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Review Paper

# Clinical Implications and Therapeutic Strategies for Avascular Necrosis of the Femoral Head

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## ABSTRACT

Avascular necrosis of the femoral head (ANFH) is a debilitating condition caused by ischemia, which leads to bone necrosis and collapse. This condition involves a complex interplay of endothelial dysfunction, coagulation pathways, lipid biosynthesis disturbances, and apoptotic mechanisms, all of which contribute to the progression of ANFH. The integrity of the vascular system is crucial for bone repair and remodeling, and the disruption of angiogenesis plays a central role in the development of ANFH. This review discusses the role of endothelial cells in maintaining vascular health, how impaired angiogenesis exacerbates the condition, and the impact of coagulation pathways, lipid biosynthesis, and apoptosis in the pathophysiology of ANFH. Furthermore, the paper examines the significance of bone remodeling and the potential genetic factors linked to inherited forms of ANFH. Also, the potential for therapeutic strategies targeting these mechanisms, including pro-angiogenic factors, metabolic modulation, and anticoagulant therapies, is examined. Understanding these molecular and cellular processes holds promise for effective treatment and prevention of femoral head collapse, with implications for clinical management and future research.

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## Introduction

Avascular necrosis of the femoral head (ANFH) is a progressive and debilitating condition that involves the death of bone tissue due to a lack of blood supply. This disorder is typically accompanied by chronic pain, significantly impairing the patient's quality of life (QoL). The condition presents substantial challenges for clinicians, as achieving effective therapeutic outcomes often requires addressing complex factors such as disease progression, bone integrity, and patient response to treatment [1, 2]. Although the etiology of ANFH remains complex and not fully understood, more than 80% of cases are associated with corticosteroid use and excessive alcohol consumption, factors that have garnered considerable research attention [3, 4]. Moreover, several conditions and medical treatments have been identified as key risk factors for the onset and progression of ANFH. Systemic lupus erythematosus, an autoimmune disorder characterized by systemic inflammation, can impair blood circulation, thereby increasing the risk of bone tissue death. Traumatic injuries, such as fractures and dislocations, particularly those involving the hip, can disrupt the blood supply to the femoral head, accelerating the development of ANFH. Sickle cell disease (SCD), a genetic blood disorder characterized by the production of abnormal red blood cells, can block blood vessels, thereby further compromising circulation and increasing the risk of avascular necrosis.

In addition to these conditions, certain medical interventions can contribute to the progression of ANFH. Chemotherapy and radiation therapy, commonly used in cancer treatment, can adversely affect vascular function, reducing blood flow to the bones. Likewise, hip surgeries, particularly those involving joint replacement or fracture repair, can disrupt the blood supply to the femoral head, heightening the likelihood of necrosis. Together, these factors highlight the complex and multifactorial nature of ANFH, underscoring the importance of tailored preventive and therapeutic approaches [5-9]. Although the exact pathophysiological mechanisms underlying ANFH are not yet fully elucidated, there is a broad consensus that the health of the femoral head is critically dependent on its vascular system. The primary pathogenic process in ANFH is ischemia, which can arise from a variety of factors, including trauma, systemic diseases, or medical interventions. Insufficient blood flow to the femoral head disrupts the normal supply of oxygen and nutrients to the bone tissue, which is vital for maintaining bone integrity and function. As a result of this ischemic insult, the subchondral bone structure, which plays a key role in supporting the overlying articular cartilage, undergoes progressive degeneration. This degeneration leads to the necrosis of bone cells and the subsequent collapse of the femoral head. The collapse of the femoral head often results in joint instability and altered biomechanics, further exacerbating the damage. Additionally, the ischemic process triggers an inflammatory cascade, which contributes to the pain, swelling, and limited range of motion typically observed in patients with ANFH. This cascade of events ultimately leads to the clinical manifestations of the disease, which can include chronic pain, joint dysfunction, and, if left untreated, severe osteoarthritis or joint collapse requiring surgical intervention [10, 11]. Numerous studies have highlighted the strong connection between angiogenesis and the onset and progression of various diseases, emphasizing that abnormal or impaired angiogenesis serves as a key indicator of disease development [12, 13]. A significant body of research has established that vascular injury is the principal factor contributing to the onset of ANFH, with impaired angiogenesis playing a crucial role in its pathogenesis. The disruption of blood supply to the femoral head, due to various factors such as trauma, disease, or medical treatments, leads to a reduction in the formation of new blood vessels, further exacerbating ischemia and promoting the progression of the disease. This impairment in angiogenesis is considered a key mechanism through which vascular damage leads to bone tissue death and subsequent joint collapse [14-16].

The significance of angiogenesis has been well established by researchers, who have more recently focused on investigating its molecular mechanisms. Building upon this knowledge, both pro-angiogenic and anti-angiogenic drugs have been explored as potential therapeutic options, contributing to the development of new perspectives and strategies for treating related diseases. In the context of ANFH, studies have suggested that promoting angiogenesis through various pathways may offer a promising approach to treating this condition [17, 18].

### Vascular supply and femoral head

The femoral head, although one of the most structurally significant bones in the human body, relies heavily on a complex and highly vascularized network to maintain its mechanical integrity, function, repair, regeneration, and remodeling. This intricate vascular system plays a crucial role in supplying essential oxygen, nutrients, and growth factors, all of which are vital for sustaining the bone's health and ensuring its optimal functionality. Without a sufficient blood supply, the femoral head's

ability to regenerate and maintain its strength and structure is significantly compromised, leading to increased susceptibility to conditions such as avascular necrosis [19]. Vascular injury is the primary cause of avascular necrosis of ANFH, with impaired angiogenesis being a key factor in its progression [14-16]. In contrast, promoting angiogenesis and restoring blood vessel formation in the necrotic area can reestablish the blood supply, thereby enhancing collateral circulation and aiding in the repair of damaged tissue.

