide-1 receptor agonists (GLP-1RAs), known as GLP-1 analogs, and their dual and triple agonists. They mimic the action of the natural intestinal hormone (GLP-1), which signals satiety to the brain, leading to stimulation of insulin secretion, stabilization of glucose levels, slowing of gastric emptying and a feeling of fullness, thereby reducing appetite and, consequently, body weight. Drugs such as semaglutide and liraglutide reduce levels of systemic markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), acting directly by modifying macrophage activity in adipose tissue and indirectly through weight loss. Tirzepatide (a dual GLP-1/GIP receptor agonist) is a newer compound that exhibits a stronger effect on reducing body weight and inflammation than classic GLP-1 agonists[7,78]. Retatrutide (a triple GLP-1/GIP/glucagon agonist), currently in clinical trials, has the potential to further promote the reduction of visceral adipose tissue (by reducing appetite while simultaneously increasing energy expenditure), which is crucial for suppressing inflammation[79]. Furthermore, GLP-1RAs cross the blood-brain barrier and reduce inflammation by inhibiting the NF-κB pathway and modulating the activity of microglia and astrocytes[78], whose excessive activation leads to the chronic release of neurotoxic substances and neuronal death[63,69]. Studies in patients with PD have demonstrated a slowing of the progression of motor and cognitive impairments following exenatide administration. Liraglutide and semaglutide, on the other hand, demonstrate the ability to reduce amyloid plaques and tau protein in AD models. Although the EVOKE study did not show a significant effect of semaglutide on AD progression, other analyses suggest an overall decrease in the incidence of dementia among individuals using these drugs[78].

Another promising pharmacological strategy involves the modulation of peroxisome proliferator-activated receptors gamma (PPARγ), which, according to recent reports, enables the reprogramming of the inflammatory phenotype of adipose tissue in obese patients. Evidence from preclinical studies in animal models indicates that PPARɣ activation restores TH2 cells' sensitivity to anti-inflammatory signals, which effectively corrects macrophage polarization defects and reverses leptin resistance, a hallmark of chronic inflammation. These findings are supported by clinical trials of new PPARɣ agonists, such as lobeglitazone, whose use led to a significant reduction in C-reactive protein (hs-CRP) levels (by 32%) while simultaneously reducing visceral adipose tissue volume by as much as 18%. Such a marked improvement in metabolic parameters suggests that these modulators exert a direct effect on the endocrine function of adipocytes, making them a promising tool for suppressing systemic inflammation[7].

6.2. Non-Pharmacological Interventions: Diet and Physical Activity

Pharmacotherapy, however, remains only the next step in the treatment of obesity - the foundation of therapy, which has the greatest impact on immune balance, is invariably a healthy lifestyle - specifically, dietary choices and physical activity.

The Dietary Inflammatory Index (DII) is a scientifically developed indicator that assesses the pro-inflammatory or anti-inflammatory potential of the food consumed. It determines how diet affects the levels of inflammatory markers (e.g., CRP, TNF-α, IL-6) in the body. A low DII value indicates an anti-inflammatory diet, while a high value indicates a pro-inflammatory diet[80].

One diet with low inflammatory potential is the Mediterranean diet, which is based on a high intake of plant-based foods (fruits, vegetables, legumes, nuts, and whole grains) and olive oil, and is therefore rich in polyphenols, fiber, and omega-3 fatty acids, which effectively lower levels of key inflammatory markers[11]. Additionally, a diet with a low DII index improves the composition of gut microbiota, leading to increased production of short-chain fatty acids (SCFAs). These metabolites suppress inflammation in adipose tissue by influencing molecular mechanisms, including the inhibition of the NLRP3 inflammasome and toll-like receptor signaling[7]. Clinical studies have shown that following the principles of the Mediterranean diet - even without intentional calorie restriction - allows for weight loss (an average of 2.8 kg per year) in obese individuals and also brings about a marked improvement in fatty liver disease and cardiovascular parameters[81]. By reducing adipose tissue inflammation, this diet helps reverse systemic insulin resistance, improving glucose and lipid metabolism[7,11].

Physical activity is, alongside diet, the most important factor in the fight against obesity. It has been shown that regular aerobic exercise (of moderate or high intensity, 30–60 minutes, 2–3 times a week) improves

insulin sensitivity through mechanisms such as reducing ceramide levels, improving pancreatic β-cell function, and increasing skeletal muscle vascularization. During exercise, skeletal muscles secrete myokines (e.g., irisin, anti-inflammatory IL-6), which inhibit obesity-induced inflammatory cascades and improve insulin sensitivity. Muscle-derived interleukin-6 inhibits the production of TNF-α and IL-1β while stimulating the secretion of anti-inflammatory cytokines, such as IL-10. As a result, the inflammatory profile and glucose metabolism improve, and the activation of immune system cells decreases. Irisin also plays a significant role - a myokine that induces the "browning" of white adipose tissue and regulates energy metabolism. It has a beneficial effect on inflammation, oxidative stress, diabetes, and neurodegenerative processes. Additionally, strength training activates the mTOR and AMPK pathways, supporting myokine secretion. Physical activity can also modulate the composition of the gut microbiota, which further contributes to the reduction of systemic inflammation. Furthermore, it has a beneficial effect on the lipid profile and cardiovascular health. As a result, it constitutes an effective therapeutic intervention for the treatment of chronic inflammation associated with obesity and, in the long term, leads to a reduction in mortality from comorbidities[11].

