

# Osteonecrosis. What Is New?

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Osteonecrosis, also known as aseptic necrosis, is a pathological process that has been associated with numerous conditions. The pathogenesis of osteonecrosis and especially the treatment both remain an area of controversy. In this article we review the etiology and pathogenesis of osteonecrosis as well as the main therapeutic options.

**Key words:** Osteonecrosis. Avascular necrosis. Aseptic necrosis. Ischemic necrosis.

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### Osteonecrosis. ¿Qué hay de nuevo?

La osteonecrosis, también conocida como necrosis avascular, se ha asociado a numerosos procesos. Su patogenia y, especialmente, su tratamiento son motivo de controversia. En este artículo se revisan la etiología y la patogenia de la osteonecrosis y sus principales opciones terapéuticas.

**Palabras clave:** Osteonecrosis. Necrosis avascular. Necrosis aséptica. Necrosis isquémica.

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Osteonecrosis (ON), also known as avascular necrosis or aseptic necrosis, is a disease that has been related to multiple processes. Though in many cases the mechanisms that lead to ON are not completely clear, in others a deterioration of the vascularization of bone that produces necrosis of the bone tissue has been identified. It is a progressive process that can lead to fragmentation and sinking of the bone structure and to joint destruction secondarily, in a period of 3 to 5 years. Because ON affects mainly young adults between 20 and 40 years of age, its consequences are a real public health problem. The most frequent localization is the epiphysis and, although any part of the skeleton is liable to undergo ON, the femoral

head is the zone most frequently affected and the one in which there is the most experience regarding evolution and treatment; therefore, in this article, we will be referring especially to that localization.

### Epidemiology and Evolution

Though the true incidence of this process is not known, it is estimated that approximately 15 000 new cases present themselves each year in the United States, constituting 10% of the yearly 500 000 arthroplasties done every year in that country, with a male:female ratio of 8:1.<sup>1</sup> Because non-traumatic hip ON in its early stages is frequently asymptomatic, it is difficult to establish the natural history of this process. In spite of that, 68%-80% of patients with asymptomatic hip ON without treatment progress to the final stages of ON in 3 to 5 years, without any relationship to etiology and the time of evolution to collapse. 31%-35% will have a satisfactory evolution without surgery<sup>2</sup>; nonetheless, up to 50% of the cases require arthroplasty at 3 years since diagnosis and between 30%-70% of cases has bilateral affection of the hips.<sup>3</sup> Advance stages at the moment of diagnosis, the extension of the lesion (>50% of the femoral head) and its localization (anterolateral zone of the femoral head) are poor prognostic factors. The femoral head is the most frequent localization, but other sites can be affected also, among which the humeral head, the condyle of the femur, the proximal tibia and the carpal and tarsal bones deserve mention. Around 3% of patients present multifocal ON.<sup>1</sup>

### Etiology

Several causes associated to the development of ON have been described. In some, such as in proximal femur fracture, sickle cell anemia, or decompression illness, the cause seems evident, while in others, such as treatment with glucocorticoids (GC) or alcohol consumption, the cause is not so clear. The common denominator is the femoral head liability to ischemia, but the pathogenic mechanism is variable. In the case of a femoral fracture, compression or rupture of a blood vessel is the cause of ON, while in sickle cell anemia and in decompression illness, it is attributed to alterations in sinusoidal circulation. Several pathogenic mechanisms have been

