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The Role of Dyslipidemia and Obesity in the Pathogenesis of Osteonecrosis of the Femoral Head

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ABSTRACT

The review focuses on current concepts of the role of obesity, the chronic systemic inflammation it induces, and lipid metabolism disorders in the pathogenesis of osteonecrosis of the femoral head (ONFH) in order to substantiate new approaches to its prevention and treatment. This review analyzes modern fundamental and clinical studies focusing on the relationship between metabolic disorders, chronic inflammation, and osteonecrosis. Specifically, we examined research investigating the molecular mechanisms of adipose tissue dysfunction, lipotoxicity, oxidative stress, and their impact on bone tissue homeostasis.

The analysis established that obesity acts as a systemic risk factor for ONFH development, functioning not merely as a source of mechanical load but also as an initiator of a pathogenic cascade. Dysfunctional adipose tissue leads to chronic low-grade systemic inflammation and oxidative stress. Together, these factors provoke endothelial dysfunction, impair perfusion of the femoral head bone tissue, and induce lipotoxicity in the bone marrow. Consequently, at the local level, this cascade suppresses osteogenesis, simultaneously enhances bone resorption, and triggers osteocyte apoptosis.

Systemic metabolic and inflammatory disruptions initiated by obesity underlie impaired bone remodeling, ischemia, and necrosis of the femoral head subchondral bone. Therefore, the correction of body weight and associated metabolic disorders should be considered as an integral part of a comprehensive strategy for treating ONFH and preventing its progression. This integrated approach may improve the outcomes of joint-preserving interventions and delay the need for total hip arthroplasty in young patients.

Keywords: avascular necrosis of the femoral head, obesity, chronic systemic inflammation, dyslipidemia, oxidative stress, pathogenesis

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Роль дислипидемии и ожирения в патогенезе асептического некроза головки бедренной кости

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РЕЗЮМЕ

Представлен обзор современных данных о роли ожирения, индуцированного им хронического системного воспаления и нарушений липидного обмена в патогенезе асептического некроза головки бедренной кости (АНГБК) для обоснования новых подходов к профилактике и лечению. Проведен анализ современных фундаментальных и клинических исследований, посвященных взаимосвязи метаболических нарушений, хронического воспаления и остеонекроза. Рассмотрены работы, изучающие молекулярные механизмы дисфункции жировой ткани, липотоксичности, окислительного стресса и их влияния на гомеостаз костной ткани.

Установлено, что ожирение выступает системным фактором риска развития АНГБК, действуя не только как источник механической нагрузки, но и как инициатор патогенетического каскада. Дисфункциональное состояние жировой ткани приводит к развитию хронического вялотекущего системного воспаления и окислительного стресса. В совокупности эти факторы провоцируют развитие эндотелиальной дисфункции, ухудшают перфузию костной ткани головки бедренной кости и вызывают явления липотоксичности в костном мозге. Следствием этого на локальном уровне становится угнетение остеогенеза, одновременное усиление резорбции кости и апоптоз остеоцитов.

Инициируемые ожирением системные метаболические и воспалительные сбои формируют основу для нарушения костного ремоделирования, ишемии и некроза субхондральной кости головки бедренной кости. Следовательно, коррекция массы тела и сопутствующих метаболических расстройств должна рассматриваться как неотъемлемая часть комплексной стратегии лечения и вторичной профилактики прогрессирования АНГБК. Такой подход может улучшить результаты органосохраняющих вмешательств и отсрочить необходимость эндопротезирования у молодых пациентов.

Ключевые слова: асептический некроз головки бедренной кости, ожирение, хроническое системное воспаление, дислипидемия, окислительный стресс, патогенез

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Osteonecrosis of the femoral head (ONFH) remains one of the most common and difficult-to-treat pathologies in orthopedic practice, primarily affecting young and middle-aged patients. In different countries, the incidence of ONFH ranges from 1.5 to 3.0 per 100,000 population with a continuing upward trend. The disease is characterized by rapid progression: without effective treatment, 94% of patients develop femoral head collapse within 5 years followed by loss of hip joint function [1–3]. Despite certain advances in the development of organ-preserving methods, the difficulties of early diagnosis as well as the presence of unfavorable prognostic factors often lead to ineffective treatment and the need for total hip arthroplasty. In the USA and Europe, 2–10% of all hip arthroplasty surgeries are performed for ONFH, while in Asian countries, this figure reaches 60%. Although total hip arthroplasty improves the quality of life, it creates serious medical, social, and economic problems due to the limited service life of endoprostheses and the high probability of reoperations, especially considering that most patients with ONFH are young people [4, 5]. The need for an in-depth study of the pathogenetic mechanisms of ONFH and the search for fundamentally new ways to prevent it are becoming obvious.

The causes of ONFH are divided into traumatic, most often caused by fractures of the proximal femur, and non-traumatic, among which conditions associated with metabolic syndrome occupy a special place. Obesity as one of the key components of metabolic syndrome is not only a global health problem, but also a potential modifiable pathogenetic factor that requires detailed consideration in ONFH development. By 2035, almost two billion people are expected to suffer from obesity. It underlies the development of a cascade of complications, including type 2 diabetes mellitus, cardiovascular diseases, non-alcoholic fatty liver disease, malignant neoplasms, musculoskeletal diseases, and psychological disorders, leading to increased morbidity, mortality, and healthcare costs worldwide [6].

The key pathogenetic link between obesity and these complications is the chronic low-grade systemic inflammation induced by obesity. Dysfunctional adipose tissue produces excess proinflammatory adipokines and cytokines, while simultaneously suppressing the synthesis of anti-inflammatory factors. This process is accompanied by severe lipid metabolism disorders, insulin resistance, and oxidative stress, creating a vicious cycle of metabolic and inflammatory damage [7].

