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REVIEW

Current trends and controversies in femoral head osteonecrosis

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ABSTRACT

Osteonecrosis of the femoral head is a disabling disease with necrosis of bone and bone marrow occurring within the head that predictively leads to collapse of the subchondral infract if left untreated. Osteonecrosis can be either traumatic or non-traumatic associated with an array of systemic diseases and risk factors and frequently presents a multifocal distribution. Corticosteroids are considered a risk factor for osteonecrosis. Patients treated for myelogenous diseases and COVID-19 are particularly in elevated risk for developing osteonecrosis. At an early stage it is asymptomatic and undetectable in simple radiographs. MRI is the gold standard for diagnosis and should be prescribed early after corticosteroid therapy. Therapy is, in most cases, surgical and every attempt should be made to preserve the native joint in young patients. If articular surface collapse is established, total hip arthroplasty is the treatment of choice to maintain the quality of patients' life.

KEYWORDS: osteonecrosis; femoral head; MRI; corticosteroids; COVID-19

Introduction

Osteonecrosis (ON), also known as avascular necrosis (AVN), is defined as a pathologic process that results from a crucial disruption of blood supply to a bone segment, which usually results in the structural collapse of the osteonecrotic lesion, leading to osteoarthritis of the hip joint requiring total hip replacement [1, 2, 3]. Even though the aetiology and pathogenesis of the non-traumatic osteonecrosis are not fully understood it is associated with an array of systemic diseases and risk factors and frequently presents a multifocal distribution. It is commonly affecting the femoral head as a progressive pathology, usually in young adults in their third to the fifth decade of life [4]. In the majority of the cases (> 80%) it is bilateral and at late stages leads to collapse of the articular surface and gradual hip joint degeneration [5](Fig. 1). In the United States, more than 10,000 new patients are affected with the disease every year, and it accounts for up to 10% of total hip

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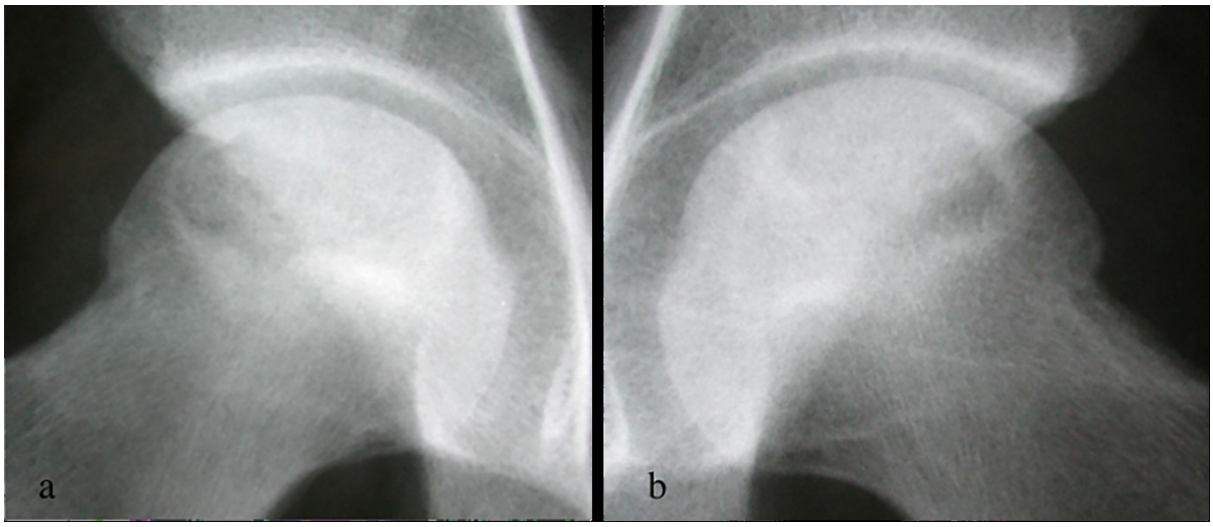

Figure 1. a & b: *Bilateral FHOn: Patient claimed for a vague groin pain on his right hip (a), reflecting to the medial aspect of the thigh and buttock. Careful clinical evaluation revealed restricted motion of the right hip joint and pain mainly elicited in flexion and internal rotation of both hips. Radiographic evaluation revealed bilateral FHOn.*

arthroplasties [4, 6, 7]. Early diagnosis and management aim to suspend the process of joint destruction through enhancement of bone repair and bone renewal.