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proposed in relation to the rest of the ON, such as vascular alterations secondary to atherosclerosis, coagulation defects, repeated microfractures, fat embolism, adipocyte hypertrophy, among others. For example, with respect to GC it has been described that the alterations in the metabolism of lipids associated to this treatment would favor the development of fat embolisms that would lead to micro vessel obstruction or would produce an increase in bone marrow fat that would lead to vascular insufficiency due to compression, leading to the development of ON. On the other hand, treatment with GC has also been associated to an increment in the production of endothelium vasoconstrictive substances such as endothelin 1, which could lower the tissue perfusion and favor the appearance of this complication.<sup>4</sup> Thrombophilia and hypofibrinolysis have also been implicated in the development of ON in some cases, causing intravascular coagulation in the bone tissue microcirculation that leads to venous or arterial thrombosis.<sup>4</sup> Osteocyte and osteoblast apoptosis has been pointed out in the past few years as an important probable etiopathogenic mechanism in this disease, concretely in relationship to ON due to GC and alcohol, signaling that it may be mediated, at least partially, by an increase in the local production of nitric oxide.<sup>5</sup> In patients with ON due to GC, an abundance of apoptotic osteocytes that affect the adjacent lining cells in the area of bone collapse have been observed. It has been proposed that this fact would lead to further bone collapse.<sup>6,7</sup> Therefore, osteocyte apoptosis seems to play a fundamental role in the local activation of osteoclasts to initiate bone resorption.<sup>8</sup> There has been several cases described recently of familial dominant autosomic ON linked to mutations in the collagen type II (*COL2A1*) gene.<sup>9</sup> Though this mutation constitutes an infrequent cause of ON, because it has not been observed in patients with idiopathic ON without a family history, it implicates the functional alterations of type II collagen in the development of some cases of ON.

### Frequent Causes of Osteonecrosis

Besides posttraumatic ON, be it due to femoral neck fracture (especially the sub capital fractures) or hip luxation (especially if reduction is performed late rather than early), treatment with GC is one of the most common causes of ON. Between 3% and 25% of patients using GC develop ON,<sup>1</sup> with a dose dependent risk. In this sense, the use of moderate doses of GC (<15-20 mg/day) are associated with a low risk of ON (<3%), while larger doses used for longer periods of time confer a higher risk.<sup>10</sup> Nonetheless, one must remember that these patients frequently have multiple associated risk factors that can lead to the development of this process. Some studies indicate that 100% of the cases of ON associated to GC treatment had continued treatment with prednisone in excess of 20

mg/day.<sup>10</sup> There is evident that points out that the initial dose of GC can be as important as the total dose and the duration of treatment. In transplant patients, the development of ON is a relatively frequent complication, with prevalence oscillating between 2% and 24% and depends on the dose employed and the transplanted organ.<sup>11</sup> The incidence of ON tends to be lower, in the order of 2%-3%, after liver or heart transplant than after lung or kidney transplant, where incidence is around 10% and 34%.<sup>14,15</sup> In these patients, a history of osteopenia and hyperparathyroidism are risk factors that have been associated to the risk of ON.<sup>16</sup> Frequently ON in renal transplant patients can affect more than one localization (50%-70% of cases).<sup>17,18</sup> Nonetheless, its incidence has lowered since the introduction of new immunosuppressants such as tacrolimus, allowing for a reduction in the dose of GC.<sup>19</sup> Bone marrow transplant (BMT) has also been associated to this complication, especially allogenic BMT, with a frequency around 5%<sup>20,21</sup>; graft-versus-host disease and the cumulative dose of GC are risk factors related to the development of ON in these patients.<sup>22</sup> But other factors such as the type of hematologic disease and the gender, both of the patient and the donor, have also been related to this complication. Thus the patients with acute lymphoblastic leukemia and women who have received a transplant from another woman, present ON with a greater frequency.<sup>23</sup>

In other diseases such as systemic lupus erythematosus (SLE), the development of ON has been observed in 4% of patients<sup>24,25</sup>; but if treatment with GC, especially at a dose >20 mg/day, constitutes one of the main risk factors for the development of ON in these patients,<sup>26-28</sup> dyslipidemia, and antiphospholipid antibodies are other factors relating to the development of ON in this process.<sup>29</sup> Though the role of antiphospholipid antibodies in the development of ON in patients with SLE is controverted,<sup>30-34</sup> their relationship with the development of ON in patients with primary antiphospholipid syndrome seems evident. Thus, it has been recently shown that 20% of these patients develop ON.<sup>35</sup> Some studies, though not all, have also observed an increment in the incidence of antiphospholipid antibodies in patients with ON.<sup>29,36,37</sup> Isolated cases of patients with multifocal ON and associated antiphospholipid antibodies have been described.<sup>38-40</sup> Other isolated studies implicate alterations in other coagulation factors with relation to the development of ON, such as the presence of a mutation in the factor V Leiden gene<sup>41,42</sup> or the inhibition of plasminogen activation factor.<sup>43</sup>