In terms of ONFH pathogenesis, obesity in addition to the mechanical load factor is a condition that systemically disrupts metabolic and immune homeostasis. It directly contributes to the key pathogenetic mechanisms of ONFH: it exacerbates endothelial dysfunction, dyslipidemia, and hypercoagulation, promotes intravascular fat embolism, increases intraosseous pressure due to adipocyte hyperplasia, and creates persistent chronic systemic inflammation. This inflammation mediated by altered secretion of adipokines and cytokines damages the vascular endothelium, disrupts bone remodeling, and accelerates osteocyte apoptosis. Therefore, studying the causal relationships between obesity-induced metabolic inflammation and the development of ONFH is important to identify new potential biomarkers and therapeutic strategies aimed at correcting the metabolic and inflammatory status as part of a comprehensive approach to ONFH treatment [8–10] (Fig. 1).

The review aims to systematize current knowledge on the relationship between obesity, lipid metabolism disorders, chronic systemic inflammation and the development of ONFH. The article will discuss the molecular basis of obesity-induced inflammation as well as the integrated pathways through which these systemic disorders lead to ischemia, impaired remodeling, and necrosis of the femoral head.

SEARCH STRATEGY

A comprehensive systematic search was performed in electronic databases indexed in PubMed to identify relevant publications. The search covered the period from January 2020 to December 2025. The search strategy was based on using combinations of key terms and their synonyms: (“avascular necrosis” OR “osteonecrosis” OR “aseptic necrosis”) AND (“femoral head” OR “hip head”) AND (“obesity” OR “adipose tissue” OR “metabolic syndrome” OR “lipid metabolism” OR “dyslipidemia” OR “hyperlipidemia”). A manual search was also conducted on the reference lists of included articles and relevant review papers.

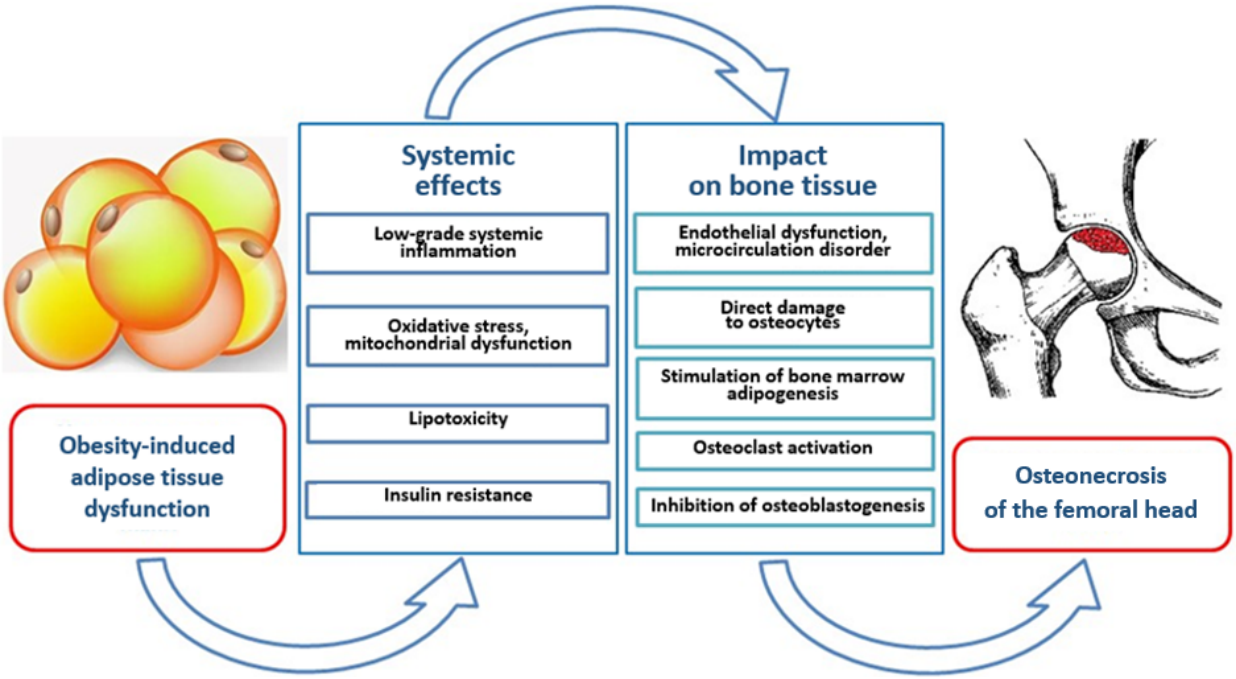

Fig. 1. The role of dyslipidemia and obesity in the pathogenesis of osteonecrosis of the femoral head

INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria were original studies (clinical and experimental in animals), systematic reviews, and case reports focusing on the relationship between obesity, lipid metabolism parameters, and the development or progression of ONFH, as well as the description of the pathogenetic mechanisms linking metabolic disorders to bone damage. The exclusion criteria were articles devoted to secondary ONFH solely due to trauma, decompression sickness, and corticosteroid use (without analyzing concomitant metabolic factors); articles that mention obesity or dyslipidemia only as a demographic characteristic without analyzing their pathogenetic role; isolated case reports without analyzing mechanisms; letters to the editor, conference abstracts; and the absence of a full-text article.

DATA EXTRACTION

The authors independently extracted the following data from the selected studies: first author's last name and year of publication, study design, biomarkers examined, experimental models used, the strength of the association between metabolic parameters and ONFH risk, described pathogenetic pathways, and the authors' conclusions about the role of obesity and dyslipidemia in the pathogenesis of the disease. Any disagreements that arose between the co-authors during the data extraction phase were resolved through a joint discussion.

