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Femoral head avascular necrosis: etiopathogenesis, diagnostics and treatment – literature review

Vėjas Jokubynas[1]

[1]*Faculty of Medicine, Vilnius University, Vilnius, Lithuania*

Abstract

Background. Avascular necrosis of the femoral head is characterized by diminished blood flow to the femur's head, which leads to osteonecrosis, and results in the eventual structural collapse of the femoroacetabular joint. Changes in blood supply can arise due to a traumatic incident or stem from a non-traumatic origin (corticosteroids usage; alcohol consumption). To date, there is no consensus on treatment, and existing methods are controversial.

Aim: Review the literature on femoral head avascular necrosis and present its etiopathogenesis, diagnostic and treatment options.

Methods. A literature review was performed on PubMed using the keywords “avascular necrosis,” “femoral head,” and “osteonecrosis,” focusing on articles published in the last 12 years, excluding non-English and those centered solely on surgical treatments.

Results. Fractures of femur and hip dislocations are the most frequent traumatic causes of avascular necrosis. Cortisone-like drugs and excessive spiritis consumption were traditionally viewed as the primary contributing factors for emerging avascular necrosis. Recent studies emphasize impaired angiogenesis, coagulopathy and endothelial dysfunction as significant risk factors. Magnetic resonance imaging remains the gold standard for diagnosis, while nuclear diagnostic methods are used for predicting prognosis. Biphosphonates, statins, vasodilators prove to be effective but remain to be prescribed without guidelines. For patients with early disease, it is commanly recommended to do decompression of femoral head core.

Conclusions. Impaired angiogenesis, coagulopathy and endothelial dysfunction are identified as predisposing factors for AVN. Pharmacotherapy and core decompression are effective therapies for low stage disease.

Keywords: avascular, femur, head, necrosis, osteonecrosis.

1. Introduction

Aseptic necrosis of the femoral head, clinically known as avascular necrosis, is a progressive degenerative disorder characterized by the gradual deterioration of bone tissue, which is primarily initiated by a significant reduction in blood flow to the subchondral bone (1,2). Reduction of blood flow leads to a cascade of cellular events that compromise bone integrity, function and inability to remodel over time, which can cause structural collapse of the femoral head and subsequent joint dysfunction (1,2,3). This vascular compromise leads to the death of osteocytes and culminates in bone tissue necrosis without infection (2). The pathogenesis of AVN is multifactorial and complex, with exact mechanisms remaining unclear (3). Recognized risk factors for avascular necrosis include chronic excessive spiritrs consumption, long-term use of steroids, and a range of underlying medical conditions such as systemic lupus erythematosus, sickle cell disease, coagulopathies, and malignancies (2,4). Additionally, interventions like high-dose radiation therapy and previous surgical procedures on the hip joint can significantly contribute to the development of this condition (2,3). AVN typically manifests in physically active individuals aged 20 to 40 (1,4). Interestingly, AVN is one of the leading causes of total hip arthroplasty in patients younger than 50 years old (3, 4). Traumatic events, such as displaced femoral neck fractures or hip dislocations, can precipitate AVN by disrupting blood flow through the lateral epiphyseal vessels (4). Displaced fractures, which cause significant disruption to the vascular supply of the femoral head, show more than double the risk of developing avascular necrosis (AVN) compared to non-displaced fractures, with AVN occurring in approximately 15% of displaced cases versus around 6% of non-displaced ones (5). Non-traumatic AVN, on the other hand, is frequently linked to high corticosteroid doses and chronic alcohol abuse (6). The increase in AVN cases during the COVID-19 pandemic has been linked to the widespread administration of high-dose corticosteroids such as prednisolone (7). Research has shown that corticosteroid doses exceeding 2 grams of prednisone equivalent per day are associated with a prevalence of AVN in approximately 67 out of 1,000 individuals (7). Furthermore, each 10 mg/day increase in corticosteroid dosage raises the risk of developing AVN by 3.6% (7). The role of alcohol in the development of AVN, though not fully elucidated, is significant, with alcohol abuse accounting for 20–30% of cases (1,7). Chronic alcohol consumption is believed to contribute to AVN by increasing intracellular triglyceride accumulation, leading to osteocyte pyknosis and diminished bone formation by promoting the differentiation of stromal cells into adipocytes (8). Despite these identified risk factors, approximately 30% of non-traumatic AVN cases remain idiopathic (1). This uncertainty has led to investigations into the molecular pathology of AVN, revealing that impaired angiogenesis, coagulopathies, and endothelial dysfunction play crucial roles in disease progression (9). These findings have introduced new therapeutic opportunities, particularly in early-stage AVN. Pharmacological agents like bisphosphonates, statins, and vasodilators are currently being explored as potential treatments, although there are no standardized guidelines for their use (8). Surgical interventions for AVN vary based on the stage of the disease. Joint-preserving procedures, such as core decompression and osteotomy, are generally recommended for younger patients in the pre-collapse stage (2,8). These techniques aim to delay the need for total joint replacement by slowing disease progression (8). However, in advanced cases where the femoral head has already collapsed and joint integrity is significantly compromised, total hip