The excessive consumption of alcohol is also a frequent cause of ON. Even though the mechanism by which this complication is produced in these patients, several etiopathogenic mechanisms have been proposed in relation to the development of ON in this process, such as fat embolus, venous stasis or the increase in the concentrations of cortisol, among others. The

development of ON is frequent in other diseases such as sickle cell anemia, in which up to 50% of patients can present the complication, and in Gauchers' disease, a metabolic entity in which approximately 60% of patients develop ON. Lastly, human immunodeficiency virus (HIV), independent of the degree of immune system compromise, can produce an increment in the risk of ON; in these patients a prevalence of up to 4% has been noted, occasionally presenting as multifocal ON. Factors such as dyslipidemia secondary to the treatment of protease inhibitors, GC treatment, hypolipemics or testosterone could be related to its development.<sup>44</sup> The role that the complications linked to HIV, mainly coagulation disorders (antiphospholipid antibodies or S protein deficit) and vasculitis have been a motive of discussion but their participation has not been able to be confirmed. It is probable that in these patients the development of ON is multifactorial.<sup>45,46</sup> A recent study that analyzes the factors related to ON in patients with HIV indicate that the majority of patients (86%) had at least one known risk factor for this complication.<sup>47</sup>

## Diagnosis

Upon suspicion of ON, a simple x-ray study must be carried out. When the x-ray is normal and there is a clinically based suspicion of ON, the imaging method of choice is magnetic resonance (MR). At the beginning of symptoms, the radiological studies tend to be normal; the first findings are changes in the bone mineral density followed by sclerosis and the appearance of cysts as the disease progresses. The pathognomonic sign is the "half-moon" image, indicating subchondral collapse. In advance stages of the disease there is an objective loss of sphericity of the femoral head and a narrowing of the joint space as well as degenerative changes of the acetabulum. Both hips should always be x-rayed to evaluate bilateral affection. MR constitutes the most sensitive technique for diagnosis of ON and allows for its diagnosis in early stages of disease. The study must include imaging in T1 and T2 with coronal and sagittal

cuts. Bone scanning is a less sensitive and specific technique than MR in early stages, though it is useful in the diagnosis of multifocal illness. Another imaging technique is computed tomography (CT) that can be useful in the detection of an occult subchondral fracture, but is less sensitive in the early diagnosis of ON (stage I). As with MR, CT is not necessary for the diagnosis of ON in late stages of disease because diagnosis with simple x-rays is easy.

## Classification and Staging of Osteonecrosis

Several staging indexes for ON based on the degree of x-ray affection, histological damage, and clinical symptoms have been proposed. The classification of Ficat et al<sup>48</sup> stands out among them, basing itself on the x-ray findings and has been used extensively (Table 1), as does the index of the Association for the Research of Circulation of the Bone (ARCO),<sup>49</sup> that unifies the results of several classifications (Table 2). The latter is difficult to apply in daily practice and is mainly employed in research studies.

## Treatment

A controversial topic in ON is, without a doubt, its therapeutic approach. Thus, in many occasions, conservative treatment is indicated for this process, including joint rest and analgesia. Nonetheless, this type of treatment does not seem to modify the natural evolution of ON nor prevent bone collapse, because with this kind of treatment, only 23% of hips present a good clinical result after a mean follow up of 34 months.<sup>50</sup> Central decompression by single or multiple perforations (forage) through the femoral neck is another kind of treatment that has frequently been used. It is a surgical procedure in which several perforations of a small caliber or a larger one are done attaining decompression at the same time the necrotic bone tissue is removed. When the intraosseous pressure diminishes, pain is relieved and, theoretically, revascularization of the necrotic tissue