RESULTS

The initial search using the developed strategy revealed 101 records. After applying a time filter (excluding publications published before 2020), 48 papers were excluded, leaving 53 studies for further consideration. At the title and abstract screening stage, 25 articles were excluded because their subject matter did not match the aim of this review. Evaluating the full text of each of the remaining 28 articles to determine whether they met the inclusion criteria resulted in the exclusion of six studies. An additional manual search of the reference lists of relevant publications allowed us to include 28 more studies that met all the criteria. Thus, the final set of analyzed works consisted of 50 full-text articles, which ensured a comprehensive coverage of the topic and representative data for subsequent qualitative synthesis.

DISCUSSION

Adipose tissue dysfunction, lipid metabolism disorders, and chronic inflammation form a single pathogenetic pathway. Its final result is a combined damage to the vascular network and cell populations

of the femoral head, which is confirmed as a mechanism of ONFH development. Research has demonstrated that specific changes in the lipid profile collectively contribute to the progression of ONFH by disrupting the integrity of cell membranes, causing oxidative stress, leading to endothelial dysfunction, and impairing the regulation of signaling pathways involved in bone cell survival and function [11, 12].

DISORDERS OF LIPID METABOLISM

The relationship between dyslipidemia and ONFH is bidirectional, as the presence of necrotized bone tissue leads to destabilization of systemic lipid metabolism, which aggravates the pathological process in the bone and makes it self-sustaining [13, 14]. Severe disorders of systemic lipid metabolism manifested by hypercholesterolemia, hypertriglyceridemia, increased levels of low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B, as well as decreased levels of high-density lipoprotein cholesterol (HDL-C) and adiponectin, contribute to the formation of fat emboli, which, in combination with endothelial dysfunction exacerbated by dyslipidemia, disrupts the microcirculation of subchondral bone tissue and leads to its ischemia, triggering osteonecrosis [15]. X. Yu et al. (2024) demonstrate that non-HDL-C and apolipoprotein B levels are risk factors for the progression of ONFH, serving as a clinically accessible reflection of the role of lipid metabolism disorders in the development of this pathology [16].

Excess lipids and free fatty acids affecting the differentiation of mesenchymal stem cells, which are common precursors of adipocytes and osteoblasts, lead to an imbalance between adipogenesis and osteogenesis in the bone marrow in favor of the former. Excessive accumulation of adipocytes in the bone marrow caused by both excess lipid production and impaired lipid elimination mechanisms leads to intraosseous hypertension and reduced bone tissue perfusion. R. Toribio-Fernández et al. (2024) demonstrated that apolipoprotein E gene polymorphism may increase the likelihood of subclinical atherosclerosis progression due to impaired reverse cholesterol transport [17]. Moreover, a study conducted by Y. Chen et al. (2025) showed a decrease in the expression of apolipoprotein E in articular cartilage samples of the hip joint in patients with ONFH compared to intact cartilage, which may indicate common mechanisms for the development of ONFH and vascular pathology [18].

During lipolysis of bone marrow adipocytes, saturated fatty acids (SFA) are released, which are key mediators of damage. In particular, palmitic acid has multiple negative effects on bone metabolism. Palmitate inhibits the expression of key osteogenic transcription factors (Runx2, DLX5) and enhances adipogenesis through activation of peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer-binding protein alpha (C/EBPα). In addition, palmitate induces the secretion of proinflammatory cytokines (interleukin-6 (IL-6) and -8 (IL-8)), which activate the RANK/RANKL/OPG (receptor activator of nuclear transcription factor kappa B / receptor activator of nuclear transcription factor kappa B ligand / osteoprotegerin) ligand – receptor system, promoting the differentiation and activation of osteoclasts and enhancing bone resorption [19].

Activation of the ERK signaling pathway in response to palmitate leads to apoptosis of mesenchymal stem cells and osteoblasts. In this case, the critical factor is not the absolute amount of SFA, but the balance between saturated and monounsaturated fatty acids (MUFA). In particular, oleic acid has a protective effect, neutralizing the lipotoxicity of palmitate due to its esterification into triglycerides and deposition into lipid droplets. A high intracellular SFA/MUFA ratio in bone marrow may potentially act as a prognostic marker for the risk of developing ONFH [20].

Different lipids have opposing causal relationships with this disease. Phosphatidylcholine and phosphatidylethanolamine provide a protective effect being key components of cell membranes that ensure their integrity, participating in lipid transport, and possessing anti-inflammatory activity. Elevated levels of these may reflect compensatory mechanisms aimed at membrane restoration. Conversely, elevated levels of triacylglycerols and sterol esters are associated with an increased risk of ONFH due to lipotoxicity and adipocyte hypertrophy, which further exacerbates tissue damage and promotes the progression of osteonecrosis. The accumulation of sterol esters reflects a disturbance in the reverse transport of cholesterol, which brings the pathogenesis of ONFH closer to atherosclerosis [21–23].

Thus, lipid metabolism disorders play a multifaceted role in the pathogenesis of ONFH acting both as a cause and a consequence of osteonecrosis. The identification of specific lipid markers opens new perspectives for early diagnosis, screening of at-risk groups, and the development of targeted therapeutic strategies. Further research focusing on the mechanisms of local lipid metabolism in hip joint tissue is needed to fully elucidate the role of lipid biomarkers and their potential as therapeutic targets.