A. Pathogenesis

Osteonecrosis of the FH may be related to:

i. Ischemia from a:

1) Direct blood vessel injury (after trauma such as fracture of the femoral neck, hip dislocation, fracture of the femoral head).

2) Intra-luminal obliteration of vascular supply from embolic matter such as clots, lipids, immune complexes, or sickle cells can also occlude the terminal arterioles in the subchondral bone.

3) Extra-luminal obliteration of the small vessels within the bone marrow. The common final mechanism is ischemia. The lack of collateral vessels at the sub-chondral zone of the weight bearing area, leads to the establishment of an infarct underneath the articular surface [8, 9, 10].

ii. Cellular toxicity

1) Pharmacologic agents (Corticosteroid use, non-steroidal chemotherapeutic agents for leukemia and other myelogenous diseases including tyrosine kinase inhibitors, monoclonal antibodies, mammalian target of rapamycin inhibitors, radiopharmaceuticals, selective estrogen receptor modulators and immunosuppressants)

2) Alcohol overuse

3) Irradiation

4) Oxidative stress [11, 12, 13, 14, 15, 16]

Overuse of glucocorticoids, and alcoholism are implicated in >80% of the cases and it is well established that the mechanism which causes blood vessel functional impairment in these cases does not have an embolic pattern and probably is characterized by genetic predisposition. A recent review article by Wang et al. listed five major theories about the pathogenesis of steroid induced ONFH referred to a. lipid metabolism disorders, b. decreased osteogenesis potential, c. insufficient blood supply, d. cell apoptosis, and e. gene polymorphism [17]. The ARCO (Association Research Circulation Osseous) has proposed classification criteria of corticosteroid-associated ONFH including: 1) history of corticosteroid use > 2 g of prednisolone or its equivalent within a 3-month period, 2) osteonecrosis should be diagnosed within 2 years after corticosteroid usage, and 3) patients should not have other risk factor(s) besides corticosteroids [18]. In this template as well, alcohol-associated ONFH is defined by the following conditions: 1) history of alcohol intake > 400 mL/week (320 g/week, any type of alcoholic bev-

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erage) of pure ethanol for more than 6 months, 2) ONFH diagnosed within 1 year after alcohol intake of this dose and 3) patients should not have other risk factor(s) than alcohol abuse [19].

iii. Genetic and epigenetic aetiologies regulating blood vessel tone, collagen production and the metabolism of steroids and alcohol such as mutations in the *COL2A1*, VEGF, eNOS (endothelial NO synthetase) and peroxisome proliferator activated receptor gamma (PPARG) genes, have been associated with the pathogenesis of osteonecrosis [20, 21, 22]. Moreover, significantly high prevalence of common thrombophilic states with genetic basis like the factor V Leiden mutation, the prothrombin gene G20210A mutation, antithrombin III deficiency, protein C and protein S deficiency and the methylene-tetrahydrofolate reductase (MTHFR) C677T gene polymorphism have been identified in patients with primary ONFH [23, 24]. Molecular techniques like genome-wide association study (GWAS), which identifies single nucleotide polymorphisms (SNPs) in the genome and establishes their relative association to a particular phenotype are going to enlighten us significantly in the future regarding the genetic basis of femoral head osteonecrosis pathology.

Pathogenesis: The underlying bone pathology is developed as the necrotic trabecular and the sub-chondral bone plate denuded from the proteins and the organic elements, upregulates tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts, attracted by the local cytokines from the adjacent living bone, to gradually resorb the dead bone of the infarct. This inflammatory "repair tissue front" reaction is triggering osteoclastogenesis and scavenging with lysis of the dead trabeculae. This process is accompanied by new bone formation from the osteoblasts, but within the hypoxic environment the osteoblastic healing reaction is un-coupled early on, as the weakened trabeculae are fractured under the contact forces on the articular surface from weight bearing and repetitive loading. After collapse of the articular surface, the detached cartilage and the sub-chondral bone plate are dehisced and appear on the x-rays as a "crescent sign". This process is progressively expanding, and the collapsed infarct is sequestered and disintegrates, leading to secondary joint destruction [2, 25, 26].