A complex network of blood vessels nourishes the femoral head. These vessels comprise branches from the medial femoral circumflex artery (MFCA), inferior gluteal artery (IGA), lateral femoral circumflex artery (LFCA), obturator artery, superior gluteal artery, and the first perforating branch of the deep femoral artery. However, the deep branch of the MFCA is the primary and most essential vascular source for the femoral head, providing the majority of its blood supply. Additionally, the IGA contributes to the femoral head's circulation by forming an anastomosis with the MFCA through its piriformis branch, indirectly supporting its blood flow. In certain anatomical variations, the IGA may become the dominant vascular source. Notably, research indicates that during fetal development, more than 50% of fetuses between 16 and 29 weeks of gestation rely predominantly on the IGA as the primary blood supply to the femoral head [20]. The LFCA plays a significant role in supplying blood to the femoral neck, primarily through its anterior nutrient artery. However, it contributes minimally to the blood supply of the femoral head.

In comparison, other arteries such as the superior gluteal artery, obturator artery, and the first perforating branch of the deep femoral artery provide only a small fraction of the overall vascular supply to the femur. These arteries are not primary sources of blood to the femoral head but rather offer supplementary contributions. Despite their limited role in the femoral head's vascularization, these vessels are important in supporting the overall circulatory system of the femur, with the primary blood flow being supplied by MFCA. The contribution of these secondary arteries remains relatively small, underscoring the femoral head's dependence on the primary vascular network for its health and function [21].

As the primary source of blood supply to the femoral head, MFCA is the vascular structure most likely related to the development of ANFH. However, due to the femoral head's high reliance on blood flow, damage or blockage of other vessels can also result in compromised blood supply to the femoral head. Suppose this blood supply is not promptly restored. In that case, it leads to the progressive death of bone cells, followed by collapse of the joint surface, degenerative osteoarthritis, and ultimately the onset of femoral head necrosis [22, 23]. Recent studies have also highlighted a vascular subtype known as H-type vessels, which play a key role in mediating subchondral remodeling. These vessels play a crucial role in the complex processes that maintain bone structure and function, particularly in the subchondral region [24, 25]. All of these studies provide valuable insights that help researchers approach the treatment of femoral head necrosis from a new perspective, offering potential avenues for more effective therapeutic strategies.

## Strategies for modulating angiogenesis in treating ANFH

As previously outlined, angiogenesis is the biological process in which endothelial cells (ECs), typically in a dormant state, are activated in response to local ischemia, hypoxia, or various other stimuli, resulting in the formation of new blood vessels. This process is meticulously balanced between pro-angiogenic and anti-angiogenic factors. The dynamic interplay between these factors drives the generation of new blood vessels, promoting the expansion and remodeling of the existing vascular network. Such regulation ensures that the formation of new vessels is appropriately matched to the physiological needs of the tissue, facilitating improved blood supply and promoting tissue repair and regeneration in response to injury or other pathological conditions [26, 27]. Common angiogenic factors include hypoxia-inducible factor-1 (*HIF-1α*), vascular endothelial growth factor (*VEGF*), its receptors (*VEGFRs*), VE-cadherin, CD31, and DLL4-Notch-nog signaling pathway, among others. These factors are essential for regulating and promoting angiogenesis, playing pivotal roles in the formation and remodeling of blood vessels [28]. These angiogenic factors affect the molecular pathways and promote both angiogenesis and bone repair in necrotic regions by associating the processes of blood vessel formation and bone regeneration [29].

### *VEGF*

Especially during the early stages of ANFH, VEGF is obviously upregulated in necrotic regions. *VEGF* stimulates angiogenesis and the formation of new blood vessels, as well as osteogenesis. *VEGF* helps restore blood supply to ischemic areas via promoting the growth of new blood vessels, a crucial step in tissue repair. Furthermore, its involvement in osteogenesis supports the regeneration of bone tissue, thereby playing a key role

in the progression and potential recovery from ANFH. Additionally, *VEGF* stimulates the proliferation of ECs, contributing to the restoration of vascular networks. Thus, *VEGF* is a crucial factor in the repair process of hypoxia-induced osteonecrosis, as it supports both the regeneration of blood supply and the healing of bone in the affected areas [30-35]. *HIF-1α* upregulates *VEGF* expression in response to ischemic and hypoxic conditions. *VEGF* contributes to the repair of necrotic regions in the femoral head, supporting tissue regeneration and the recovery of function [36, 37]. In the absence of *VEGF*, the local processes of angiogenesis and repair in necrotic areas of femoral head necrosis are notably hindered. However, the overexpression of *VEGF* has been shown to significantly enhance both osteogenesis and angiogenesis, particularly through the activation of adipose-derived (MSCs). *VEGF* not only promotes the growth and differentiation of ECs, thereby stimulating angiogenesis, but it also plays a crucial role in directly recruiting bone marrow-derived endothelial progenitor cells. This recruitment contributes to the formation of new blood vessels in the necrotic regions, facilitating the repair and regeneration of the femoral head. By enhancing both the vascular network and bone formation, *VEGF* supports the restoration of the femoral head's integrity and function, offering potential therapeutic avenues for treating avascular necrosis [38, 39]. Without *VEGF*, local angiogenesis and the repair of necrotic regions in femoral head necrosis are hindered. However, the overexpression of *VEGF* has been shown to enhance both osteogenesis and angiogenesis, facilitating the repair of the necrotic regions by promoting the formation of new blood vessels and supporting bone regeneration [40, 41].