**TABLE 1. ON Classification According to Ficat et al<sup>48</sup>**

Stage 0	Diagnosis techniques are normal and patient is asymptomatic
Stage 1	Normal x-ray, asymptomatic or, mild symptoms, bone scan shows a cold spot on the femoral head and biopsy is positive
Stage 2	x-ray changes, mild symptoms, and increased uptake on bone scan. According to x-ray affection it can be classified into A or B
Stage 3	x-ray changes, loss of sphericity and collapse, mild to moderate symptoms, increase in bone uptake
Stage 4	x-ray changes, joint space narrowing and acetabulum changes, moderate to severe symptoms and increased uptake in bone scan

**TABLE 2. Osteonecrosis Classification According to ARCO<sup>49,\*</sup>**

Stage 0	The diagnostic tests are normal, patients are asymptomatic, diagnosis is histological
Stage 1	Normal x-ray and CT, MR and biopsy are negative. According to the extension of the lesion it is subclassified in: A: <15% B: 15%-30% C: >30%
Stage 2	Radiographic changes without collapse. According to the degree of affection it is sub classified in A, B, or C
Stage 3	“Half moon” sign is characteristic; indicating collapse. MR or CT can be necessary for diagnosis. The extension of the lesion is sub classified in A, B, or C
Stage 4	There is a flattening of the femoral head with joint space narrowing and early signs of arthrosis. Collapse usually occurs in the anterolateral or superior loading area. The best technique to observe collapse is CT. This stage can be subdivided in: A: extension of the collapse <15% and 2 mm depression B: collapse 15%-30%, depression 2-4 mm C: collapse >30%, depression >4 mm
Stage 5	All of the abovementioned radiographic changes and a narrowing of the joint space. Collapse secondary to arthrosis, sclerosis, cysts, and marginal osteophytes
Stage 6	Extensive destruction of the femoral head

\*MR indicates magnetic resonance; CT, computerized tomography.

occurs. In the last few years there have been numerous studies attempting to evaluate the efficacy of this technique.<sup>51</sup> For example, in a randomized study that compared the efficacy of this technique versus conservative treatment the results showed that, even if there were significant differences in favor of treatment with decompression in relation to the improvement of pain, no differences were observed regarding radiographic evolution,<sup>52</sup> while a meta-analysis comparing the efficacy of both procedures indicated that the forage could only be useful in the treatment of stage I hip ON<sup>53</sup>; therefore this type of treatment is indicated in patients presenting early stages of disease and limited extension lesions.<sup>54,55</sup> Recently it has been pointed out that additional treatment with local growth factors such as morphogenetic protein could improve this treatments efficacy.<sup>56,57</sup> Another surgical procedure cited frequently is femoral neck osteotomy, consisting in the modification of the loading axis on the femoral head. This procedure would facilitate recovery by modifying the load over the necrotic lesion. But the results of clinical trials are variable and, curiously, the best results are observed in Japanese populations where, after a follow up period of 2-9 years, patients show excellent results of up to 90%.<sup>58</sup> This procedure is currently being abandoned.

There are other techniques that also imply a surgical approach of the bone lesion, such as the cortical-spongy bone implant and the revascularized bone implant. In the former a cortical or spongy bone implant (autologous or allogenic) is introduced through the decompression zone into the necrotic area after debridement. The bone implant offers structural support for the subchondral bone, theoretically preventing bone collapse. Marcus et al<sup>59</sup> described the results of this technique in a group of

48 patients with different stages of affection (I-IV). Therefore, while 64% of the patients in stages I and II presented a good evolution with this type of treatment, no patient I stages III and IV had satisfactory results. Another technique that has been employed is the impacted bone implant, with interesting results in extensive ON.<sup>60</sup> On the other hand, the implant of vascularized free or pediculated bone consists in the implantation of cortical or spongy bone tissue with its vascular appendage (usually free peroneus through microsurgery) to the interior of the femoral neck through a decompression tract. The results described with this type of implant are better.<sup>61</sup> In a study that included 101 hips (in all stages of ON) from 86 patients and with a minimum follow-up of 5 years, there was a hip survival of 61% at 5 years.<sup>62</sup>