TABLE 1.

Non-traumatic Osteonecrosis associated conditions	
Coagulation disorders	Hematologic diseases
Deficit of antithrombin III	Haemophilia
Deficit of protein C	Hemoglobinopathies
Deficit of protein S	Polycythaemia
Resistance to activated protein C	**Metabolic diseases**
Deficit of plasminogen activator	Hyperparathyroidism
Subplace of plasminogen activator inhibitor (PAI)	Gout
PAI 1 polymorphisms	Cushing disease
eNOS (endothelial NO synthetase) polymorphisms	Gaucher disease
Factor V mutation	**Exogenous risk factors**
Secondary conditions of hypercoagulation	Smoking
Intake of steroids, alcoholism	Decompression disease (divers- caisson disease)
Malignancy	Irradiation
Myelodysplastic syndromes	Haemodialysis
Pregnancy	Chemotherapy
Contraceptive use	
Hyperlipidaemia	
Collagen diseases	
Ehlers–Danlos syndrome	
Raynaud's disease	
Diabetes mellitus	
Antiphospholipidemic antibodies (APLA)	
Alimentary system diseases (Pancreatitis)	
Antiretroviral therapy for HIV	

B. Risk factors

ONFH may be associated with trauma (traumatic osteonecrosis) but in most cases it is non-traumatic.

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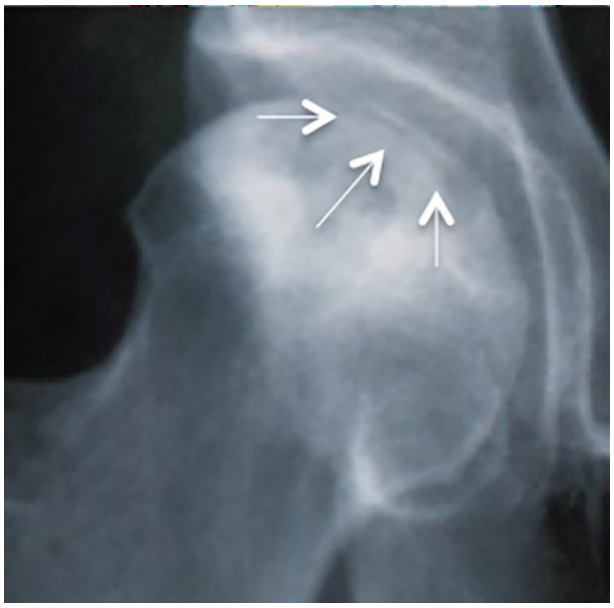

Figure 2. *Radiographic image of a femoral head with osteonecrosis depicting the sub-chondral fracture "Crescent sign".*