ADIPOSE TISSUE DYSFUNCTION AS A CAUSAL FACTOR FOR SYSTEMIC INFLAMMATION

Accumulated data indicate that in the adipose tissue of individuals with normal body weight, the majority of resident macrophages are of the anti-inflammatory M2 phenotype. Macrophages maintain tissue homeostasis by promoting repair and increasing insulin sensitivity, releasing anti-inflammatory cytokines, such as interleukin-4, -10, -11, and -13 (IL-4, IL-10, IL-11, IL-13), IL-1 receptor antagonist (IL-1Ra), arginase-1, and transforming growth factor-β (TGFβ), as well as anti-inflammatory adipokines, such as adiponectin and apelin [24]. As excess lipids accumulate, adipocytes undergo hypertrophy, which results in the development of local hypoxia zones, as the enlarged cells become distant from the capillary network. Hypoxia induces the expression of the transcription factor HIF-1α, which triggers metabolic reprogramming of cells associated with the activation of glycolytic pathways, and also causes increased production of proinflammatory cytokines and chemotactic factors, including monocyte chemotactic protein-1 (MCP-1), which attract monocytes from the bloodstream to adipose tissue and promote their activation [25].

Polarization of adipose tissue macrophages towards the proinflammatory M1 phenotype occurs. Activated macrophages become a source of proinflammatory mediators: tumor necrosis factor-alpha (TNFα), IL-6, and interleukin-1β (IL-1β), as well as plasminogen activator inhibitor-1 (PAI-1) and adipokines, such as leptin, visfatin, and resistin [26]. Thus, a vicious cycle of inflammation develops: dysfunctional adipocytes attract macrophages, which, upon activation, intensify inflammation and further exacerbate adipocyte dysfunction and insulin resistance. This localized inflammatory process in adipose tissue is the primary source of chronic low-grade systemic inflammation, which determines the metabolic and vascular complications of obesity.

Dysregulation of adipokine secretion in obesity generates a powerful endocrine signal aimed at damaging the vascular endothelium. Despite differences in their primary receptors and signaling pathways, leptin, visfatin, and resistin converge in activating key proinflammatory transcription factors, primarily nuclear factor kappa-B (NF-κB) [27, 28]. This leads to the induction of oxidative stress and suppression of endothelial antioxidant protection, a decrease in the bioavailability of nitric oxide (II) (NO) due to the suppression of endothelial NO synthase expression, and the creation of a proadhesive and prothrombotic state through an increase in the expression of adhesion molecules. Elevated levels of IL-1β promote the recruitment of a large number of immune cells and enhance local inflammation by increasing the expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and MCP-1 [29, 30]. Hypercoagulation caused by high PAI-1 levels and platelet activation creates the preconditions for microthrombosis. The resulting endothelial dysfunction includes loss of vasodilatory properties, increased permeability, and adhesion, which directly predisposes to microthrombosis, impaired perfusion, and subchondral bone ischemia.

Proinflammatory cytokines (TNFα, IL-1β, and IL-6) act as direct mediators of insulin resistance by disrupting the insulin receptor signal transduction. IL-1β leads to activation of the serine/threonine kinase, Janus kinase (JAK-1), which inactivates insulin receptor substrates (IRS-1,2), resulting in suppression of insulin signaling and subsequent elevation of blood glucose levels. TNFα directly interferes with peripheral glucose uptake by enhancing serine phosphorylation of IRS-1, inhibits translocation of glucose transporter-4 (GLUT-4) to the plasma membrane, and leads to peripheral insulin resistance [31]. These molecular mechanisms determine the development of persistent peripheral insulin resistance, linking chronic inflammation to metabolic dysfunction.

A study by H. Zhang et al. (2023) demonstrated that the microRNA miR-22-3p contained in adipocyte exosomes affects skeletal muscle and promotes the development of insulin resistance by reducing the levels of signaling molecules, such

as phosphorylated protein kinase B (p-AKT) and IRS-1 (p-IRS-1) [32]. Resistance of dysfunctional adipocytes to the antilipolytic effect of insulin leads to the uncontrolled breakdown of triglyceride stores, resulting in an increased release of free fatty acids (FFA) into the systemic circulation, a key component of lipotoxicity. Thus, adipose tissue dysfunction in obesity manifested through mechanisms of endocrine dysregulation and immune activation creates a systemic metabolic and inflammatory environment that is a risk factor for ONFH development and progression.

Other factors in the chronic inflammatory process observed in metabolic syndrome are receptors of the innate immune system, such as Toll-like receptors (TLR). TLR are involved in pathogen recognition and modulate the innate immune response by activating downstream inflammatory signaling pathways that lead to the release of various cytokines (TNFα, IL-6, IL-1β, and monocyte chemotactic protein-1 (MCP-1)). The immune response is triggered by TLR recognition of ligands, which include pathogen-associated molecular patterns (PAMPs) released by pathogens (e.g. lipopolysaccharides) and damage-associated molecular patterns (DAMPs) released by damaged inflamed tissues [33]. Among DAMPs, many endogenous ligands – SFA, modified LDL-C, advanced glycation end products, extracellular matrix degradation products, and heat shock proteins – are recognized by TLRs, especially TLR2 and TLR4, and activate the proinflammatory cascade [34].

A systemic inflammatory response causes a hypercoagulable state, accompanied by endothelial damage, which also increases the likelihood of ONFH. Endothelial cells respond to injury by producing proinflammatory molecules, including IL-1β, interferons, TNFα, colony-stimulating factors, and vascular cell adhesion molecule-1 (VCAM-1). The proinflammatory background at the site of osteonecrosis induces macrophages, neutrophils, and other immune cells to migrate to damaged endothelial cells and promote further development of inflammation, which leads to acute and chronic changes in vascular permeability. Normally, resolution of inflammation eliminating the consequences of damage promotes tissue regeneration. However, endothelial dysfunction causes prolonged inflammation, impeding bone tissue restoration. Damaged endothelium activated platelet-derived factors and disrupted extracellular matrix serve as sources of DAMPs.