*VEGF* has garnered significant attention from researchers in the field of stem cell-based treatments for ANFH due to its crucial role in promoting angiogenesis and osteogenesis. Its ability to stimulate EC growth and blood vessel formation makes it an essential factor for improving blood supply to the femoral head, which is vital for the repair and regeneration of necrotic bone tissue. Consequently, *VEGF* is considered a promising therapeutic target in stem cell therapies aimed at treating femoral head necrosis [42, 43]. Since MSCs have been shown to promote angiogenesis in vivo by inducing the release of *VEGF*, researchers have proposed using arterial perfusion of MSCs to improve blood supply to the femoral head as a potential treatment for ANFH. This approach has been validated in dog models of ANFH, where the infusion of MSCs via arterial perfusion successfully enhanced local blood circulation, promoting angiogenesis and aiding in the repair of necrotic bone tissue. This strategy highlights the potential of MSC-based therapies in addressing the underlying vascular insufficiency that contributes to the progression of ANFH [44, 45]. A three-year follow-up study on the efficacy of MSCs in treating ANFH further confirmed the beneficial role of MSC transplantation. The study demonstrates that MSCs not only promote the regeneration of new blood vessels and improve local circulation but also contribute to the repair of necrotic bone tissue by stimulating osteogenesis. Patients who underwent MSC transplantation show significant improvements in both clinical outcomes and radiographic findings, including reduced pain, better joint function, and stabilization of the femoral head. These results highlight MSC therapy as a promising approach for treating ANFH, offering potential for long-term benefits in managing this challenging condition [46]. Several researchers have investigated innovative therapeutic methods by joining MSC-targeted arterial perfusion with porous tantalum scaffolds or via directly embedding *VEGF165* transgenic MSCs into animal models of femoral head necrosis, made by femoral neck osteotomy. These strategies aim to enhance both angiogenesis and osteogenesis within the necrotic areas of the femoral head. The use of porous tantalum provides a scaffold for new bone growth. At the same time, the implantation of *VEGF165* transgenic MSCs directly promotes the local production of *VEGF*, stimulating blood vessel formation and bone regeneration. These combined approaches have shown promise in improving the repair of femoral head necrosis by facilitating better vascularization and bone regeneration, highlighting potential advancements in the treatment of avascular necrosis [47, 48].

Alternatively, the combined application of platelet-rich plasma clot releasate (PRCR) and MSCs has been investigated as a therapeutic strategy for treating ANFH. The synergistic effects of PRCR and MSCs have been shown to enhance angiogenesis, osteogenesis, and tissue repair. PRCR, rich in growth factors, can promote the proliferation and migration of MSCs, while MSCs contribute to the regeneration of damaged tissues and the formation of new blood vessels. This combined approach has shown promising results in preclinical and clinical studies, as it helps restore the local blood supply, repair the necrotic bone, and prevent further degeneration of the femoral head, potentially offering an effective treatment strategy for ANFH [49]. By enhancing blood vessel formation in the necrotic area, these approaches help restore the blood supply to the femoral head, a crucial step for tissue repair and bone regeneration. This restoration of vascularization supports the healing process, potentially slowing or halting the progression of necrosis, reducing pain, and

improving the function of the hip joint. As a result, strategies like the use of MSCs and PRCR show promise as part of a comprehensive treatment plan for ANFH [47, 49-60] (Figure 1).

## Hypoxia-inducible factor

HIFs are a family of transcription factors that play a crucial role in regulating cellular responses to low oxygen conditions, or hypoxia. These factors function as heterodimers, consisting of a constitutively expressed *HIF-β* subunit and an oxygen-sensitive *HIF-α* subunit. The *HIF-α* subunit is stable and active under low oxygen conditions, while the *HIF-β* subunit is consistently expressed. Together, these subunits regulate the expression of genes involved in critical processes, such as angiogenesis, erythropoiesis, and cellular metabolism, enabling cells to adapt to the challenges posed by reduced oxygen availability [61]. Under hypoxic conditions, the hydroxylation of *HIF-α* subunits is suppressed due to reduced oxygen availability. As a result, under conditions of hypoxia, the *HIF-α* subunits accumulate and translocate into the nucleus. Once in the nucleus, they dimerize with the constitutively expressed *HIF-β* subunits, forming active HIF complexes. These HIF dimers then bind to hypoxia-responsive elements (HREs) in the promoter regions of target genes, initiating the transcription of genes involved in adaptive responses such as angiogenesis, cell survival, and metabolic reprogramming. This process enables cells to cope with the reduced oxygen supply by promoting physiological adaptations that improve oxygen delivery and cellular function. This complex regulates the transcription of over 100 target genes, including *VEGF* and erythropoietin. Through this mechanism, HIFs play a critical role in the ischemic and hypoxic environment, influencing both physiological and pathological angiogenesis [62-65]. Previous studies have demonstrated that glucocorticoids suppress the expression of *HIF-1α,* thereby inhibiting angiogenesis. This inhibition contributes to femoral head collapse and the development of ANFH. The downregulation of the *HIF* signaling pathway is considered a significant factor in the pathogenesis of ANFH [66, 67].