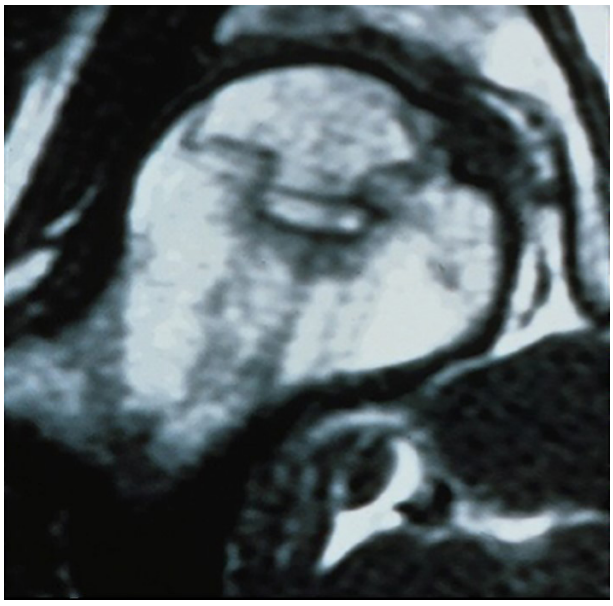

Figure 3. *MRI for the diagnosis of FH ON*

Nontraumatic ONFH has traditionally been classified as idiopathic or secondary, depending on the absence or presence of known causes. Non- traumatic osteonecrosis may be associated with the use of high dose of corticosteroids in patients under chemotherapy and in auto-immune diseases, coagulopathies, special conditions causing secondary hyper-coagulate status, hematological and metabolic diseases, alimentary system diseases, while certain other risk factors such as smoking, overuse of alcohol, decompression disease, radiation and hemodialysis have also been correlated to the disease (Table 1). Not all patients exposed to a certain risk factor develop osteonecrosis of the femoral head, indicating that development of osteonecrosis is a complex, multifactorial, and not fully understood process involving both environmental influence and genetic predisposition. Steroids seems to be the major risk factor in acute lymphoblastic leukemia, chronic myeloid leukemia and acute myeloid lymphoma in which there is an increased risk of osteonecrosis [16, 27]. Osteonecrosis (ON) has been increasingly documented, particularly in pediatric ALL and well-known risk factors for this complication in this group of patients are the age above 10 years, female sex, use of dexamethasone (DEX), insufficient level of 25(OH)D, plasminogen activator inhibitor-1 (PAI- 1) and vitamin D receptor gene (VDR) polymorphisms [28, 29].

Use of corticosteroid-based therapy to reduce inflammatory-induced lung injury has been described for patients with severe COVID-19 like the use of corticosteroids to treat severe acute respiratory syndrome (SARS) during the SARS outbreak in 2003. However, improper use of systemic corticosteroids can increase the risk of osteonecrosis of the femoral head (ONFH) [30, 31, 32]. The otherwise limited modern literature suggests that corticosteroids should be considered only for patients undergoing septic shock, or in critical cases and in general should be minimized in dose and duration, and moreover the use of multiple types should be avoided [30, 32, 33]. Early screening, at three to four months after corticosteroids therapy, is suggested for COVID-19 patients.

C. Diagnosis:

The multifactorial etiologic profile of the disease requires a high degree of suspicion by the treating physicians (oncologists, haematologists, rheuma-

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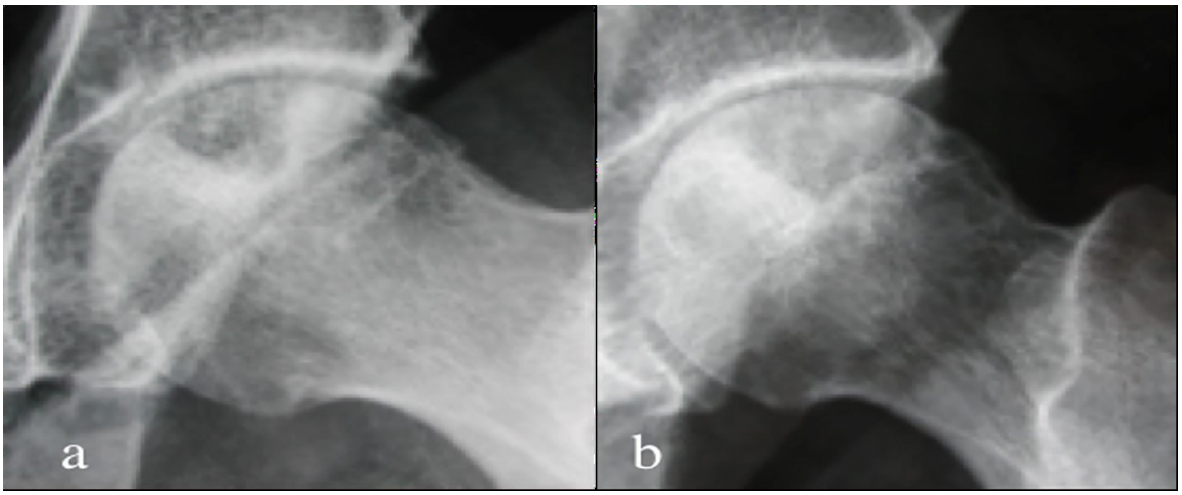

Figure 4. ***(a)*** *Small lesion involving less than 30% of the femoral head, may last for years before collapse.* ***(b)*** *More extended lesion involving >30% of the femoral head associated with higher collapse risk.*

tologists etc) in all patients with the predisposing risk factors, as the disease may remain quiescent for an unpredictable period of months after the infarct is established. It is advised to screen with an MRI of the hips every patient at risk of developing osteonecrosis, for the early detection of the disease which might lead to early management and possible hip joint-sparing.