Various immune cells recognize these stimuli via pattern recognition receptors (PRR) and further activate a cascade of inflammatory responses, exacerbating endothelial damage. In addition to intensive secretion of reactive oxygen species and proteolytic enzymes, activated neutrophils are capable of releasing DNA into the extracellular space with the formation of neutrophil extracellular traps (NETs), creating a prothrombotic state [35]. The scaffold formed by DNA fibers and histone networks activates platelets, leukocytes, erythrocytes, and plasma proteins. The microvessels of the femoral head contain significant numbers of neutrophils and NETs in patients with ONFH. NET-mediated activation of the coagulation pathway and inhibition of anticoagulation potentially play a role in the pathogenesis of ONFH. M. Nonokawa et al. (2020) showed that intravenous administration of NET-forming neutrophils is associated with ischemic changes in femoral head osteocytes [36].

Chronic systemic inflammation is not simply an accompanying phenomenon, but a significant pathogenetic factor determining the progression of ONFH and affecting the outcomes of organ-preserving surgeries. Systemic inflammation creates an unfavorable background impairing the processes of neoangiogenesis and osteogenesis necessary for successful repair after decompression and contributing to microcirculatory disorders and bone resorption. C. Li et al. (2025) found that preoperative systemic immune-inflammatory index (SII), which comprehensively reflects the activity of neutrophils, lymphocytes, and platelets, serves as an independent prognostic marker of increased risk of failure after medullary canal decompression [37].

Thus, experimental and clinical studies consistently confirm that disturbances occurring in dysfunctional adipose tissue through mechanisms of endotheliopathy, lipotoxicity, and chronic inflammation create a pathological environment in the femoral head leading to ischemia, suppressed repair, and necrosis. Dyslipidemia, free fatty acid flux, oxidative stress, and lipotoxicity act synergistically, damaging the femoral head vasculature, inhibiting bone formation, and triggering bone cell death. These systemic metabolic disturbances create a foundation for local risk factors to induce ischemic necrosis.

OXIDATIVE STRESS

Oxidative stress is a fundamental pathobiochemical mechanism that mediates the transformation of systemic signals into direct cellular damage in the subchondral region of the femoral head. Reactive oxygen species (ROS) are natural byproducts of aerobic respiration in the mitochondria. During oxidative phosphorylation, which includes the Krebs cycle and the respiratory chain enzyme complexes, most of the oxygen is used for the synthesis of ATP, and only a small proportion is inevitably converted into ROS due to a small leakage of electrons, which leads to the direct reduction of oxygen to radicals. Low concentrations of ROS produced by osteocyte mitochondria are either neutralized by the antioxidant system or can perform signaling functions, for example, by activating the transcription factor Nrf2 and promoting osteoblast differentiation during osteogenesis [38]. However, excessive intake of free fatty acids leads to their increased oxidation in mitochondria, which is accompanied by increased ROS formation and the development of oxidative stress.

Adiponectin and apelin act as protective factors in maintaining metabolic homeostasis and redox balance. Adiponectin has an insulin-sensitizing effect; a decrease in its level deprives tissues of the ability to effectively enhance fatty acid oxidation by activating AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha (PPARα) [39–41]. Apelin promotes the synthesis of antioxidant enzymes via the Ras/Raf/mitogen-activated protein kinase (MAPK/ERK) and AMPK pathways and suppresses the expression of pro-oxidant enzymes [42, 43]. Their reduction in obesity and chronic inflammation directly contributes to the development and worsening of insulin resistance and oxidative stress.

Excess of ROS leads to a reduction in the population of viable osteocytes in several pathways. First, excessive ROS production is one of the mechanisms of programmed osteocyte death. High levels of ROS increase the phosphorylation of p66(shc), a key mediator of osteocyte apoptosis. Phosphorylated p66(shc) at Ser-36 is transported into the mitochondria, triggering an oxidative stress cascade and the release of cytochrome C, which ultimately activates caspases and leads to programmed osteocyte death. Notably, p66(shc) also has oxidoreductase activity, creating a vicious cycle by further increasing mitochondrial ROS production [44]. Secondly, excessive ROS production inhibits the differentiation of mesenchymal stem cells into osteoblasts by blocking the Wnt/beta-catenin pathway. The retention of the beta-catenin-binding transcription factor FoxO in the nucleus blocks its interaction with the TCF/LEF signaling pathway, suppressing the expression of key early osteoblastogenesis genes Runx2 and Osterix. It should be noted that the same ROS, while suppressing osteoblastogenesis, simultaneously stimulate the activity and proliferation of osteoclasts. It has been shown that the removal of ROS inhibits osteoclastogenesis induced by the receptor activator of NF-κB ligand (RANKL) [45].

Mitochondria being the centers of ROS production under pathological conditions are themselves most sensitive to them. Exceeding the compensatory potential of the antioxidant system causes oxidative stress and creates conditions for mitochondrial membrane damage, causing massive electron leakage in the respiratory enzyme chain, which reinforces the intracellular redox imbalance. Free radicals also attack mitochondria, affecting the activity of enzymatic complexes in the membrane of these organelles and reducing their efficiency. This, in turn, disrupts oxidative phosphorylation and leads to a decrease in ATP synthesis. Mitochondrial membrane damage promotes the leakage of Ca^{2+} and cytochrome C into the cytosol and triggers apoptosis by activating the caspase cascade [46].

