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## Etiology of avascular osteonecrosis of the femoral head

Titre Français : Etiologies de l'ostéonécrose aseptique de la tête fémorale

P. Guggenbuhl\*, F. Robin, S. Cadiou, JD. Albert

Service de Rhumatologie Centre Hospitalier Universitaire de Rennes, France

\*corresponding author : P. Guggenbuhl

[pascal.guggenbuhl@chu-rennes.fr](mailto:pascal.guggenbuhl@chu-rennes.fr)

## **Abstract**

Avascular osteonecrosis of the femoral head (ONFH) is one of the causes of hip pain that clinicians need to know about. In many cases, it is a fortuitous discovery when pelvic X-rays is performed for another reason. In the other cases, pain reveals the disease. For the rheumatologist a major part of the job is to look for a cause. An etiology can be found to ONFH in about 70% of the cases. Some of them are evident and the context give the diagnosis (corticosteroids, alcohol abuse...). However, in many cases, additional tests to imaging are required to make the causal diagnosis. In some cases, the treatment of the cause can prevent the recurrence of the disease.

## **Résumé**

L'ostéonécrose aseptique de la tête fémorale (ONFH) est l'une des causes de douleur de hanche que les cliniciens doivent connaître. Dans de nombreux cas, il s'agit d'une découverte fortuite lorsque les radiographies pelviennes sont effectuées pour une autre raison. Dans les autres cas, la douleur révèle la maladie. Pour le rhumatologue, une grande partie du travail consiste à rechercher une cause. Une étiologie peut être trouvée à l'ONFH dans environ 70 % des cas. Certaines sont évidents et le contexte donne le diagnostic (corticostéroïdes, abus d'alcool...). Cependant, dans de nombreux cas, des examens complémentaires à l'imagerie sont nécessaires pour établir le diagnostic causal. Dans certains cas, le traitement de la cause peut empêcher la récurrence de la maladie.

**Keywords:** avascular osteonecrosis; osteonecrosis; corticosteroids; alcohol; avascular osteonecrosis of the femoral head

## 1. Introduction

Avascular osteonecrosis of the femoral head (ONFH) is one of the causes of hip pain that clinicians need to know about. In many cases, it is a fortuitous discovery when pelvic X-rays is performed for another reason. In the other cases, it is pain that reveals the disease. Hip pain is most commonly pain felt in the groin and anterior thigh, of sudden appearance after an effort or a change of position. Pain can be initially strong with nocturnal awakenings mimicking an inflammatory pain. However, rapidly and typically, the pain become mechanical, occurs when the patient put his foot on the floor and disappear in discharge with a functional impotence and variable joint limitation amplitudes, notably internal rotation. It is a differential diagnosis of all hip diseases, especially arthritis or osteoarthritis but also bone diseases. The context, and above all imaging (which is covered in another chapter of this issue) make the diagnosis.

For the rheumatologist, a major part of the job is to look for a cause and in some patients, it is the opportunity to discover an unknown disease. For others it is a complication of an already known disease.

In this paper, we will review the main causes of ONFH emphasizing the most frequent ones and those for which an etiological treatment can be considered.

The term “avascular” osteonecrosis suggests an interruption of the physiological vascularization. The femoral head vasculature is a terminal one and as in heart or brain, an arterial obstruction or interruption leads to organ necrosis, in this case osteonecrosis [1]. However, ONFH physiopathology is more complex and it is admitted that it is the result of an interaction between vessels damages, alteration of bone cells, especially osteocytes which are mechanosensory cells and some non-well-known genetic factors [2].

Two kinds of mechanisms can result in ONFH: **traumatism**s, which constitute local causes or **systemic**

**conditions.** In the first case, ischemia is secondary to generally a huge traumatism followed by a fracture or a luxation and vasculature damages. It can be sometimes secondary to micro traumatisms. In the second case, the vascular lesions can come from pathologic intravascular obstruction (lipids or gaseous microemboli; hypercoagulability state), extravascular compression (medullary adipocytes hypertrophy, intra-medullary edema, intra-medullary proliferation) or bone damages especially of osteocytes (drugs or alcohol cytotoxicity) [3]. Femoral head is the more frequent location of osteonecrosis. It may be due to its particular vascularization. The majority of the blood supply originates from the retinacula arteries supplying the superolateral weight-bearing portion of the femoral head [2,4].

