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Research Progress on Circulating Inflammatory Proteins and Osteonecrosis of the Femoral Head

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Abstract: ***Osteonecrosis of the femoral head (ONFH) is a common orthopedic condition with a complex pathogenesis involving multiple factors. Recent studies have highlighted the significant role of inflammation in its development. Circulating inflammatory proteins, such as cytokines, chemokines, and acute phase response proteins, contribute to the onset and progression of avascular necrosis of the femoral head by regulating the immune response, promoting inflammatory cascades, and disrupting bone metabolism. This paper begins by analyzing the epidemiological characteristics, clinical manifestations, diagnostic methods, and treatment strategies related to avascular necrosis of the femoral head, along with the links to the inflammatory response within its etiology and pathological mechanisms. It then discusses the fundamental concepts, classification, and mechanisms of circulating inflammatory proteins in relation to inflammation. Furthermore, it examines the connection between these proteins and avascular necrosis of the femoral head, including their potential as biomarkers for early diagnosis and disease monitoring, as well as their prospects as therapeutic targets. The aim is to provide a comprehensive theoretical framework to enhance understanding of the pathogenesis of avascular necrosis of the femoral head and to explore new diagnostic methods and therapeutic avenues.***

Keywords: Osteonecrosis, Circulating inflammatory proteins, Osteonecrosis of the femoral head, Cytokines**.**

1. Introduction

Osteonecrosis is a disease characterized by cell death resulting from interrupted blood supply to bone tissue. It commonly affects weight-bearing areas, such as the femoral head and knee joint. In severe cases, it can lead to joint collapse and dysfunction [1]. Of these cases, ONFH accounts for more than 50%. ONFH is a progressive orthopedic condition marked by osteocyte death, apoptosis of bone marrow components, and destruction of bone tissue structure, leading to severe joint pain and movement disorders. Patients in the middle and late stages often require joint replacement, imposing significant physical and economic burdens on patients and their families [2]. As one of the most disabling diseases in orthopedics, ONFH's incidence is increasing annually worldwide, posing a serious global health challenge. There are notable differences in ONFH prevalence among various races and regions, likely related to genetic susceptibility, levels of medical testing, and exposure to risk factors [3,4]. Age distribution studies [5] indicate that part of the disease is concentrated in individuals aged 20-40 years, primarily due to autoimmune diseases such as trauma and systemic lupus erythematosus (SLE), while another concentration occurs in those aged 50-65 years, mostly associated with metabolic syndrome and long-term hormone use. The number of male patients is significantly higher than that of female patients; however, the proportion of female patients is greater among those with SLE.

Circulating inflammatory proteins are a class of proteins found in the bloodstream that participate in systemic and local inflammatory reactions. They play a crucial role in the onset, progression, and outcomes of various inflammatory diseases [15]. Recent advancements in proteomics, single-cell sequencing, and molecular imaging techniques have gradually revealed the biological functions of these proteins and their mechanisms in diseases, particularly in the pathological processes of bone metabolic diseases such as osteonecrosis. Circulating inflammatory proteins primarily include cytokines, chemokines, growth factors, and acute-phase response proteins. They significantly contribute to various chronic inflammatory diseases by mediating the recruitment and activation of immune cells, regulating vascular permeability, and participating in tissue damage and repair [16]. Cytokines, such as members of the interleukin (IL) family and tumor necrosis factor (TNF), regulate the activation, proliferation, and differentiation of immune cells while mediating the cascade amplification of the inflammatory response. Chemokines facilitate inflammatory infiltration and tissue damage repair by guiding immune cells to migrate to sites of inflammation. Growth factors, including vascular endothelial growth factor (VEGF), promote cell proliferation, migration, and angiogenesis during tissue repair and regeneration. Acute-phase reactive proteins, such as C-reactive protein (CRP) and fibrinogen, increase rapidly during inflammation and play a role in the early regulation of the inflammatory response and tissue damage repair.

This article is a review of studies on osteonecrosis of the femoral head and circulating inflammatory proteins.

2. Current Status of Research on Osteonecrosis of the Femoral Head

2.1 Etiology and Pathological Mechanism of Osteonecrosis of the Femoral Head

The etiology of ONFH is complex and diverse, encompassing both traumatic and non-traumatic factors [6]. Traumatic factors, such as hip dislocation and femoral neck fractures, can directly disrupt the blood supply to the femoral head, resulting in avascular necrosis of the bone tissue [7]. Non-traumatic factors are more prevalent [8], with long-term heavy drinking being a significant contributor to ONFH.