It must be said that a recent technique has been applied to this disease, the implantation of a tantalum rod or screw, that consists in the collocation of a porous bar made tantalum in the interior of the femoral neck (Figure); its indication is based on the fact that it will serve as mechanical support and the intrinsic properties of tantalum in the induction of osteogenesis.<sup>63,64</sup> The marked porosity of tantalum provides this material with biomechanical properties that improve the stability of the bone-metal interphase and favors osteoinduction and neovascularization.<sup>64</sup> But even though the initial clinical results seem promising, long term, comparative studies are needed to determine this procedures usefulness.<sup>65</sup> Another technique with which there have been good results but that is still being studied is the transplantation of autologous bone marrow in the necrotic lesion of the femoral head. This procedure has shown promising results regarding safety and efficacy in the

**Figure 1.** Tantalum rod in an osteonecrotic femoral head.

early stages of ON. Thus, a recent randomized study that included 13 patients with ON (18 hips) in stages I and II compared the effects of this procedure with forage and observed that, even if the majority of the hips (63%) included in the treatment group with forage worsened, ending in a stage III disease after 24 months of follow-up, only 10% of the group treated with a bone marrow transplant progressed to that stage.<sup>66</sup> Other treatments, such as stimulation through electromagnetic fields have also been indicated for the treatment of this process, either as a primary therapy or as a coadjuvant associated with nucleus decompression and also with bone implant.<sup>67</sup> This treatment could stimulate osteogenesis and neovascularization, but studies to confirm their effectiveness are needed<sup>68</sup>; in the same manner, treatment with extracorporeal shock waves have been effective in the clinical evolution of femoral head, early-stage ON, though long term studies to confirm these results are needed.<sup>69</sup>

No doubt an interesting aspect is the role that bisphosphonates could play in the treatment of this disease. Ibandronate, zoledronate, and alendronate<sup>3,70,71</sup> have demonstrated effectiveness in the prevention of bone collapse associated to ON in various animal experimentation models when administered in early stages of disease. This effect has been attributed to a reduced bone remodeling produced that leads to a repair zone in the area of avascular necrosis and preserves the trabecular structure, therefore preventing bone collapse.<sup>3</sup> It is important to remember that among the etiopathogenic mechanisms implicated in osteonecrosis, there is also an increase in osteocytic apoptosis in patients treated with GC, something that is very interesting because bisphosphonates prevent osteocyte apoptosis.<sup>72,73</sup> A recent prospective, uncontrolled study that included 60 patients<sup>3</sup> that were treated with alendronate (10 mg/day or 70 mg/week p.o.) for femoral ON with

a 3 month to 5 year follow-up indicated that bisphosphonates are associated to reduced pain and radiographic progression that exempted most patients from an early surgical intervention. Also, a randomized study that included 40 patients with femoral head ON treated with alendronate (70 mg/week), with a follow-up of 24-28 months,<sup>74</sup> showed less progression to bone collapse than in patients treated with alendronate in the control group (2/29 femoral heads in the group treated with alendronate and 19/25 in the control group). This data is certainly insufficient to indicate treatment with bisphosphonates in these patients, but it does point to a necessity in controlled studies in the long term that include a larger number of individuals and analyze these treatments.

Lastly, for patients in an advanced stage of the disease with pain and associated functional limitation, total hip arthroplasty is the treatment of choice. But the results of this procedure in younger patients are less consistent, thus the majority of studies communicate a worse prognosis than in other diseases. A study that compared the evolution of hip arthroplasty in patients with ON and coxarthrosis indicated a much higher review rate in patients with ON (28% and 6%) with a shorter review time (5 years before patients with ON). The authors commented that it is possible that patients with ON have a worse quality of life and higher weight and, by virtue of being younger, more physical activity.<sup>75</sup> This fact has led to the current consideration being made for resurfacing prosthesis of the femoral head in young patients.<sup>76</sup>

The treatment of ON continues to be a controversial subject and depends of several factors such as age, the stage of ON and symptoms. The development of new procedures and the potential of bisphosphonates open new perspectives in the therapeutic approach of this process.

## Addendum

Since the review of this article, new therapeutic approaches to ON have been published based on animal model experiments, such as the treatment with subcutaneous osteoprotegerin and the intraosseous of ibandronate in the ischemic femoral head. Both treatments have shown a reduction in femoral head deformity after ischemic ON. For more information on these experiments please consult the following references:

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