arthroplasty (THA) remains the definitive treatment (8).

2. Methods

A comprehensive literature review was performed utilizing the PubMed database, employing the search terms “avascular necrosis,” “femoral head,” “pharmacotherapy,” and “osteonecrosis.” The analysis focused on English-language articles published within the last decade (2014-2024). After applying the established inclusion criteria, a total of 39 scientific articles were deemed suitable for this review. This systematic approach ensures a robust evaluation of the current understanding and advancements in the pharmacological management of avascular necrosis.

3. Results

3.1. Etiopathogenesis

Avascular necrosis (AVN) of the femoral head is a multifactorial condition, with its precise pathomechanism still not fully elucidated (3). The onset of AVN is believed to stem from various factors, including underlying medical conditions, genetic predispositions or even some medications, which collectively increase the risk of vascular impairment and bone ischemia (10). In adults, the femoral head's primary vascular supply originates from the rami circumflexi medialis et lateralis of the arteria profunda femoris, branching from the arteria femoralis (12). These vessels are crucial for sustaining the subchondral bone and cartilage, with the medial circumflex artery being particularly important, as it supplies the majority of the femoral head (3). Disruption of this delicate microvascular network, whether due to trauma, thrombosis, or other pathological mechanisms, can rapidly compromise the oxygenation and nutrient delivery to osteocytes, setting the stage for ischemic bone necrosis and subsequent joint degeneration (12). The obstruction of these subchondral microcirculatory pathways, particularly the retinacular vessels, is often responsible for ischemia and osteonecrosis (11). If left untreated, AVN has been reported to cause secondary degenerative osteoarthritis in approximately 68-81% of patients, often resulting in significant hip mobility limitations due to accumulated microfractures within the necrotic bone (12). Various systemic diseases increase susceptibility to AVN by impairing oxygen and nutrient supply to osteocytes, leading to chronic bone ischemia (1). Hemoglobin disorders, including sickle cell disease and Gaucher’s disease, along with other anemias, reduce the blood’s oxygen-carrying efficiency, contributing to chronic bone ischemia and subsequent necrosis (2,13,15). Non-traumatic triggers of AVN, such as prolonged corticosteroid use and chronic alcohol consumption, are linked to dysregulated adipogenesis (6,7). This process involves an increase in adipocyte size and number, culminating in accumulation of lipids inside the cells. The resulting rise in intramedullary pressure compresses surrounding blood vessels and promoting vascular damage what initiates a chain of pathological changes, including coagulopathy and ischemia. (6). New insights into AVN research point to the vital roles played by defective angiogenesis, blood clotting disorders, and endothelial dysfunction in its development. A 2023 study challenged traditional views by proposing that these three mechanisms—collectively referred to as the "molecular troika"—are central to AVN development (17). Normally, angiogenesis compensates for ischemic events by promoting new blood vessel formation to re-establish tissue perfusion (18). However, in AVN patients, this process is impaired, resulting in insufficient and abnormal neovascularization. The newly formed vessels are often leaky and structurally defective, leading to local edema and further aggravating