Alcohol consumption can lead to lipid metabolism disorders, fat embolism, and adverse effects on bone metabolism. Additionally, prolonged use of glucocorticoids is a major risk factor for non-traumatic ONFH, as these medications can cause dyslipidemia and osteoporosis, thereby increasing the risk of femoral head necrosis. Other non-traumatic factors include blood disorders, coagulation abnormalities, and autoimmune diseases. A deeper understanding of the etiology of ONFH will enhance our knowledge of its pathogenesis and provide a theoretical foundation for developing targeted prevention and treatment strategies.

The pathological mechanism of ONFH has not been completely clarified, and it fully understood and is currently believed to result from the interaction of various factors, primarily including fat embolism, vascular endothelial injury, intraosseous hypertension, and inflammatory reactions [9]. Among these, the fat embolism theory suggests that free fatty acids in the blood combine with calcium to form fatty acid calcium, which deposits in the arterioles of the femoral head, resulting in vascular obstruction and subsequent ischemia and necrosis of the bone tissue. The vascular endothelial injury theory indicates that certain factors, such as glucocorticoids and alcohol, can damage the endothelial cells of the blood vessels in the femoral head, leading to vasoconstriction, thrombosis, and ultimately osteonecrosis. According to the intraosseous hypertension theory, increased intraosseous pressure disrupts blood circulation, causing ischemia and necrosis of the bone tissue. Additionally, inflammatory reactions play a significant role in the onset and progression of ONFH. These pathological mechanisms are interconnected and collectively contribute to the development of ONFH.

2.2 Clinical Manifestations of Osteonecrosis of the Femoral Head

The clinical manifestations of ONFH have certain concealment and diversity; early symptoms are often subtle. As the disease progresses, patients gradually experience pain, restrictions in joint mobility, and other symptoms [6]. Pain is the most common initial symptom of ONFH, typically presenting as a dull ache or soreness in the hip joint or surrounding area, which may radiate to the groin, buttocks, or inner thigh. In the early stages, pain is often exacerbated by activity and relieved by rest. However, as the disease advances, pain can become persistent and difficult to alleviate, even at rest, significantly impacting the patient's sleep and daily life. Limitations in joint movement are also a key clinical manifestation of ONFH. Patients may struggle with daily activities such as walking, squatting, and putting on shoes and socks, while the range of motion in the hip joint—specifically internal rotation and abduction—can be markedly reduced. Some patients may also exhibit signs such as limb shortening and claudication, further increasing their physical and mental burden. A thorough understanding of the clinical manifestations of ONFH is crucial for early diagnosis and timely treatment, which can effectively delay disease progression and improve patient prognosis.

2.3 Diagnosis of Osteonecrosis of the Femoral Head

The diagnosis of ONFH is mainly based on the clinical manifestations, medical history, physical examination, and imaging studies. During the medical history collection and physical examination, the doctor will inquire in detail about the patient's past medical history, medication use, and lifestyle habits. A comprehensive physical examination of the hip joint will include assessments of joint mobility, tenderness, and any snapping sensations. Imaging is a crucial component in diagnosing ONFH [10]. X-ray is the most commonly used preliminary screening method, as it can reveal morphological changes in the femoral head, osteoporosis, and alterations in joint space. However, the sensitivity of X-rays for early ONFH is low. When X-ray results are normal but clinical suspicion remains high, magnetic resonance imaging (MRI) is the preferred next step. MRI offers high sensitivity and specificity, clearly showing bone marrow edema, subchondral fractures, and other early lesions. Additionally, CT scans, bone scans, and other imaging techniques can provide diagnostic value in certain cases. In recent years, advancements in medical imaging technology have led to the adoption of new methods, such as three-dimensional CT reconstruction and magnetic resonance spectroscopy, enhancing early detection and accurate evaluation of ONFH.

2.4 Treatment of Osteonecrosis of the Femoral Head

ONFH has various treatment methods, primarily divided into conservative and surgical approaches [11]. The selection of a specific method should be based on a comprehensive assessment of the patient's disease stage, age, physical condition, and other factors. Conservative treatment is appropriate for patients with early and mild symptoms and mainly includes rest, weight avoidance, physical therapy, and drug therapy. Rest and weight-bearing avoidance can reduce stress on the femoral head and delay disease progression. Physical therapy, such as hot compresses, can alleviate pain and improve joint function. Drug therapy typically involves non-steroidal anti-inflammatory drugs, lipid-lowering medications, and anticoagulants, all of which can relieve symptoms and enhance blood circulation. Surgical treatment is recommended for patients with severe disease or those who do not respond to conservative measures. Common surgical options include core decompression, vascularized bone transplantation, and artificial joint replacement. Core decompression reduces pressure in the femoral head and promotes blood circulation, making it suitable for early-stage patients [12]. Vascularized bone transplantation provides a fresh blood supply to the femoral head, promoting the regeneration and repair of bone tissue, ideal for middle-stage patients [13]. Artificial joint replacement is the final option for patients with advanced femoral head necrosis and significant joint damage, effectively relieving pain and restoring joint function [14]. In recent years, the rapid development of biotechnology, including stem cell therapy and tissue engineering, has opened new avenues for the treatment of ONFH, offering renewed hope for patients.