## **2. Avascular osteonecrosis of the femoral head risk factors**

Clinicians have to check for risk factors, especially those, few, which can be modified or treated. It must be said that many mechanisms are common to all causes, most often intricate. In a few cases, not very well estimated (approximately 15 to 30%), no cause is identified and no cause is found [3,5,6] (Fig. 1).

### *a. The most frequents risk factors*

Corticosteroids and alcohol are the causal agents in more than 80% of the cases [7].

#### *i. Corticosteroids*

This is the most frequent cause of non-traumatic ONFH. In a series of 3000 cases of non-traumatic osteonecrosis, corticosteroids were in question in 30% of the cases, followed by alcohol, in 20%. Corticosteroids seemed to be more deleterious in case of systemic lupus erythematosus (SLE), another potential cause of ONFH [8]. If the risk increases with the increasing doses and the treatment duration, it is not possible to found thresholds in the literature. In a meta-analysis of Fifty-seven studies including 23,561 patients, Mont et al found that ONFH incidence was 6.7% if corticosteroid treatment exceeded

2 g prednisone-equivalent with a 3.6% increase with each 10 mg/d increase. A threshold superior to 20 mg/d increased the risk, which was lower if < 15 mg/d [9]. Even short periods of treatment with relatively low doses increase the risk. Dilisio found in a huge US cohort that patients who received one 21-tablet, 4-mg methylprednisolone taper pack taken over 6 days had an increased risk of 1.6 compared to patients who did not had this treatment [10].

Many mechanisms have been evoked to explain the occurrence of a steroid induced ONFH. At the bone remodeling level, osteocytes apoptosis and/or increase of osteoblast autophagy have been described. Adipocytes differentiation increase at the detriment of osteoblasts differentiation, which is similar in case of alcohol toxicity. This increase of adipocytes number and size with intracellular accumulation of lipids cause an increase in bone pressure and disruption in interosseous microcirculation and bone structural changes in the femoral head. Steroids induce vascular endothelial cells damages and a complex coagulopathy leading to vessels thrombosis. There is also a potential role for the microbiome, oxidative stress, genetic and epigenetic and mi-RNAs, which regulate the differentiation of mesenchymal stem cells into adipogenic or osteogenic progenitor cells. Finally the concept of “multi-hit hypothesis” as emerged from Kenzora and Glimcher [11], suggesting that a single mechanism is not sufficient to induce osteonecrosis; for example corticosteroids induced ONFH is more frequent in patients with SLE than in healthy people or patients with other pathological conditions [8].

## ii. Alcohol abuse

Overuse of alcohol has been associated to approximatively 20-30% of the patients who developed a hip osteonecrosis. As for steroid induced ONFH, several mechanisms have been suggested such as decreased bone formation, osteocyte apoptosis or excess lipid deposition; many of them seem likely to be shared. In an original way, it has recently be described that mi-RNAS could be aberrantly expressed in alcohol-induced osteonecrosis of femoral head, with bone or vessel genes targets including IGF2,

PDGFA, RUNX2, PTEN, and VEGF. These observations could be of physiopathological and diagnosis interest [12].

*b. The other classic risk factors*

i. Gaucher disease

Gaucher disease is a classic etiology of ONFH, very often in a context of multiple osteonecrosis. It is due to a deficiency in the lysosomal enzyme  $\beta$ -glucocerebrosidase, which leads to accumulation of glucocerebroside in the lysosomes of mononuclear phagocytes, predominantly in the liver, spleen, and bone marrow. Osteoarticular manifestations are often inaugural and contribute significantly to the morbidity and disability associated with Gaucher disease [13] [14].

ii. Systemic lupus erythematosus

Osteonecrosis in Lupus has been reported in 3-30% of the cases [15] and as said before, corticosteroids seemed to be a major risk factor. However, the susceptibility to steroids induced osteonecrosis seems to be stronger than for other diseases [8]. Very recently a genetic predisposition has been suggested with some Single Nucleotide Variations (SNVs) in NOS3, COL2A1, and CR2 genes, respectively involved in bone or cartilage formation and for CR2 in autoimmunity [16].

iii. Dysbaric osteonecrosis (Caisson disease)[17]

It is another very classic, but rare etiology of ONFH, outside of undersea divers and workers breathing compressed air or gas. The most accepted theory is that it is due to a long-term manifestation of sub-clinical decompression sickness (DCS). Decompression lead to dissolution of gas in blood with gas bubble formation and emboli in bone microcirculation with activation of coagulation process. The consequence is an increase in intraosseous pressure and osteonecrosis. Diaphysis osteonecrosis of the femur and the tibia can occur sometimes, with pain under load, sometimes very intense with a

significant risk of fracture.