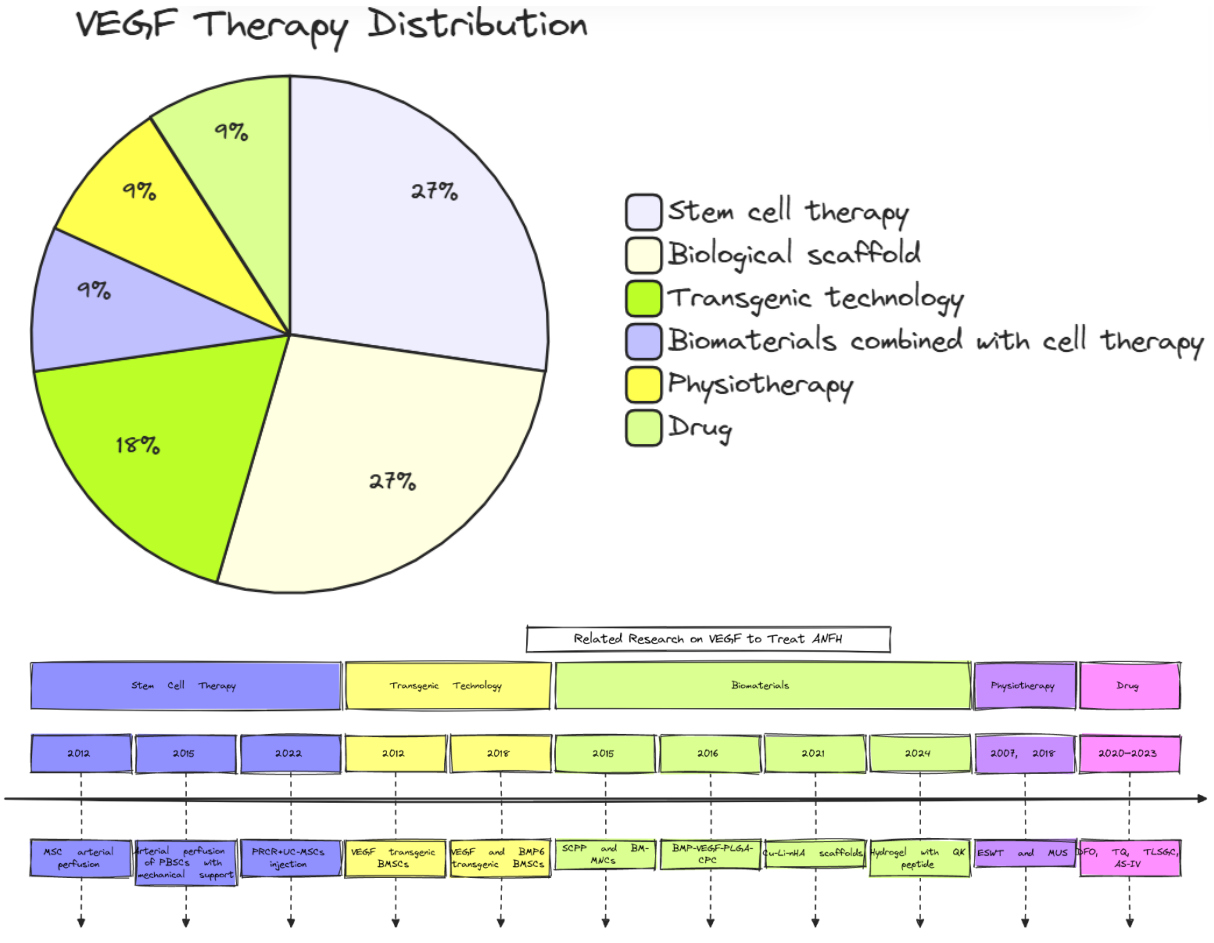


**Figure 1.** VEGF to treat avascular necrosis of the femoral head

Furthermore, *HIF-1α* plays a crucial role in the local repair mechanisms of ANFH, highlighting its significance in the disease pathology. While *HIF-1α* influences the expression of numerous target genes, *VEGF* is likely its primary target in the context of ANFH [34, 68]. As previously noted, *HIF-1α* acts as an upstream regulator of *VEGF*. When *HIF-1α* and transgenic bone marrow cells are transplanted into the necrotic region of the femoral head, *VEGF* expression is significantly upregulated. This increase in *VEGF* levels stimulates enhanced angiogenesis, promoting the formation of new blood vessels within the necrotic area. The improved vascularization supports tissue repair and regeneration, facilitating the restoration of the femoral head's structure and function. This approach highlights the potential of using *HIF-1α* and bone marrow-derived cells to promote healing in femoral head necrosis by improving blood supply and stimulating the regenerative processes necessary for recovery [37].

Regarding specific therapeutic applications, several drugs that target the HIF pathways have been examined in ANFH models. For example, astragaloside IV enhances local angiogenesis by arbitrating *HIF-1α*, leading to intensified *VEGF* expression and improved blood vessel formation in necrotic areas. Similarly, desferoxamine (DFO), either alone or in combination with alendronate, has been found to activate *HIF-1α*, thereby promoting angiogenesis and offering a protective effect against the progression of ANFH. These findings suggest that modulating the *HIF-1α* pathway may provide a promising therapeutic strategy for enhancing vascularization and mitigating the detrimental effects of ANFH [60, 69, 70]. 3, 4-Dihydroxybenzoate (EDHB) has been demonstrated to prevent the onset of ANFH by inhibiting the degradation of *HIF-1α*. This inhibition results in the stabilization of *HIF-1α*, which subsequently enhances the expression of *VEGF*. The increased expression of *VEGF* promotes angiogenesis, thereby improving blood vessel formation and restoring vascular supply to the affected areas. By supporting angiogenesis and enhancing blood flow, EDHB presents a potential therapeutic strategy for slowing the progression of ANFH and promoting tissue repair [71].