3. Current Status of Circulating Inflammatory Proteins

3.1 Mechanisms of Circulating Inflammatory Proteins in Inflammatory Response

Inflammatory reactions play a crucial role in the early stages of osteonecrosis. Circulating inflammatory proteins, such as

TNF-α, IL-1β, and IL-6, are upregulated in osteonecrosis. These cytokines activate osteoblasts and osteoclasts, which leads to increased bone resorption and inhibits bone formation [17]. Apoptosis is another significant mechanism involved in osteonecrosis; research shows that osteocyte apoptosis is significantly elevated in glucocorticoid-induced osteonecrosis. Inflammatory proteins like TNF-α can induce osteocyte apoptosis through receptor-mediated signaling pathways [18]. Insufficient angiogenesis is a key factor in the development of osteonecrosis. Inflammatory proteins such as VEGF (vascular endothelial growth factor) are inhibited in osteonecrotic tissue, resulting in reduced local angiogenesis. Furthermore, inflammation may exacerbate bone ischemia by impairing the survival and function of vascular endothelial cells [19].

3.2 Detection and Clinical Application of Circulating Inflammatory Proteins

Currently, the methods for detecting circulating inflammatory proteins primarily include enzyme-linked immunosorbent assays, chemiluminescence immunoassays, and flow cytometry. These techniques accurately quantify various inflammatory proteins in the blood, providing essential tools for clinical research and practice. In clinical settings, circulating inflammatory proteins serve as biomarkers for early diagnosis, disease monitoring, and evaluation of treatment efficacy. For instance, in diagnosing rheumatoid arthritis, measuring the levels of circulating inflammatory proteins, such as anti-cyclic citrullinated peptide antibodies in serum, enhances the accuracy and sensitivity of early diagnosis [20]. During treatment, monitoring the dynamic changes in circulating inflammatory proteins allows for timely adjustments to the treatment plan, thereby improving outcomes. Furthermore, targeted therapeutic drugs, such as anti-TNF-α monoclonal antibodies, have shown significant efficacy in treating various inflammatory diseases [21], offering new hope to patients.

4. Current Status of Circulating Inflammatory Proteins in Osteonecrosis of the Femoral Head

4.1 Role of Circulating Inflammatory Proteins in Osteonecrosis of the Femoral Head

Osteonecrosis is a multifactorial disease closely related to the abnormal regulation of circulating inflammatory proteins. Recent studies have shown that proteins such as TNF-α, IL-1β, and CXCL12 significantly impact the metabolic balance and structural integrity of bone tissue by regulating osteoblastic differentiation, angiogenesis, and osteoclast migration.

TNF-α influences the structure and function of bone tissue by regulating osteocyte apoptosis and the balance of bone metabolism. In patients with steroid-induced osteonecrosis [22], researchers observed a positive correlation between serum TNF-α levels and osteonecrosis volume. TNF-α activates the NF-κB and MAPK pathways by binding to the TNFR1 receptor, upregulating pro-apoptotic proteins, and inhibiting anti-apoptotic protein expression, which induces programmed osteocyte death [23]. Additionally, studies have shown that TNF-α inhibits key transcription factors involved in osteoblast differentiation, activates the RANKL/OPG system, promotes the differentiation of osteoclast precursors into mature osteoclasts, and accelerates bone resorption [24].

IL-1β also plays a crucial role in the process of osteonecrosis. It induces the expression of MMP-9 and MMP-13 through the AP-1 signaling pathway, leading to the degradation of subchondral collagen and proteoglycan. This degradation weakens the structural support of bone, resulting in microfractures and articular surface collapse, ultimately inducing osteonecrosis [25]. Furthermore, in an animal study [26], IL-1β knockout mice exhibited significantly reduced bone resorption and cartilage damage in a hormone-induced osteonecrosis model.

In addition, IL-10 promotes angiogenesis and osteogenic differentiation by inducing M2 macrophages to secrete TGF-β and VEGF [27]. TGF-β upregulates Runx2 and Osterix expression through Smad2/3 phosphorylation, facilitating the differentiation of mesenchymal stem cells into osteoblasts [28]. CXCL12, secreted by stromal cells in the area affected by osteonecrosis, promotes the migration of osteoclast precursor cells to bone resorption sites by binding to the CXCR4 receptor, thereby accelerating local bone destruction [29]. The complex mechanisms through which these proteins operate in the progression of osteonecrosis provide potential targets for therapeutic intervention.