ischemia (18). The resultant failure to restore adequate blood flow to the necrotic femoral head initiates a cascade events that promotes joint to collapse (18). Coagulopathy, another pivotal factor in AVN, involves a disruption of the delicate balance between procoagulant and anticoagulant factors. This imbalance leads to excessive clot formation and impaired thrombolysis, causing the formation of intravascular thrombi that obstruct blood flow and exacerbate tissue ischemia (19). What is more, Endothelial dysfunction, characterized by dysregulation between vasoconstriction and vasodilation, hampers normal blood flow control and exacerbates inflammation (2,4). Endothelial cells fail to produce adequate amounts of vasoactive molecules, leading to vascular dysregulation and promoting a chronic pro-inflammatory state that accelerates osteonecrosis (20). This triad of angiogenesis impairment, coagulopathy, and endothelial dysfunction has emerged as a critical target for novel therapeutic approaches (1). Current pharmacotherapy targets the restoration of angiogenesis, improvement of anticoagulant activity, and correction of endothelial dysfunction to slow AVN progression. (21-23). These therapies seek to address the fundamental pathophysiological processes driving AVN progression, providing hope for improved management strategies that may delay or even prevent the need for invasive surgical interventions such as total hip arthroplasty (24).

3.2. Diagnostics

Diagnosis of AVN combines clinical examination findings with imaging studies. Patients typically report progressive hip pain, stiffness, and crepitus, often following a phase of minimal or intermittent symptoms (3,9). Physical examination frequently reveals restricted hip motion, with pain notably exacerbated during forced internal rotation (3). Prompt detection of AVN is key for better outcomes; however, standard X-rays often fail to detect early-stage changes. (25). Conversely, magnetic resonance imaging is recognized as the definitive method for diagnosing osteonecrosis, providing highest sensitivity (90-95%) and specificity (85-95%) in identifying early-stage avascular necrosis (26.27). MRI can detect subtle early indicators, including bone marrow edema and joint effusion in the proximal femur, which are crucial for prognosis and often invisible on computerized tomography (CT) scans (25).

Though CT scans provide detailed images of bone structures, their utility in early AVN diagnosis is limited compared to MRI (27). In cases where joint effusion or early marrow changes are suspected, MRI is preferred due to its ability to visualize soft tissue and early bone changes that precede radiographic findings. Moreover, nuclear imaging modalities such as single-photon emission computerized tomography (SPECT/CT) have been explored as diagnostic tools (25). A 2020 study demonstrated that SPECT/CT is particularly useful for determining AVN prognosis in patients over the age of 58 with displaced femoral fractures, though it offers less benefit in diagnosing AVN in younger or middle-aged individuals without fractures (26). PET and technetium bone scans may also help assess AVN progression and severity, though their roles are secondary to MRI, as they can help identify metabolic activity and predict the extent of necrosis. However, their use remains secondary to MRI for most clinical situations (27). Recent advancements in imaging have focused on diffusion-weighted MRI and dynamic contrast-enhanced MRI, which offer deeper insights into tissue perfusion and necrotic bone activity (30). These imaging techniques can enhance early diagnostic accuracy and aid in treatment planning by enabling real-time assessment of ischemic damage. Recent studies indicate that integrating advanced imaging with biochemical

markers of bone turnover may improve diagnostic and prognostic accuracy in AVN (31).

3.3. Treatment

Most AVN patients are middle-aged and lead active lifestyles, which makes conservative treatment options more favorable than surgical interventions (10). The main goals of pharmacotherapy in AVN management are to maintain hip function, delay collapse of the femoral head, alleviate pain, and slow necrotic progression. Various pharmacological agents have been proposed, including anticoagulants, statins, vasodilators, and bisphosphonates, among others currently under investigation (3). However, the efficacy of these treatments remains limited, and no definitive guidelines for their use have been established due to the lack of robust evidence from clinical trials (34). While bisphosphonates, which inhibit osteoclast activity to reduce bone resorption, have been tested, results from clinical trials have been inconsistent. While some trials suggest that bisphosphonates may slow down the progression of AVN by preventing bone degradation, the overall evidence remains inconclusive, making it difficult to establish standardized recommendations regarding the dosage and duration of treatment (34). Similarly, other pharmacological agents such as anticoagulants and statins have yielded inconsistent outcomes when tested in AVN populations (34). Despite these efforts, many patients eventually progress to the point where surgical intervention becomes necessary. An interesting area of research is extracorporeal shockwave therapy (ESWT), which has gained attention for its potential to promote tissue regeneration and relieve pain. Several studies published in 2015 demonstrated promising results, with some subjects even showing complete regression of MRI-detected necrotic changes after ESWT (1). However, despite these optimistic findings, a large proportion of AVN patients treated with pharmacotherapy eventually require surgical intervention. Surgical management of AVN typically involves joint-preserving procedures for younger patients in the pre-collapse stages of the disease, while total hip arthroplasty (THA) is reserved for patients with advanced-stage AVN and significant femoral head collapse. Core decompression is the most frequently utilized joint-sparing technique for adressing early-stage avascular necrosis (2). This procedure involves the removal of a core of bone from the affected area, which helps reduce intraosseous pressure, enhances blood flow, and promotes healing within the necrotic region. By facilitating better vascularization, core decompression can slow the progression of AVN and potentially delay or prevent the need for total joint replacement (9). As a first-line treatment, it is particularly effective when initiated during the early stages of the disease, where intervention can lead to favorable outcomes for patients (2). The principle behind CD is to relieve intraosseous pressure within the femoral head and restore blood flow by drilling into the necrotic bone, thus facilitating new blood vessel formation. This technique is cost-effective and has demonstrated favorable long-term outcomes, with clinical improvements observed in many patients Over time, the procedure has evolved to include multiple drilling, which has shown greater efficacy in reducing intraosseous pressure and enhancing revascularization (6).