Additionally, researchers have transfected BMSCs with an adenovirus containing triple-point mutations (at amino acids 402, 564, and 803) in the *HIF-1α* coding sequence. Exosomes derived from these genetically modified BMSCs were subsequently injected into the necrotic region, successfully promoting the repair of femoral head avascular necrosis by enhancing local angiogenesis [18]. Additionally, other studies have demonstrated that hypoxia pre-stimulation of BMSCs enhances the expression of *HIF-1α*. This preconditioning improves their ability to stimulate local angiogenesis and promote bone regeneration following transplantation, offering a promising approach for the treatment of ANFH [72]. Before hypoxia induction, transfecting BMSCs with the *HIF-1α* gene or infecting them with a lentivirus encoding *HIF-1α* has been shown to enhance therapeutic outcomes further. Similarly, transplanting endothelial progenitor cells transfected with Ad-BMP-2-IRES-HIF-1α into the site of femoral head avascular necrosis can yield comparable benefits by promoting local angiogenesis and bone regeneration [73, 74]. Related research on using HIF to treat ANFH focuses on enhancing angiogenesis and tissue repair in femoral head necrosis by modulating the *HIF-1α* pathway. Studies have shown that activating *HIF-1α*, either through gene therapy or by using drugs like DFO and astragaloside IV, can increase *VEGF* expression, promote blood vessel formation, and improve local bone regeneration in the ischemic environment of ANFH [18, 37, 53, 60, 69-74] (Figure 2).

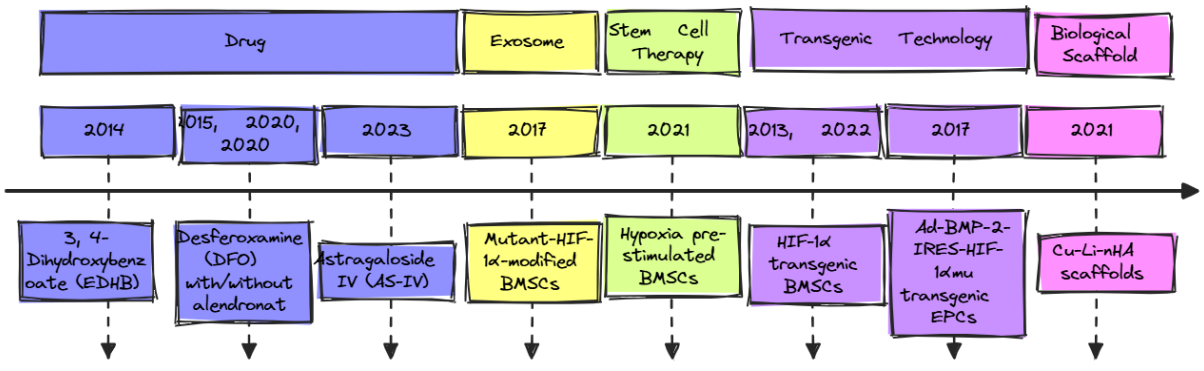


**Figure 2.** Hypoxia-inducible factor to treat avascular necrosis of the femoral head

## Other factors

Beyond the factors previously mentioned, which have been thoroughly investigated and utilized in the context of ANFH, other angiogenic factors have also been explored in this disease model. For instance, a genetic association study identified single-nucleotide polymorphisms in the *NRP1* gene as a protective factor against the development of ANFH, potentially reducing its incidence [75]. Furthermore, in steroid-induced necrosis of the femoral head, hormone-induced suppression of platelet-derived growth factor-BB (PDGF-BB) expression leads to a reduction in H-type angiogenesis. This disruption impairs the coupling between local angiogenesis and osteogenesis, contributing to the development of ANFH [66]. It has been demonstrated that PDGF-BB can enhance local blood flow in ANFH. As a result, some researchers transfected MSCs with a lentivirus carrying the *PDGF-BB* gene, controlled by the phosphoglycerate kinase (PGK) promoter, to generate PGK-PDGF-BB-MSCs. These cells were then used in experiments with rabbit models of ANFH [76]. Research has demonstrated that injecting specific substances into the bone tunnel during core decompression can successfully endorse angiogenesis in the early stages of ANFH. This process enhances the formation of new blood vessels, which helps restore blood supply to the affected areas. By improving vascularization, these injections reduce the likelihood of further progression to ANFH. This approach shows promise as a therapeutic strategy to prevent or slow the development of ANFH by addressing the underlying issue of inadequate blood flow in the femoral head [77]. Cartilage oligomeric matrix protein angiopoietin-1 (COMP-Ang1), when directly injected into the area of necrosis as an angiogenic factor, can stimulate angiogenesis and lead to increased vascularity in the affected region [78]. The combination of BMP-2 and COMP-Ang1 has been shown to more effectively enhance angiogenesis in the necrotic area of the femoral head, thereby providing greater protection to the femoral head [79, 80].