4.2 Clinical Application of Circulating Inflammatory Protein in Avascular Necrosis of Femoral Head

Changes in inflammatory protein levels can serve as biomarkers to monitor the progression of osteonecrosis. Elevated levels of inflammatory factors such as IL-1, IL-6, and TNF-α in the blood may indicate increased osteonecrosis activity [30]. Regular detection of these inflammatory protein levels allows for timely assessment of disease progression, providing valuable insights for clinical treatment. Additionally, monitoring changes in inflammatory protein levels during osteonecrosis treatment can help evaluate the effectiveness of the intervention. If treatment is effective, levels of inflammatory proteins may gradually decrease; for instance, significant reductions in TNF-α and IL-6 levels after treatment typically indicate control of the inflammatory response and enhanced bone tissue repair capacity. Conversely, a continued rise in inflammatory protein levels may suggest disease progression or treatment failure.

Anti-inflammatory therapy targeting circulating inflammatory proteins is a key focus in the treatment of osteonecrosis. Nonsteroidal anti-inflammatory drugs and glucocorticoids can inhibit the expression of inflammatory proteins and alleviate the inflammatory response. However, long-term use of corticosteroids may lead to increased osteonecrosis, so caution is warranted [31]. In recent years, biological agents such as anti-TNF-α monoclonal antibodies and IL-1 receptor antagonists have shown promise in treating osteonecrosis. These agents specifically inhibit the activity of inflammatory proteins and reduce the inflammatory response in bone tissue. Additionally, chronic inflammation can be mitigated by modulating the immune system, such as shifting macrophage polarization from the pro-inflammatory M1 type to the anti-inflammatory M2 type. Gene therapy and cell therapy also present novel strategies for osteonecrosis

treatment [32]. For example, genetically engineering mesenchymal stem cells to overexpress the anti-inflammatory cytokine IL-4 and transplanting them into osteonecrosis sites can provide an anti-inflammatory effect and promote bone repair. Moreover, isolated, expanded, and delivered autologous or allogeneic mesenchymal stem cells can also be utilized to repair bone defects and treat osteonecrosis [33].

5. Conclusion and Prospect

ONFH is a progressive bone disease with a high rate of disability in the orthopedic field. Its pathogenesis is complex and involves multi-system interactions. Characterized by bone cell death and the destruction of bone tissue structure, ONFH not only severely affects patients' joint function but also often leads to joint collapse and disability, placing a heavy burden on patients' quality of life and social medical resources. In recent years, the study of the pathological mechanisms of ONFH has increasingly focused on the role of circulating inflammatory proteins in its development.

The pathogenesis of ONFH involves the interplay of various factors, both traumatic and non-traumatic, that disrupt the blood supply to the femoral head, induce intraosseous hypertension, cause fat embolism, or damage vascular endothelium. Recent studies have highlighted the crucial role of inflammation in the development and progression of ONFH.

Circulating inflammatory proteins, including cytokines, chemokines, and acute phase response proteins, serve as key mediators of the inflammatory response. They form a complex regulatory network within the inflammatory microenvironment of bone tissue. By regulating the balance of bone metabolism, inducing osteocyte apoptosis, and inhibiting angiogenesis, these proteins are deeply involved in the pathological processes of ONFH.

In this paper, we review the epidemiological characteristics, etiological mechanisms, clinical diagnosis and treatment strategies, and the role of inflammatory proteins in ONFH, revealing the complex regulatory mechanisms of the inflammatory network in the development of osteonecrosis. Circulating inflammatory proteins not only play a critical role in the early inflammatory response of ONFH but also influence disease progression by regulating bone metabolism and angiogenesis. Moreover, these proteins, as biomarkers, have demonstrated significant clinical value in the early diagnosis, disease monitoring, and evaluation of treatment effects in ONFH, providing a theoretical framework for more accurate diagnosis and treatment in the future.

Future studies should further investigate the dynamic changes and regulatory mechanisms of inflammatory proteins at different stages of ONFH, analyze the spatial and temporal heterogeneity of the inflammatory microenvironment using multi-omics techniques, and develop novel diagnostic markers and therapeutic targets based on inflammatory proteins. Through interdisciplinary research, we aim to construct a new system for the prevention and treatment of ONFH, centered on inflammation regulation, which is expected to provide systematic solutions for improving patient prognosis and reducing the social burden of disease.

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