Some mitochondrial components due to their similarity to bacterial and viral molecules can act as PAMPs and, consequently, as ligands for PRRs, for example, cyclic mitochondrial DNA. In addition, mitochondrial DNA, N-formyl peptide, cardiolipin, mitochondrial RNA, and fumarate can act as DAMPs that activate PRRs and induce an inflammatory response [47, 48]. Mitochondrial DNA leakage into the cytoplasm that occurs during mitochondrial damage leads to activation of the cGAS-STING pathway, which can activate the NF-κB signaling pathway, and activated NF-κB induces the production of proinflammatory stimulators, including TNFα, IL-1β, and IL-6 [49]. Mitochondrial DNA is rich in CpG islands, a structure that can be recognized by TLR9 and directly activate the NF-κB signaling pathway, thereby triggering inflammation. Unlike

nuclear DNA, it is more susceptible to mutations and oxidation. The accumulation of damaged mitochondrial DNA disrupts the homeostasis of these organelles, exacerbating mitochondrial damage and leading to their inability to control the inflammatory response in bone tissue [50]. As a result, a decrease in osteoblast numbers coupled with increased osteoclast activity leads to bone resorption rates exceeding the rate of bone formation. This microenvironment is unable to support healthy bone tissue. Therefore, maintaining proper mitochondrial function to prevent excessive ROS production is critical for both bone health and the treatment of associated metabolic diseases.

Oxidative stress is also a causative factor in endothelial dysfunction, which disrupts the regulation of vascular tone and blood flow, leading to bone ischemia. Modulation of the vascular system is crucial for initiating the angiogenesis – osteogenesis process, which is necessary for the complete regeneration and restoration of osteocytes in necrotic areas. Therefore, blocking oxidative stress processes represents a potentially important therapeutic target in the comprehensive treatment and prevention of ONFH progression.

CONCLUSION

The analysis suggests that obesity is not simply a mechanical overload factor, but a systemic metabolic and inflammatory disease that forms a universal pathogenic basis for the development and progression of ONFH. Adipose tissue dysfunction, acting as a driver of chronic low-grade systemic inflammation, through a complex set of interconnected mechanisms – endocrine dysregulation (adipokine imbalance), oxidative stress, lipotoxicity, and endothelial dysfunction – creates an environment in the femoral head that leads to ischemia, suppression of bone remodeling, and osteocyte death. Dyslipidemia exacerbates these processes, contributing to microthrombosis, fat embolism, and disruption of intraosseous lipid homeostasis.

Thus, it can be concluded that the pathogenesis of ONFH in obesity appears to be a cascade of processes initiated at the systemic level and resulting in localized bone damage. Integrating measures aimed at correcting body weight and lipid metabolism into comprehensive prevention and treatment regimens will not only improve the immediate results of organ-preserving surgeries but also, by addressing the underlying causes of the disease, improve the long-term prognosis and delay or avoid the need for hip arthroplasty, which is especially important for young patients. Overall, improving our understanding of the role of metabolic factors in ONFH opens new opportunities for prevention, early diagnosis, and the development of personalized treatments.

REFERENCES

1. Quan H., Ren C., He Y., Wang F., Dong S., Jiang H. Application of biomaterials in treating early osteonecrosis of the femoral head: research progress and future perspectives. *Acta Biomater.* 2023;164:15–73. DOI: 10.1016/j.actbio.2023.04.005.
2. Quan H., Ren C., Xie H., He Z., Ding H., Li J. et al. An injectable hydrogel loaded with miRNA nanocarriers promotes vessel-associated osteoclast (VAO)-mediated angiogenesis and bone regeneration in osteonecrosis of the rat femoral head. *Biomaterials.* 2025;320:123252. DOI: 10.1016/j.biomaterials.2025.123252.
3. Konarski W., Poboży T., Śliwczyński A., Kotela I., Krakowiak J., Hordowicz M. et al. Avascular necrosis of femoral head-overview and current state of the art. *Int. J. Environ. Res. Public Health*. 2022 ;19(12):7348. DOI: 10.3390/ijerph19127348.
4. Zheng C., Wu Y., Xu J., Liu Y., Ma J. Exosomes from bone marrow mesenchymal stem cells ameliorate glucocorticoid-induced osteonecrosis of femoral head by transferring microRNA-210 into bone microvascular endothelial cells. *J. Orthop. Surg. Res.* 2023;18(1):939. DOI: 10.1186/s13018-023-04440-x.
5. Konarski W., Poboży T., Konarska K., Śliwczyński A., Kotela I., Hordowicz et al. Osteonecrosis related to steroid and alcohol use-an update on pathogenesis. *Healthcare (Basel).* 2023;11(13):1846. DOI: 10.3390/healthcare11131846.
6. Müller T.D., Blüher M., Tschöp M.H., DiMarchi R.D. Anti-obesity drug discovery: advances and challenges. *Nat. Rev. Drug Discov.* 2022;21(3):201–223. DOI: 10.1038/s41573-021-00337-8.
7. Khanna D., Khanna S., Khanna P., Kahar P., Patel B.M. Obesity: a chronic low-grade inflammation and its markers. *Cureus.* 2022;14(2):e22711. DOI: 10.7759/cureus.22711.
8. Lin X., Li H. Obesity: epidemiology, pathophysiology, and therapeutics. *Front. Endocrinol. (Lausanne).* 2021;12:706978. DOI: 10.3389/fendo.2021.706978.
9. Peng W., Zhang L., Wen F., Tang X., Zeng L., Chen J. et al. Trends and disparities in non-communicable diseases in the Western Pacific region. *Lancet Reg. Health West Pac.* 2023;43:100938. DOI: 10.1016/j.lanwpc.2023.100938.
10. Müller T.D., Blüher M., Tschöp M.H., DiMarchi R.D. Anti-obesity drug discovery: advances and challenges. *Nat. Rev. Drug. Discov.* 2022;21(3):201–223. DOI: 10.1038/s41573-021-00337-8.
11. Yan Y., Wang J., Wang Y., Wu W., Chen W. Research on lipidomic profiling and biomarker identification for osteonecrosis of the femoral head. *Biomedicines.* 2024;12(12):2827. DOI: 10.3390/biomedicines12122827.

