Pathogenesis of atraumatic osteonecrosis of the femoral head

Symptomatic hip osteonecrosis remains a disabling condition with a poorly understood pathogenesis and aetiology. Most likely a common final pathway exists involving compromised subchondral microcirculation. Numerous and varied associations are linked with this condition. Corticosteroid use, alcohol intake, and smoking are thought to be major contributing factors. Several treatments have demonstrated the ability to optimise femoral head circulation, interrupt bone resorption and preserve subchondral bone. We highlight current understanding of the pathogenesis of atraumatic osteonecrosis of the femoral head and outline possible future patient specific approaches.

There is little evidence to show that early identification and intervention alter the final outcome, and the optimal management approach remains uncertain and controversial. Several treatment options have been described with the aim of preventing femoral head collapse. These include non-operative management and joint preserving procedures. Once femoral head collapse has occurred total hip replacement remains the only reliable treatment option.

National Joint Registry data cites osteonecrosis as being the indication for primary total hip replacement surgery in 2% of cases. Despite extensive published reviews the exact pathophysiological mechanism remains uncertain. Several treatments have demonstrated the ability to optimise femoral head circulation, interrupt bone resorption and preserve subchondral bone, however the development of effective prophylaxis or biological treatments remain a distant prospect. This article highlights current understanding of the pathogenesis of atraumatic osteonecrosis of the femoral head and outlines possible future patient specific approaches.

Introduction

Despite significant research, symptomatic hip osteonecrosis remains a disabling condition with a poorly understood aetiology and pathogenesis, often requiring total hip replacement at a young age. The UK incidence is estimated to be 3 per 100,000 and numbers are increasing. This may be due to increased reporting, the increasing use of predisposing therapies (corticosteroids, chemotherapeutic agents and antiretroviral therapy), as well as the increasing prevalence of many associated diseases and risk factors.
Pathophysiology

One problem hampering the identification of a unifying pathophysiological pathway is the numerous and varied associations of the disease. Corticosteroid use, alcohol intake, and smoking are thought to be major contributing factors in more than 80% of cases.[1]

Other recognised associations include; immunosuppressive therapy, autoimmune diseases such as Systemic Lupus Erythematosus (SLE) and Rheumatoid arthritis, inherited and acquired haematological and thrombotic disorders, malignancies, metabolic disorders, and renal failure. A clear aetiological role has been established for some of these factors, but not for the majority.[10,11,14] Vascular occlusion can occur as a result of thrombosis, emboli, nitrogen bubbles, or sickle cell crisis.[15]

Extra vascular haemorrhage and the cellular elements of bone marrow can result in extra-vascular compression of both arteries and veins. Femoral head blood vessels can also be damaged by vasculitis, irradiation, or chemical toxicity.[15] The early stages of pathophysiology remain unclear as patients are largely asymptomatic and present later in the disease process. In all probability a common final pathway exists with compromised subchondral microcirculation (Figure 4).[10,11,14] The terminal event is osteocyte death induced by either critical ischaemia or the action of toxins, on a background of genetic predisposition, metabolic factors and local factors affecting the blood supply.[10,11,15]

**Corticosteroids**

High dose corticosteroid use is one of the most common risk factors for osteonecrosis of the femoral head.[16-21] The extent of use that constitutes a risk is still under debate with conflicting reports on the importance of peak or cumulative dose.[22,23] Although many patients receiving corticosteroid therapy have at least one other confounding factor, often smoking or alcohol use, corticosteroid use, especially in high dose, is an independent risk factor. Hypotheses centered on the concepts of small vessel occlusion by fatty emboli, and a reduction in intraosseous blood flow resulting from adipocyte cell hypertrophy causing increased compartment pressure within the femoral head have been proposed.[24-27] Impairment of circulating endothelial progenitor cells has also been implicated.[28] Corticosteroids have also been shown to alter vascular sensitivity to vasopressors and vasodilators, both with having the ability to cause reduced blood flow and ischaemia.[29] Vasodilators, such as Iloprost, acting on the terminal vascular bed could counteract this vasopressor effect.[30] Jager reported a significant improvement in pain, functional and radiological outcomes in patients with bone marrow oedema and the early stages of femoral head osteonecrosis following the use of Iloprost.[31]

