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Recent Advances in the Pathogenesis of Steroid-induced Osteonecrosis of the Femoral Head

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Abstract: ***Steroid-induced osteonecrosis of the femoral head is an orthopedic disease caused by prolonged or excessive use of steroids, leading to bone necrosis and joint dysfunction in the femoral head. It has the highest incidence among non-traumatic femoral head osteonecrosis and is a major challenge in clinical orthopedic practice. In recent years, significant progress has been made in understanding the pathogenesis of steroid-induced osteonecrosis of the femoral head, with deeper studies into its etiology. This article aims to summarize the pathogenesis of steroid-induced osteonecrosis of the femoral head, with the goal of providing references for clinical treatment and basic research.***

Keywords: Glucocorticoid, Steroid-induced necrosis of femoral head, Pathogenesis**.**

1. Introduction

Steroid-induced osteonecrosis of the femoral head (SONFH) is a refractory orthopedic disease caused by excessive use of glucocorticoids (GC). The main symptoms include hip pain, impaired mobility, and gait abnormalities. In severe cases, the condition may lead to joint deformities and functional impairment, and ultimately cause collapse of the hip joint surface [1]. Due to the side effects of GC, GC has a double-edged sword effect [2], but its irreplaceability in clinical treatment still requires ongoing exploration of the pathogenesis of SONFH. Especially during the COVID-19 pandemic, corticosteroid treatment was recommended for a large number of critically ill COVID-19 patients [3]. So far, the mechanism of GC-induced osteonecrosis of the femoral head (ONFH) remains unclear. Still, it appears to be related to factors such as osteocyte apoptosis, endothelial cell injury, or lipid metabolism disorders [4,5]. The occurrence of SONFH results from the interaction of multiple factors, leading to imbalances across several pathways, which together form a complex pathological network that promotes the onset of the disease. This article aims to summarize the pathogenesis of SONFH, providing a theoretical basis and reference for its prevention and treatment.

2. Mechanisms of Cell Apoptosis

Apoptosis refers to the physiological process in which cells undergo death through endogenous programmed mechanisms under specific signaling. GC can directly induce the apoptosis of osteoblasts and osteocytes, increase osteoclast activity, and inhibit osteoblast activity, thereby triggering the onset of SONFH [6]. Research has found that [7] the effect of exogenous GC is strongly cell-type and dose-dependent. Excessive GC inhibits the proliferation and differentiation of osteoblasts and enhances the apoptosis of osteoblasts and osteocytes, ultimately leading to reduced bone formation. Apoptosis of osteoblasts prevents normal repair and regeneration of bone tissue, leading to a reduction in trabecular bone and the occurrence of microfractures. As mechanical load increases, the collapse and necrosis of the femoral head gradually worsen [8]. The osteoblastic apoptosis mechanism of SONFH involves multiple targets and signaling pathways, such as Bax, Bcl-2, Caspase 3, and PI3K/AKT [9,10] A study showed that [11] Astragaloside IV regulates the Akt pathway, downregulates the levels of Bax, Cleaved Caspase-3, and Cytochrome C, inhibits cell apoptosis and oxidative stress, thereby suppressing SONFH, and significantly reduces the apoptosis of osteocytes in SONFH. Another study reported that [12] GC reduces the expression of HIF-1α and PDK1 in osteoblasts, and PDK1 agonists can reverse glucocorticoid-induced osteoblast apoptosis.

3. Lipid Metabolism Disorders

The action of GC can lead to increased lipid accumulation, thereby altering lipid metabolism and increasing the turnover of circulating lipids. Clinical studies have confirmed that patients using GC long-term have significantly higher levels of free fatty acids and low-density lipoprotein in their serum, while high-density lipoprotein levels are significantly lower [13]. These changes lead to increased bone pressure, enlargement of bone marrow adipocytes, promotion of the differentiation of bone marrow mesenchymal stem cells (BMSCs) into adipocytes, resulting in fat deposition and a filling effect, decreased blood circulation, accumulation of fat in the circulatory system, and may ultimately trigger femoral head necrosis [14]. A study found that [15] the use of GC promotes the release of fatty acids in adipose tissue, leading to elevated blood lipid levels. The increase in blood lipids promotes the accumulation of fat particles, which may enter the bone marrow through the bloodstream and accumulate within the bone, affecting normal blood supply and leading to ischemic necrosis of the femoral head. Furthermore, scholars in the last century proposed a relationship between femoral head necrosis and blood lipids [16], indicating that excessive hormones can elevate blood lipid levels, form diffuse fat emboli, and subsequently cause vascular embolism and bone necrosis in the femoral head. A study found that [17] the accumulation and expansion of bone marrow adipocytes lead to increased intra-bone pressure, and the closed structure of the femoral head results in reduced blood perfusion. In a high-fat state, the apoptosis rate of osteoblasts is significantly elevated and is closely related to lipid metabolism imbalance.