12. Yu X., Zhang S., Zhang B., Dai M. Relationship of idiopathic femoral head necrosis with blood lipid metabolism and coagulation function: A propensity score-based analysis. *Front. Surg.* 2023;9:938565. DOI: 10.3389/fsurg.2022.938565.
13. Baek S.H., Kim K.H., Lee W.K., Hong W., Won H., Kim S.Y. Abnormal lipid profiles in nontraumatic osteonecrosis of the femoral head: a comparison with osteoarthritis using propensity score matching. *J. Bone Joint Surg. Am.* 2022;104(Suppl. 2):19–24. DOI: 10.2106/JBJS.20.00520.
14. Wang C., Cen C., Su H., Peng Y., Wang T., Li J. et al.. Integrated multi-omics analysis identifies lipid metabolism biomarkers in ONFH and reveals therapeutic potential of retinoic acid. *Sci .Rep.* 2025;15(1):30716. DOI: 10.1038/s41598-025-13703-y.
15. George G., Lane J.M. Osteonecrosis of the femoral head. *J. Am. Acad. Orthop. Surg. Glob. Res. Rev.* 2022;6(5):e21.00176. DOI: 10.5435/JAAOSGlobal-D-21-00176.
16. Yu X., Dou S., Lu L., Wang M., Li Z., Wang D. Relationship between lipid metabolism, coagulation and other blood indices and etiology and staging of non-traumatic femoral head necrosis: a multivariate logistic regression-based analysis. *J. Orthop. Surg. Res.* 2024;19(1):251. DOI: 10.1186/s13018-024-04715-x.
17. Toribio-Fernández R., Tristão-Pereira C., Carlos Silla-Castro J., Callejas S., Oliva B., Fernandez-Nueda I. et al. Apolipoprotein E-ε2 and Resistance to Atherosclerosis in Midlife: The PESA Observational Study. *Circ. Res.* 2024;134(4):411–424. DOI: 10.1161/CIRCRESAHA.123.323921.
18. Chen Y., Zhou Z., Che H., Li D. Lipid metabolism and osteonecrosis: unraveling causal mechanisms via multi-omics and mendelian randomization. *Front. Physiol.* 2025;16:1642153. DOI: 10.3389/fphys.2025.1642153.
19. Ren Y., Deng Z., Gokani V., Kutschke M., Mitchell T.W., Aruwajoye O. et al. Anti-interleukin-6 therapy decreases hip synovitis and bone resorption and increases bone formation following ischemic osteonecrosis of the femoral head. *J. Bone Miner. Res.* 2021;36(2):357–368. DOI: 10.1002/jbmr.4191.
20. Li L., Zhao S., Leng Z., Chen S., Shi Y., Shi L. et al. Pathological mechanisms and related markers of steroid-induced osteonecrosis of the femoral head. *Ann. Med.* 2024;56(1):2416070. DOI: 10.1080/07853890.2024.2416070.
21. Posor Y., Jang W., Haucke V. Phosphoinositides as membrane organizers. *Nat. Rev. Mol. Cell Biol.* 2022;23(12):797–816. DOI: 10.1038/s41580-022-00490-x.
22. Motta F., Timilsina S., Gershwin M.E., Selmi C. Steroid-induced osteonecrosis. *J. Transl. Autoimmun.* 2022;5:100168. DOI: 10.1016/j.jtauto.2022.100168.
23. Yan Y., Wang J., Huang D., Lv J., Li H., An J. et al. Plasma lipidomics analysis reveals altered lipids signature in patients with osteonecrosis of the femoral head. *Metabolomics.* 2022;18(2):14. DOI: 10.1007/s11306-022-01872-0.
24. Taylor E.B. The complex role of adipokines in obesity, inflammation, and autoimmunity. *Clin. Sci. (Lond.).* 2021;135(6):731–752. DOI: 10.1042/CS20200895.
25. Singh S., Anshita D., Ravichandiran V. MCP-1: Function, regulation, and involvement in disease. *Int. Immunopharmacol.* 2021;101(Pt. B):107598. DOI: 10.1016/j.intimp.2021.107598.
26. Planat-Benard V., Varin A., Casteilla L. MSCs and inflammatory cells crosstalk in regenerative medicine: concerted actions for optimized resolution driven by energy metabolism. *Front. Immunol.* 2021;12:626755. DOI: 10.3389/fimmu.2021.626755.
27. Romacho T., Valencia I., Ramos-González M., Vallejo S., López-Esteban M., Lorenzo O. et al. Visfatin/eNampt induces endothelial dysfunction *in vivo*: a role for toll-like receptor 4 and NLRP3 inflammasome. *Sci. Rep.* 2020;10(1):5386. DOI: 10.1038/s41598-020-62190-w.
28. Obradovic M., Sudar-Milovanovic E., Soskic S., Essack M., Arya S., Stewart A.J. et al. Leptin and obesity: role and clinical implication. *Front. Endocrinol. (Lausanne).* 2021;12:585887. DOI: 10.3389/fendo.2021.585887.
29. Ghanbari M., Momen Maragheh S., Aghazadeh A., Mehrjuyan S.R., Hussen B.M., Abdoli Shadbad M. et al.Interleukin-1 in obesity-related low-grade inflammation: from molecular mechanisms to therapeutic strategies. *Int. Immunopharmacol.* 2021;96:107765. DOI: 10.1016/j.intimp.2021.107765.
30. Calabrese L., Fiocco Z., Satoh T.K., Peris K., French L.E. Therapeutic potential of targeting interleukin-1 family cytokines in chronic inflammatory skin diseases. *Br. J. Dermatol.* 2022;186(6):925–941. DOI: 10.1111/bjd.20975.
31. Lee S.H., Park S.Y., Choi C.S. Insulin Resistance: From Mechanisms to Therapeutic Strategies. *Diabetes Metab. J.* 2022;46(1):15–37. DOI: 10.4093/dmj.2021.0280.
32. Zhang H., Zhang X., Wang S., Zheng L., Guo H., Ren Y. et al. Adipocyte-derived exosomal miR-22-3p modulated by circadian rhythm disruption regulates insulin sensitivity in skeletal muscle cells. *J. Biol. Chem.* 2023;299(12):105476. DOI: 10.1016/j.jbc.2023.105476.
33. Ma M., Jiang W., Zhou R. DAMPs and DAMP-sensing receptors in inflammation and diseases. *Immunity.* 2024;57(4):752–771. DOI: 10.1016/j.immuni.2024.03.002.
34. Fahed G., Aoun L., Bou Zerdan M., Allam S., Bou Zerdan M., Bouferraa Y. et al. Metabolic syndrome: updates on pathophysiology and management in 2021. *Int. J. Mol. Sci.* 2022;23(2):786. DOI: 10.3390/ijms23020786.
35. Xiang M., Yin M., Xie S., Shi L., Nie W., Shi B. et al. The molecular mechanism of neutrophil extracellular traps and its role in bone and joint disease. *Heliyon.* 2023;9(12):e22920. DOI: 10.1016/j.heliyon.2023.e22920.
36. Nonokawa M., Shimizu T., Yoshinari M., Hashimoto Y., Nakamura Y., Takahashi D. et al. Association of neutrophil extracellular traps with the development of idiopathic osteonecrosis of the femoral head. *Am. J. Pathol.* 2020;190(11):2282–2289. DOI: 10.1016/j.ajpath.2020.07.008.
37. Li C., Guo H., Han Z., Wang T., Wu D., Yang Z. et al. Association of the systemic immune inflammation index with failure after core decompression for osteonecrosis of the femoral head: a prospective time-to-event analysis. *Ann. Med.* 2025;57(1):2566867. DOI: 10.1080/07853890.2025.2566867.
38. Sánchez-de-Diego C., Pedrazza L., Pimenta-Lopes C., Martinez-Martinez A., Dahdah N., Valer J.A. et al. NRF2 function in osteocytes is required for bone homeostasis and drives osteocytic gene expression. *Redox. Biol.* 2021;40:101845. DOI: 10.1016/j.redox.2020.101845.
39. Szumilas K., Szumilas P., Słuczanowska-Głąbowska S., Zgutka K., Pawlik A. Role of adiponectin in the pathogenesis of rheumatoid arthritis. *Int. J. Mol. Sci.* 2020;21(21):8265. DOI: 10.3390/ijms21218265.
40. Zorena K., Jachimowicz-Duda O., Ślęzak D., Robakowska M.,