As previously discussed, BMP is often combined with other angiogenic factors to treat ANFH, such as *VEGF*, *HIF-1α*, COMP-Ang1, and basic fibroblast growth factor (bFGF), all of which have been studied in conjunction with BMP. Moreover, studies have shown that various agents, such as DFO, low-intensity pulsed ultrasound, and microbubble-mediated ultrasound, may boost the local expression of BMP-2, thus encouraging angiogenesis and reinforcing bone repair in the early stages of ANFH. These therapies promote the formation of new blood vessels and facilitate bone regeneration, which is crucial for repairing necrotic bone tissue. Additionally, hepatocyte growth factor (HGF) has been identified as a key regulator that increases BMP-2 expression and improves angiogenesis in local fractures. This finding suggests that HGF could potentially be applied in ANFH models to explore further its ability to enhance vascularization and promote bone healing, offering new avenues for therapeutic intervention in ANFH [51, 52, 56, 69, 74, 79, 81-85]. Finally, besides the methods mentioned above, PRP, vitamin K2, shockwave therapy, arterial infusion of autologous liposuction cells (LPCs), and interleukin-6 blockade are considered effective methods for promoting angiogenesis and protecting against the progression of ANFH [86-89, 90].

Research on the use of other angiogenesis regulatory factors for treating ANFH has garnered significant attention in recent years. These factors are primarily employed to stimulate the formation of new blood vessels in the necrotic area, which can aid in tissue regeneration and prevent disease progression. For instance, the combination of angiogenic factors such as *VEGF*, *HIF-1α*, and COMP-Ang1 with BMP-2 has shown positive results in enhancing angiogenesis and improving bone conditions in the necrotic region. Additionally, adjunct therapies such as PRP, vitamin K2, shockwave therapy, and arterial infusion of autologous LPCs have been reported as effective strategies for promoting angiogenesis and protecting the femoral head from the development of ANFH. These approaches are considered particularly complementary to primary therapies, enhancing the healing process and bone regeneration (Figure 3).

## EC metabolism

EC metabolism is an increasingly recognized regulatory factor in angiogenesis, attracting growing interest from researchers in recent years. Given that many metabolic enzymes are amenable to pharmacological targeting, EC metabolism holds significant potential for the development of novel therapeutic approaches [93]. In EC metabolism, oxidative phosphorylation is not considered the primary metabolic pathway because mitochondria comprise only 2-5% of the cytoplasmic volume. Instead, glycolysis serves as the primary pathway for adenosine triphosphate (ATP) production, accounting for approximately 85% of the total ATP generated in ECs [94, 95]. Other metabolic pathways in angiogenic ECs include the distinctive use of fatty acid (FA) oxidation for nucleotide synthesis, as well as the utilization of glutamine for anaplerosis of the tricarboxylic acid (TCA) cycle and for the synthesis of asparagine. These processes have been thoroughly discussed in related reviews [85, 94].

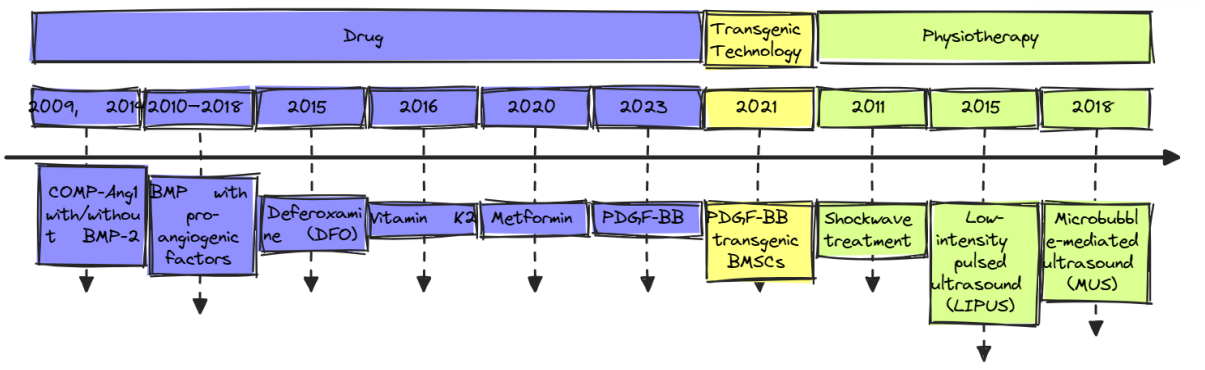


**Figure 3.** Angiogenesis regulatory factors to treat avascular necrosis of the femoral head

Changes in EC metabolism can result in impaired or abnormal angiogenesis, potentially leading to the development of vascular irregularities [96-99]. Although direct evidence linking EC metabolism disruption to the onset of ANFH is lacking, transcriptome analysis of bone tissue from ANFH patients has identified differentially expressed genes (DEGs) between necrotic and control groups. These DEGs are mainly involved in the *PI3K-Akt* signaling pathway and have a significant role in the glycolysis/gluconeogenesis pathway [100]. Additionally, studies have shown that both glycolysis and the TCA cycle are significantly disrupted in patients with ANFH [85, 101]. All of these findings suggest that ANFH disrupts the normal EC metabolism in the affected area. It can be hypothesized that the impairment of normal EC metabolism may also impact local angiogenesis in the femoral head, contributing to the development of ANFH. This finding presents a potential new direction for research in the field of ANFH.

## The relationship between avascular necrosis and the coagulation pathway

Glucocorticoids are the leading non-traumatic cause of ANFH, with research indicating that between 5% and 40% of individuals on long-term glucocorticoid therapy may develop the condition [102]. Additionally, regarding the regulatory effects of glucocorticoids (GCs) on procoagulation factors such as factor VIII, IX, and von Willebrand factor (VWF), as well as the fibrinolysis inhibitor plasminogen activator inhibitor-1 (PAI-1), GCs may play a crucial role in modulating coagulation processes [103-105].