**Alcohol**

Alcohol abuse is a well established risk factor.[32] Various cellular events have been implicated including; fat emboli, adipocyte hypertrophy, venous stasis, and increased cortisol levels.[33] Excess alcohol use has been shown to cause multi-potent bone marrow cells to be driven into an adipocyte cell lineage, causing reduced osteoblastic potential.[34] This has also been demonstrated in idiopathic osteonecrosis,[35] and has led to interest in the use of pro-osteogenic substances such as Statins to promote repair in necrotic bone.[36]
Thrombophilia and hypo-fibrinolysis have both been shown to cause venous thrombosis and impaired blood flow in the femoral head. Patients with inherited coagulation disorders may be at increased risk of osteonecrosis of the femoral head. It may be possible to screen those individuals with an autosomal dominant coding defect. Raised coagulation factor levels have also been reported in those without an identifiable inherited coagulation disorder. The exact causative role of hypercoagulability in osteonecrosis remains controversial. Thrombophilia is not always seen in cases of osteonecrosis of the femoral head, and is often seen in other conditions affecting the femoral head including osteoarthritis. An underlying genetic predisposition to form microvascular thrombi through abnormally low rates of fibrinolysis or thrombophilia can lead to amplified thrombus formation resulting in impaired blood flow in the osseous circulation. Genetic polymorphisms involved in corticosteroids and alcohol metabolism, and other key factors in the coagulation cascade have been identified in cases of familial autosomal dominant osteonecrosis of the femoral head. Anticoagulants have a potential preventive role in slowing progression of primary hip osteonecrosis, which could reduce the incidence of total hip replacement surgery in this patient group.

Systemic Lupus Erythematosus and Anti-Phospholipid Syndrome

Osteonecrosis, often multifocal, frequently develops in patients with SLE a relatively short time after commencing corticosteroid therapy. There are conflicting reports around the association of anti-phospholipid antibodies in SLE and the development of osteonecrosis. Patients with SLE using corticosteroids have a higher risk of developing osteonecrosis than patients not receiving corticosteroids.

HIV

Osteonecrosis has been linked to HIV, possibly because these patients have additional risk factors (corticosteroids, chemotherapy, and alcohol) or secondarily because of antiretroviral therapy.

Genetic biomarkers

Various immune mechanisms have been studied and several genes and biomarkers that may play a role in the development of osteonecrosis have been identified, and are summarised by Mont in the recent review (Figure 5). Genetic polymorphisms involved in corticosteroids and alcohol metabolism,

Smoking

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Biomarker Source and Function

**GENES**
- **ApoB C7623T**
  - Gene for catalase
  - Encodes proteins that are important in lipid transport.
  - Catalase is a major antioxidant enzyme.
- **Various cytokine polymorphisms**
  - Certain genotypes of IL-1a, TGF-b, IL-10, IL-23, IFN-a, and TNF-a are associated with osteonecrosis.
- **Overexpression of p53-mediated apoptosis**
  - Tumour suppressor protein linked to osteocyte apoptosis
- **Matrix protein polymorphisms**
  - BMPR2, BMP-2, 4, 6, and 7 as well as MMP-2
- **Lipid protein polymorphisms**
  - Genes that regulate lipid biosynthesis.

**PROTEINS**
- **Adiponectin**
  - Protein highly expressed in adipocytes
- **Interleukin-33**
  - Interleukin expressed on osteoblasts, endothelial cells, and epithelial cells; up regulated in pro-inflammatory situations.
- **Tissue Plasminogen Activator**
  - Various serum proteins identified in a comparative analysis of serum proteomes.
- **Endothelial cell markers**
  - Endothelial cell markers included vWF antigen levels, factor VIII, vWF.
- **Thrombotic factors**
  - These include plasminogen, D-dimer, protein-C, and antithrombin III.
- **VEGF**
  - Involved in vascular repair and vasculogenesis.
- **Cryofibrinogen**
  - Promotes thromboembolic events by inhibiting plasmin, fibrinolysis, and augmenting fibrinogen.

**Discussion**

The exact pathogenesis of osteonecrosis of the femoral head together with the optimal treatment approach remains unknown. Current research demonstrates that both corticosteroids and alcohol promote adipogenesis at the expense of osteoblastic proliferation or function. Although the exact mechanisms may differ, the final common pathway is of bone marrow fat oedema, impaired vascularity, and reduced reparative capacity contributing to cellular death and osteonecrosis. The role of underlying genetic predisposition is not fully understood. Various authors have attempted to use laboratory biomarkers for diagnosis, however, clinical imaging remains the gold standard for diagnosis. The key to future successful treatment lies in early identification of at risk individuals, and quantifying risk in terms of clinical and pathophysiological characteristics. Future studies will need to focus on ways to screen the ‘at risk groups’, allowing risk factor modification or elimination, and timely or ideally prophylactic treatment. This would allow early and focused intervention to prevent osteocyte death and hopefully to prevent femoral head collapse.

**References**

References can be found online at www.boa.ac.uk/publications/JTO or by scanning the QR Code.

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**Figure 5: Potential Biomarkers**
References