6.3. Microbiota and Probiotic Therapy

Modulation of the gut microbiome is a new, promising approach to treating inflammation and obesity[15,82]. Probiotics (primarily Lactobacillus and Bifidobacterium strains) support the integrity of the intestinal barrier, which prevents the penetration of lipopolysaccharides (LPS) into the bloodstream and inhibits so-called metabolic endotoxemia[6,83]. The fermentation of prebiotics by gut bacteria leads to the production of short-chain fatty acids (SCFAs), such as butyrate and propionate, which, by serving as an energy source for colon epithelial cells (colonocytes), also support the intestinal barrier, exert systemic anti-inflammatory effects via GPR41/43 receptors[15,44,84] and may stabilize the blood-brain barrier[15,82]. Meta-analyses conducted to date indicate that synbiotic supplementation significantly reduces CRP and IL-6 levels in individuals with metabolic disorders[85]. Additionally, preclinical studies point to the existence of psychobiotic strains - according to research, for example, the Lactiplantibacillus plantarum strain may restore BDNF levels in the hippocampus and reduce levels of beta-amyloid and α-synuclein, whose abnormal accumulation in the brain leads to neuronal destruction and the development of major neurodegenerative diseases (dementia and movement disorders). Attention is also drawn to the benefits of using synbiotics - formulations that combine probiotics (live, beneficial bacteria) and prebiotics (food for these bacteria, e.g., fructans from asparagus), which work synergistically to restore neurochemical balance and mitigate neurodegeneration caused by a high-fat diet[82].

6.4. Future Directions and Molecular Therapeutic Targets

Research is currently focused on precisely targeting the molecular "switches" of inflammation.

6.4.1 NLRP3 Inflammasome

One of the molecular therapeutic targets currently under investigation is the NLRP3 inflammasome, which has been identified as a key complex activating the IL-1β and IL-18 cytokine cascade in obesity[86]. New findings indicate that in obesity, NLRP3 is hyperactivated through phosphorylation of the SAMHD1 protein, leading to the leakage of mitochondrial DNA into the cytoplasm and an exacerbation of inflammation. Elucidating the causes of this phosphorylation will be the subject of future research, while finding ways to eliminate this phosphorylation, prevent the transport of deoxynucleotides into mitochondria, or block the interaction between oxidized mitochondrial DNA and NLRP3 could become a breakthrough in treatment[82,87]. The NLRP3 inflammasome is responsible for the maturation of the cytokines IL-1β and IL-18 in macrophages and microglia as well[88]. Inhibition of NLRP3 (e.g., by the molecule MCC950) is therefore being investigated as a strategy to prevent neuronal damage in obesity[86].

6.4.2 Epigenetic Modifications (m6A)

A growing body of evidence points to the significant role of the epigenetic modification N6-methyladenosine (m6A) in regulating inflammatory and metabolic processes in obesity. M6A regulates the formation and number of adipocytes, influences their structure and function - including hypertrophy and the transition between white and brown adipose tissue - controls the activation, infiltration, and polarization of immune cells, and participates in the regulation of angiogenesis. All these mechanisms play a significant role in the development and maintenance of inflammation in adipose tissue - M6A modification is therefore a key component of epigenetic regulation in obesity and its metabolic complications, and its modulation offers a new avenue for gene therapy[8].

6.4.3 Modern Technologies and CRISPR/Cas9 Genetic Engineering

Research is underway to use CRISPR to convert white adipose tissue into "brown-like" tissue, which would increase energy expenditure and reduce inflammation. The most advanced research involves the creation of so-called HUMBLE cells (human brown-like adipocytes). Scientists are using CRISPR/Cas9 to activate endogenous genes responsible for thermogenesis in human white adipose tissue preadipocytes. Cells modified in this way exhibit characteristics of brown fat, including high mitochondrial density and increased expression of the UCP1 (uncoupling protein 1) protein, which dissipates energy as heat rather than storing it in the form of ATP. Studies conducted to date have shown that transplanting HUMBLE cells into mice fed a high-fat diet prevented the development of obesity and alleviated symptoms of metabolic syndrome, improving glucose tolerance and insulin sensitivity[6,14,82]. The transformation of white adipose tissue into brown-like tissue has a direct effect on the resolution of inflammation through mechanisms such as: changes in the secretory profile - brown and beige adipose tissue secrete a beneficial profile of adipokines and cytokines with anti-inflammatory effects, and effects on macrophages: the browning process induced by genetic modifications promotes the polarization of macrophages toward the M2 (anti-inflammatory) phenotype and inhibits the infiltration of M1 macrophages, which breaks the "vicious cycle" of obesity and chronic inflammation. Additionally, improved vascularization (angiogenesis) accompanying the browning process reduces local tissue hypoxia, which is the main trigger of inflammation in hypertrophied white adipose tissue[8]. Nanoparticles (e.g., polymeric NPs with simvastatin) are also being developed to specifically deliver anti-inflammatory drugs to adipose tissue or the brain, minimizing side effects and increasing the efficacy of therapy[89].