#### iv. Organ transplantation and Chronic renal failure/hemodialysis

The prevalence of ONFH in organs transplantation has been estimated between 3 to 41%. Patients with renal transplant have been the most studied. Most of the studies are retrospective, with different steroids and immunosuppressive therapies regimen and imaging modalities. In a prospective study, the incidence was lower with an osteonecrosis of the femoral head in 11% of the hips [18]. The total dose of steroid received by the patients in the 2 weeks following renal transplantation is related to osteonecrosis development [19]. In a recent retrospective study, the decrease of the incidence of ONFH in kidney transplant recipients (4.1% at ten years after the transplantation) was attributed to the replacement of cyclosporine by tacrolimus over the last decade. Males were independently associated to osteonecrosis. The hypothesis of an ischemic steal syndrome due to the allograft kidney leading to an early osteonecrosis at the allograft side has been proposed [20]. It is probable that the decrease of steroids doses in the modern management of kidney transplantation is also implicated in the decrease of ONFH in kidney transplant recipients.

#### v. Hyperlipidemia

Hyperlipidemia is a classic cause of osteonecrosis. However, few studies have addressed this topic. In 112 patients (children and young adults) with acute lymphoblastic leukemia, 22 experienced symptomatic osteonecrosis. In this population, hyperlipidemia was associated with an increased risk of developing osteonecrosis with increased triglycerides and cholesterol levels. There was a tendency of an inverse relationship between higher HDL cholesterol and osteonecrosis. However, prolonged increase of LDL cholesterol was not associated with osteonecrosis [21]. High serum triglyceride level seems also to be a risk factor for ONFH in systemic lupus erythematosus [22].

#### c. Hematological disorders

i. Sickle cell disease

A chapter of this review is specifically dedicated to this etiology. The ONFH is frequent in this context due to the intravascular obstruction linked to the red globules shape. The clinical context generally help in the diagnosis.

ii. Leukemia and lymphoma

In acute lymphoblastic leukemia, chronic myeloid leukemia and acute myeloid lymphoma there is an increased risk of osteonecrosis. Steroids seems to be the major risk factor [15,23]. High doses of corticosteroids are the main explanation. Osteonecrosis is also a complication of bone marrow transplantation and graft versus host reaction in adults and children. The frequency has been estimated between 6% and 19%, 3 years after transplantation. ONFH is the most common localization. Steroids and immunosuppressants are the major risk factors [24].

*d. Less frequently [3]*

A great number of other causes have been described or published in smaller series, potentially related to osteonecrosis mechanisms described before: diabetes [25], Cushing disease [26], pancreatitis, intravascular coagulation [1], hyperuricemia/gout, HIV [27], hemochromatosis [28], radiation [29], smoking...

### **3. Conclusion**

A cause to ONFH can be found in a large number of cases. Some of them are evident and the context give the diagnosis (corticosteroids, alcohol abuse...). However, in many cases, additional tests to imaging are required to make the causal diagnosis. We propose a pragmatic approach beginning by the most frequent causes. Extra-articular symptoms and anamnesis are very important to consider (Fig. 1). In some cases, the treatment of the cause can prevent the recurrence of the disease.

### **Legend of figures**

Fig. 1. Progressive diagnosis diagram to determine the main causes of osteonecrosis of the femoral head from the most frequent causes (1) to the rarest causes (3).

**Conflict of interest: none**

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# Osteonecrosis of the femoral head

1

Corticosteroids

Alcohol

2

Lupus  
Organ transplantation  
Hyperlipidemia  
Dysbaric osteonecrosis

Gaucher disease  
Sickle cell disease  
Leukemia, lymphoma  
GVH

3

Diabetes, Cushing, pancreatitis, intravascular coagulation, hyperuricemia, HIV, Hemochromatosis, radiation, smoking