Alpha-2-macroglobulin (A2M) has been identified as a protein that modulates thrombosis via various mechanisms, including inflammation, cell shedding, inhibition of fibrinolysis, and the formation of hemostatic plugs. A2M plays a significant role in both thrombogenesis and fibrinolysis, serving as a fibrinolysis inhibitor by blocking plasmin and kallikrein, as well as a coagulation inhibitor by preventing thrombin activity [106]. Therefore, it can be concluded that GCs influence endothelial function by regulating *A2M* gene expression and promoting thrombosis formation, ultimately contributing to ischemia.

## Lipid biosynthesis in ANFH

Numerous studies indicate that multiple factors contribute to the development of ANFH, including GCs use, alcohol consumption, infections, coagulation abnormalities, and specific autoimmune conditions. However, the precise etiological and pathological mechanisms underlying ANFH have not been fully elucidated. As noted earlier, the vascular hypothesis is currently regarded as the most persuasive explanation among the proposed theories [14].

In 2008, a study investigated the relation between polymorphisms in the *SREBP-2* gene and the risk of ANFH in the Korean population. SREBPs are part of the basic helix-loop-helix family of transcription factors. They play a crucial role in regulating lipogenesis, adipocyte differentiation, and maintaining cholesterol homeostasis [107]. A polymorphism in intron 7 of the *SREBP-1* gene may be associated with an increased risk of ANFH [108]. This finding supports a connection between ANFH and lipid metabolism, suggesting that genetic factors influencing lipid regulation may contribute to the development of the condition.

## Apoptosis in ANFH

The osteocyte is the most abundant and longest-living cell in bone, playing a crucial role in regulating bone homeostasis. These cells act as orchestrators of bone remodeling by modulating the activity of osteoblasts and osteoclasts. It has been reported that in glucocorticoid- and alcohol-induced avascular necrosis, the number of

osteocytes undergoing apoptosis increases [109-111]. Glucocorticoids and alcohol can have direct toxic effects on bone cells, leading to their apoptosis. This cellular damage contributes to the disruption of bone homeostasis and the development of conditions such as avascular necrosis [112]. The precise mechanisms driving non-traumatic ANFH are still not fully understood. However, several studies conducted in the last decade have suggested that its pathogenesis results from a complex interaction of multiple pathways and factors [113]. It was observed that the expression levels of osteoprotegerin (*OPG*), receptor activator of the nuclear factor-kB (RANK), and *RANK* ligand (*RANKL*) are elevated in the necrotic regions compared to the healthy areas in osteonecrotic samples [114]. Another study revealed variations in the expression levels of BMP between the normal and the necrotic areas of femoral heads in patients with avascular necrosis [115]. The study found that inducible nitric oxide synthase (*iNOS*) expression was significantly higher in osteonecrotic samples compared to control samples, indicating an increase in nitric oxide production within the osteonecrotic tissue.

Furthermore, the apoptosis of numerous osteocytes in the avascular necrosis group was closely linked to the sustained high expression of iNOS [116]. However, the apoptosis signaling pathway is not solely mediated through mitochondrial mechanisms. Extracellular signals, such as those through *Fas/CD95*, can also activate caspases, leading to cell death. This extrinsic pathway may play a significant role in the apoptosis of osteocytes in non-traumatic ANFH. The activation of the Fas receptor, a key component of this pathway, can initiate a cascade of caspase activation, contributing to osteocyte apoptosis and subsequently influencing the pathogenesis of ANFH [117].

## Bone remodeling in the context of avascular necrosis

*OPG*, *RANK*, and *RANKL* significantly contribute to regulating the balance between osteoclasts and osteoblasts, thus affecting bone remodeling. Conversely, *OPG* acts as a distraction receptor for *RANKL*, avoiding its interaction with *RANK* and hence obstructing osteoclast differentiation. This regulation is vital for preserving bone homeostasis, as the right balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption is essential for normal bone health. Changes in the expression of these genes can considerably affect the ripening and function of osteoblasts and osteoclasts, contributing to various bone pathologies, including osteonecrosis [118]. Samara et al. proposed that the expression mechanisms of *OPG*, *RANK*, and *RANKL* may vary in different bone conditions, particularly in osteonecrosis. These molecules are crucial regulators of bone remodeling, and their altered expression in the necrotic areas of bone could significantly impact the progression of bone degradation and repair. The study suggests that changes in the balance of *OPG*, *RANK*, and *RANKL* expression could exacerbate the pathological remodeling process, contributing to the progression of osteonecrosis. By influencing osteoclast activity and disrupting the normal balance between bone resorption and formation, these factors may play a pivotal role in the degeneration of the bone structure observed in conditions like ANFH. Understanding these mechanisms is essential for developing therapeutic strategies to address bone remodeling defects in osteonecrosis [114].