4. Endothelial Cell Damage

Endothelial cells are a critical component of blood vessels, involved in maintaining the stability of the vascular environment and regulating blood flow. Endothelial cell damage and coagulation abnormalities are considered key pathological factors in femoral head necrosis [18]. During the progression of SONFH, thrombosis, thrombin abnormalities, and endothelial cell dysfunction cause microcirculatory disturbances in bone tissue, leading to bone hypoxia and nutrient deficiency, which weakens the femoral head's resistance to compression, ultimately resulting in varying degrees of femoral head collapse. Studies have shown that [19] GC directly affects endothelial cells, leading to their damage and apoptosis. GC promotes endothelial cell damage, increases vascular permeability, and alters the balance between anticoagulant and procoagulant factors on the surface of endothelial cells, thereby promoting thrombosis. Specifically, GC upregulates pro-inflammatory factors (such as TNF-α), activates endothelial cells, and increases the expression of plasminogen activator inhibitor-1 (PAI-1). Elevated PAI-1 inhibits the fibrinolytic system, reducing plasmin generation, which leads to a relatively hypercoagulable state, further promoting thrombosis [20,21]. It is noteworthy that endothelial cell damage not only directly triggers thrombosis but also exacerbates ischemic injury of the femoral head through other mechanisms, synergistically advancing the pathological process. Imbalanced coagulation mechanisms are an important trigger for the occurrence of femoral head necrosis.

5. Oxidative Stress

Oxidative stress is primarily caused by mitochondrial damage, releasing large amounts of oxygen species (ROS), which leads to the dysregulation of endogenous antioxidant defense mechanisms. Excessive ROS can cause cellular and vascular dysfunction, further weakening the blood supply to the femoral head, ultimately leading to necrosis [22,23]. Under GC intervention, the levels of ROS in osteoblasts increase, inhibiting the expression of osteogenic markers such as Alkaline phosphatase (ALP), Bone morphogenetic protein 2 (BMP2), Osteopontin (OPN), and Runt-related transcription factor 2 (RUNX2), leading to cellular dysfunction and damage [6,24]. Overexpression of ROS can lead to a significant increase in related proteins such as RANKL and Cathepsin K in osteoclasts, inducing their recruitment and activation, which ultimately causes bone loss and triggers SONFH. Research shows that [25,26] overactivation of the NADPH oxidase family generates superoxide anions (O_2^-), while the activity of antioxidant enzymes decreases, playing a crucial role in oxidative damage in bone cells. Studies indicate that studies indicate that [27] elevated glucocorticoid levels suppress the antioxidant defense system, promote the production and accumulation of reactive oxygen species, leading to oxidative stress, increasing lipid peroxidation levels, and inducing ferroptosis. ROS scavengers can effectively remove excess ROS from cells, reverse oxidative stress-induced damage to osteoblasts, and reduce their apoptosis. ROS scavengers can effectively remove excess ROS from cells, reverse oxidative stress-induced damage to osteoblasts, and reduce their apoptosis. Through this mechanism, ROS scavengers help promote osteoblast function, improve the bone formation process, and accelerate bone repair in SONFH.

6. Genetic Polymorphisms and Epigenetics

The occurrence of SONFH is not only closely related to the external use of hormones but also intricately linked to individual genetic background and regulatory changes in gene expression. The occurrence of SONFH is not only closely related to the external use of hormones but also intricately linked to individual genetic background and regulatory changes in gene expression. Recent studies suggest that [28] gene polymorphisms associated with bone metabolism may play an important role in the pathogenesis of SONFH, particularly genes related to bone density, bone structure, and inflammatory response, which may have genetic susceptibility in the development of SONFH [29]. Epigenetic changes do not involve alterations in DNA sequence but can regulate gene expression through mechanisms such as methylation and histone modification. Hormone use may alter the epigenetic marks of certain genes, thereby affecting their expression and, in turn, influencing bone metabolism and blood supply, ultimately leading to femoral head necrosis [4,30]. Studies have shown that Studies have shown that [31] GC inhibits the Wnt/β-catenin pathway through DNA methylation modifications (such as high methylation of the DKK1 gene promoter), hindering osteogenic differentiation. Hormone use further promotes the occurrence of SONFH by influencing genetic background and the regulation of gene expression.

7. Prospect

The pathogenesis of SONFH has multi-level and multi-dimensional interactive features, and its occurrence is not dominated by a single pathological factor, but is the result of the synergistic action of multiple mechanisms. From apoptosis to epigenetic dysregulation, the shift in research paradigms provides a foundation for precision treatment. In the future, there should be a stronger connection between basic research and clinical needs, promoting the innovation of diagnosis and treatment strategies through interdisciplinary collaboration. While clarifying the mechanisms of SONFH occurrence and development, effective intervention measures should also be adopted to maximize the efficacy of SONFH treatment and improve patients' quality of life. With the deep integration of interdisciplinary technologies and the rapid development of the translational medicine system, it is believed that, shortly, precision-targeted therapy at the genetic level can be achieved based on the pathogenesis of SONFH, leading to early precision treatment of SONFH.

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