Mrugacz M. Adipokines and obesity. Potential link to metabolic disorders and chronic complications. *Int. J. Mol. Sci.* 2020;21(10):3570. DOI: 10.3390/ijms21103570.
41. Al-Mansoori L., Al-Jaber H., Prince M.S., Elrayess M.A. Role of inflammatory cytokines, growth factors and adipokines in adipogenesis and insulin resistance. *Inflammation.* 2022;45(1):31–44. DOI: 10.1007/s10753-021-01559-z.
42. Li C., Cheng H., Adhikari B.K., Wang S., Yang N., Liu W. et al. The role of apelin-APJ system in diabetes and obesity. *Front. Endocrinol. (Lausanne).* 2022;13:820002. DOI: 10.3389/fendo.2022.820002.
43. Fibbi B., Marroncini G., Naldi L., Peri A. The yin and yang effect of the apelinergic system in oxidative stress. *Int. J. Mol. Sci.* 2023;24(5):4745. DOI: 10.3390/ijms24054745.
44. Lebiedzinska-Arciszewska M., Pakula B., Bonora M., Missiroli S., Potes Y., Jakubek-Olszewska P. et al. Distribution of the p66Shc adaptor protein among mitochondrial and mitochondria-associated membranes fractions in normal and oxidative stress conditions. *Int. J. Mol. Sci.* 2024;25(23):12835. DOI: 10.3390/ijms252312835.
45. Li J., Deng C., Liang W., Kang F., Bai Y., Ma B. et al. Mn-containing bioceramics inhibit osteoclastogenesis and promote osteoporotic bone regeneration via scavenging ROS. *Bioact. Mater.* 2021;6(11):3839–3850. DOI: 10.1016/j.bioactmat.2021.03.039.
46. Shimasaki M., Ueda S., Ichiseki T., Hirata H., Kawahara N., Ueda Y. Resistance of bone marrow mesenchymal stem cells in a stressed environment – comparison with osteocyte cells. *Int. J. Med. Sci.* 2021;18(6):1375–1381. DOI: 10.7150/ijms.52104.
47. Marchi S., Guilbaud E., Tait S.W.G., Yamazaki T., Galluzzi L. Mitochondrial control of inflammation. *Nat. Rev. Immunol.* 2023;23(3):159–173. DOI: 10.1038/s41577-022-00760-x.
48. Harapas C.R., Idiiatullina E., Al-Azab M., Hrovat-Schaale K., Reygaerts T., Steiner A. et al. Organellar homeostasis and innate immune sensing. *Nat. Rev. Immunol.* 2022;22(9):535–549. DOI: 10.1038/s41577-022-00682-8.
49. Decout A., Katz J.D., Venkatraman S., Ablasser A. The cGAS-STING pathway as a therapeutic target in inflammatory diseases. *Nat. Rev. Immunol.* 2021;21(9):548–569. DOI: 10.1038/s41577-021-00524-z.
50. Iliushchenko D., Efimenko B., Mikhailova A.G., Shamanskiy V., Saparbaev M.K., Matkarimov B.T. et al. Deciphering the foundations of mitochondrial mutational spectra: replication-driven and damage-induced signatures across chordate classes. *Mol. Biol. Evol.* 2025;42(2):msae261. DOI: 10.1093/molbev/msae261.

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