However, recent studies suggest that vascularized bone grafts, particularly vascularized fibular grafts, may offer superior outcomes compared to their nonvascularized counterparts due to the enhanced blood supply they provide to the affected area (13). Osteotomies, which involve cutting and realigning the bone to redistribute weight-bearing forces, are generally not recommended in AVN treatment because they can lead to joint instability and

accelerate the development of arthritis (3). For patients with advanced disease and femoral head collapse, THA remains the definitive treatment option, offering significant improvements in pain relief and joint function.

3.4. Novel treatment options

Since 2010, research has focused on mesenchymal stem cell (MSC) therapies as a potential treatment for AVN (13). Since then, there has been growing interest in this therapeutic approach, with multiple studies focusing on intralesional autologous bone marrow-derived MSC therapies for femoral head osteonecrosis. A 2023 meta-analysis of 18 studies confirmed that MSC-based therapies support revascularization and promote bone tissue regeneration., as well as providing improved functional outcomes and reduced pain, as measured by functional scores and visual analog scales (18). Due to their regenerative properties, MSCs present a promising therapeutic option for early-stage AVN, potentially delaying the need for surgery.

Moreover, advances in the understanding of MSC biology have led to innovative approaches that may enhance the therapeutic efficacy of MSCs. For example, a study by Zhao et al. demonstrated that pretreating MSCs with angiotensin II significantly enhances their ability to promote angiogenesis in the femoral head, suggesting that MSCs' therapeutic potential can be augmented by manipulating their microenvironment or priming them with specific agents (18). In this context, angiotensin II may boost the production of angiogenic factors like VEGF, thereby promoting neovascularization and improving blood supply to the necrotic tissue.

These developments highlight the future potential of MSC therapies in tissue engineering, suggesting that recent advances are progressively moving toward a clinically viable and effective solution for AVN. However, while the promise of MSC therapy is evident, more extensive clinical trials are needed to determine optimal cell delivery methods, dosages, and the long-term safety of these interventions before they can become a mainstream treatment option.

3.5. Conclusions

The pathophysiological processes associated with avascular necrosis of the femoral head are intricate and involve several interrelated factors. The primary factors involved are diminished angiogenesis, coagulation disorders, and endothelial dysfunction, all of which lead to ischemia and bone necrosis. These mechanisms contribute to the ischemia and subsequent bone necrosis that characterize the disease. While conservative approaches like pharmacotherapy and shockwave therapy show promise for early-stage AVN, their success rates vary, and many patients eventually require surgical intervention. Core decompression and vascularized bone grafting represent key surgical options aimed at preserving joint function in earlier disease stages, while total hip arthroplasty (THA) is the treatment of choice for advanced cases. Recent advances in stem cell therapies, particularly with mesenchymal stem cells (MSCs), offer promising new avenues for tissue regeneration and revascularization. However, more research is necessary to establish MSCs as a viable treatment option, with further clinical trials needed to optimize protocols and assess long-term outcomes. The future of AVN management may increasingly involve a combination of innovative medical therapies and established surgical techniques to improve patient outcomes.

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