6.4.4 Adipokines as Biomarkers and Therapeutic Targets

Adipose tissue secretes over 600 adipokines, whose profile shifts toward a pro-inflammatory state in obesity. Adipokines show numerous correlations with metabolic parameters such as insulin resistance, blood pressure, lipid profile, and inflammatory markers, making them useful diagnostic and prognostic biomarkers, and their modulation represents a promising direction for the treatment of obesity and its complications. However, due to the complexity of their action and the not yet fully understood molecular mechanisms, further research is necessary to fully exploit their clinical potential. One of the strongly pro-inflammatory adipokines, whose levels correlate directly with BMI, insulin resistance, lipid profile, and markers of inflammation, is chemarin. Chemarin receptor (CMKLR1) antagonists are a promising therapeutic target aimed at reducing inflammation. Omentin and adiponectin, on the other hand, have anti-inflammatory effects. Their concentrations are reduced in obesity, serving as a marker of metabolic dysfunction. Omentin inhibits the expression of endothelial adhesion molecules (VCAM-1, ICAM-1), promotes the polarization of macrophages toward the anti-inflammatory M2 phenotype, and inhibits the NF-κB pathway. Adiponectin and omentin have a beneficial effect on insulin sensitivity, glucose metabolism, and cardiovascular function. Restoring high levels of these adipokines represents a potential therapeutic approach to improving the metabolic profile. Leptin, in addition to suppressing appetite and increasing energy expenditure - which is metabolically beneficial - exhibits pro-inflammatory properties, and its levels rise in proportion to the amount of body fat. People with obesity often develop leptin resistance, which limits its biological effects - the brain does not respond to elevated leptin levels in the blood, leading to a lack of satiety. Leptin has already found clinical application (e.g., metreleptin in lipodystrophy), but its use in treating obesity requires overcoming resistance mechanisms[5,90]. Overcoming leptin resistance in the hypothalamus may restore appetite control and resolve inflammation in the CNS[7,91].

7. Summary and Conclusions

The current approach redefines obesity as a complex, multifactorial chronic disease that goes beyond the simple model of excess calorie intake and physical inactivity[12]. A key element of its pathogenesis is low-grade chronic inflammation, which serves as the link between excess adipose tissue and the development of numerous metabolic and organ-specific complications. Pathological expansion of adipose tissue leads to adipocyte hypertrophy, local hypoxia, endoplasmic reticulum stress, and mitochondrial dysfunction, which initiates the activation of inflammatory pathways and the formation of a vicious cycle of obesity and LGCI[7,8,86]. An additional factor exacerbating inflammation is metabolic endotoxemia resulting from gut dysbiosis and increased intestinal barrier permeability[6,15]. An important role in the development of inflammation is played by the immunological remodeling of adipose tissue, including the polarization of macrophages from the anti-inflammatory M2 phenotype to the pro-inflammatory M1 phenotype and the activation of the NF-κB, JNK,

and NLRP3 inflammasome pathways[4,7,11,13]. Increasing importance is also attributed to epigenetic mechanisms, including m6A methylation, which influences adipocyte function and the activity of immune cells[8]. Dysfunctional adipose tissue also alters the profile of secreted adipokines. In obesity, elevated levels of pro-inflammatory adipokines are observed, accompanied by a decrease in the levels of those with anti-inflammatory and insulin-sensitizing effects[5,13]. These abnormalities contribute to the development of insulin resistance, endothelial dysfunction, and chronic inflammation. The consequence of chronic adipose tissue inflammation is ectopic lipid accumulation and the development of diseases such as type 2 diabetes, cardiovascular diseases, metabolic and fatty liver disease (MASLD), neurodegenerative diseases, and cancers[7,8]. Although clinical interventions, such as bariatric surgery or lifestyle modification, can be beneficial not only for weight loss but also for reducing inflammation - which improves cognitive function and lowers the risk of comorbidities[63] - contemporary therapeutic strategies focus not only on weight loss but also on modulating inflammatory processes. GLP-1 receptor agonists and multireceptor drugs show particularly promising results, as they exhibit anti-inflammatory effects in addition to their metabolic effects[7]. The future of the fight against obesity lies in precision medicine and molecular innovations, including the development of targeted therapies such as NLRP3 inflammasome modulators, m6A epigenetic mechanisms, or strategies affecting the gut microbiota and the browning of adipose tissue[8,14]. In addition, the use of next-generation probiotics (e.g., Akkermansia muciniphila) and personalized dietary interventions (e.g., those with a low Dietary Inflammatory Index) leads to the suppression of LGCI at its source[7,13,15].

Recognizing obesity as an inflammatory disease is changing the current treatment paradigm. The goal of therapy is not only weight loss, but above all, restoring the body's immunological and metabolic balance and limiting the long-term consequences of chronic inflammation[11,12].

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