BMPs are critical growth factors that play a central role in regulating bone remodeling and healing. Belonging to the transforming growth factor-beta superfamily, BMPs are renowned for their capacity to stimulate the differentiation of MSCs into osteoblasts, the specialized cells responsible for bone formation. Through this process, BMPs facilitate the repair and regeneration of bone tissue by promoting osteogenesis and enhancing the body's ability to recover from bone injury. Their pivotal role in both bone development and healing underscores their therapeutic potential in conditions such as avascular necrosis and other bone-related disorders. BMPs play a critical role in bone repair following injury or disease, such as in the context of osteonecrosis, where they facilitate the healing process by promoting angiogenesis, osteogenesis, and cartilage repair. BMPs, particularly *BMP-2*, *BMP-4*, and *BMP-7*, have been extensively studied for their therapeutic potential in enhancing bone regeneration and treating bone-related disorders, including fractures, non-union fractures, and conditions like avascular necrosis. Dysregulation of BMP signaling can lead to impaired bone healing or pathological bone remodeling, underscoring its importance in maintaining bone homeostasis and integrity [114, 119]. The introduction of osteogenic BMPs, including BMP-2 and BMP-7, at bone and non-bone sites induces the formation of both bone and cartilage. These BMPs primarily serve as differentiation signals, guiding mesenchymal cells to differentiate into osteogenic and chondrogenic cells that contribute to the formation of bone and cartilage [120].

## Genetic avascular necrosis

Although the majority of ANFH cases are sporadic, there have been documented instances of familial occurrences, where multiple individuals within the same

family are affected. These familial cases suggest a potential genetic predisposition or inheritance pattern that could contribute to the development of ANFH, warranting further investigation into the genetic factors that may influence susceptibility to this condition. Understanding these familial patterns may provide insights into the underlying mechanisms of ANFH and offer opportunities for early identification and intervention in at-risk populations. While genetic factors are believed to contribute to the development of ANFH, the specific causative gene remains unidentified [120]. Mutations in the *COL2A1* gene have been associated with ANFH, particularly in cases involving both sides of the body. They are inherited in an autosomal dominant manner, as observed in a Japanese family. The specific mutation, p.G1170S, results in an amino acid substitution that disrupts the Gly-X-Y triple-helix repeat, a crucial structural component of type II collagen.

Furthermore, patients with ANFH have been shown to have abnormally large-diameter collagen fibrils in the epiphyseal cartilage [121]. This finding suggests that abnormal type II collagen may play a crucial role in the development of inherited ANFH, potentially contributing to the structural defects observed in the affected individuals. The disruption of collagen fibril formation due to the *COL2A1* mutation could impair the integrity of the femoral head, leading to the onset of avascular necrosis in genetically predisposed individuals [120]. In a 2008 study, Peiqiang et al. reported the same *COL2A1* mutation as being responsible for pathology specifically affecting the hip joint. This mutation presents as a spectrum of conditions, including isolated precocious hip osteoarthritis, ANFH, and Legg-Calve-Perthes disease, with the onset of these conditions occurring at varying ages depending on the individual. This outcome further supports the notion that mutations in *COL2A1* can contribute to hip joint-specific pathologies, including those seen in ANFH.

Several cytokines and growth factors, including *OPG*, *RANK*, and *RANKL*, have been identified for their role in modulating bone cell activity and regulating the bone remodeling process [119, 121]. The balance between bone resorption and formation is crucial for maintaining the integrity of the bone microenvironment. When this balance is disrupted, with an increase in bone resorption and a decrease in bone formation, the femoral head can collapse. The mechanisms outlined previously can contribute to this disruption by favoring bone resorption, thereby leading to the development of ANFH.

### Clinical implications: A wake-up call on the deteriorating bone

In the early stages of ANFH, patients may experience fatigue and lethargy, often attributed to factors such as poor posture, prolonged pressure on the bone, or complications related to obesity and a sedentary lifestyle. Clinical investigations have indicated that interventions such as intramuscular injections of vitamin B2, implantation of cryogels containing *VEGF* and *BMP-4*, or hyperbaric oxygen therapy can stimulate angiogenesis. This process ensures the supply of oxygen and nutrients to the tissue by forming alternative vascular pathways. When plaque formation obstructs blood flow to the bone, coagulopathy becomes a critical clinical issue. Endothelial dysfunction not only disrupts normal vascular function but also initiates inflammatory signaling, further compromising blood circulation [122].

In orthopedic research, particularly regarding complex skeletal pathologies like ANFH, it is crucial to conduct thorough tests and clinical trials to understand the underlying mechanisms fully. Based on current perspectives, one might argue that therapies such as oral, sublingual, or intravenous nitric oxide administration; intravenous dimethyloxalylglycine infusion; oral supplementation of Icariin, statins, L-arginine; as well as the use of anticoagulants, angiotensin-converting enzyme inhibitors, and angiotensin-II receptor blockers could offer significant benefits for preserving and protecting endothelial health [122].

## Conclusion

Avascular necrosis of ANFH is a multifactorial disease that involves endothelial dysfunction, disruptions in the coagulation pathway, lipid biosynthesis, and apoptosis, leading to compromised bone remodeling. The current therapeutic strategies aimed at regulating angiogenesis and endothelial health, including the use of pro-angiogenic factors, anticoagulants, and metabolic modulation, offer promising potential for reversing ischemic damage and preventing femoral head collapse. However, clinical trials are necessary to refine these strategies and determine their optimal application at different stages of the disease. Additionally, understanding the genetic basis of inherited ANFH could lead to the development of targeted interventions for individuals at higher risk. A multidisciplinary clinical approach that considers endothelial dysfunction, angiogenesis, and coagulation is crucial for enhancing patient outcomes and minimizing the need for invasive surgical interventions.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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### Authors' contributions

Conceptualization: Amir Aminian and Arash Aris; Writing the original draft: Khatere Mokhtari; Review & editing: Amir Aminian and Arash Aris; Supervision and project administration: Arash Aris; Investigation: All authors.

### Conflict of interest

The authors declared no conflict of interest.

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