ONFH presents an insidious onset with the patient complaining for a vague groin pain as the main symptom. In many cases it may be reflecting to the medial aspect of the thigh, the ipsilateral knee or buttock (Fig.1). The pain is relieved with rest. Careful clinical evaluation will reveal limited or restricted motion of the joint and pain mainly elicited in flexion and internal rotation of the hip. As the disease progresses so do the symptoms and in late stages, when collapse of the femoral head occurs, the patient is limping, and the hip joint deteriorates [34, 35].

D. Imaging:

Plain anteroposterior and frog-leg lateral radiographs have little to offer in early beginning of the disease, as they may appear completely normal. The initial findings include sclerosis surrounding a lucent area or segments with osteopenia within the femoral head. Radiographs are highly specific for more advanced osteonecrosis (Ficat II or III) and painful stages, the articular surface is fractured and a subchondral demarcation line is identified as the "crescent sign", but not very sensitive for early changes (Ficat I). In late stages gradual flattening of the articular surface and associated degenerative changes of the hip joint occur, which in large lesions, finally lead to progressive joint degeneration (Fig. 2) [34].

MRI is the most sensitive and specific diagnostic tool (99%), particularly helpful (for screening) in the very early stages, distinguishing premature necrotic lesions within the normal viable bone of the femoral head (Fig. 3). T1 images on MRI typically demonstrate a serpiginous "band-like" lesion with low signal intensity in the anterosuperior femoral head. A "double-line sign" can be seen on T2 sequences, which depicts a high signal intensity reparative interface of vascular reactive bone adjacent to necrotic subchondral bone. Bone marrow oedema around the necrotic lesion, may be present, mostly following a recent collapse and it is highly correlated with more hip pain [36, 37].

^{9m}Tc-methylene diphosphonate (MDP) bone scintigraphy, reflects osteoblastic activity and blood flow which are absent in osteonecrosis -"cold within hot" lesion at initial stages of asymptomatic disease. Its use is beneficial in detecting early stages of the disease and in diagnosing multifocal osteonecrosis of the skeleton. Irradiation in addition to poor specificity remain the main drawbacks of this exam, but it can be used to detect inflammatory ac-

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tivity in the femoral head when MRI is contraindicated. As more sensitive and specific, a whole-body MRI is preferable [35].

Computed tomography (CT) may be superior to MRI in detecting subchondral fractures and small areas of collapse which are suspected but not seen on plain films or MRI, but less sensitive than MRI in detecting osteonecrosis. On the other hand, the additional cost and radiation exposure are not justified [34, 38]. Recently, it has been proposed that nuclear medicine imaging technology such as SPECT/CT bone scan and 18F-fluoride PET/CT could demonstrate similar or better results in comparison to MRI in AVN of the femoral head and serve a complimentary role in equivocal cases [39].

E. Differential diagnosis:

FHON should be distinguished from Transient Bone Marrow Oedema (TBMO), a self-limiting condition presenting also with acute groin pain (occasionally throbbing) which involves women in their last months of pregnancy, or men on their 5th or 6th decade of life. Bone marrow oedema is also combined with transient osteoporosis, but subchondral lesions rarely exist. On rare occasion, reports have shown that bone marrow oedema syndrome (BMOS) may coexist with osteonecrosis. This finding has generated some controversy as to whether the two conditions coexist or if BMOS is a precursor to osteonecrosis. Other benign or malignant bone pathology of cartilaginous origin (chondroblastoma & clear cell chondrosarcomas) within the femoral head have rarely been reported. The lack of a serpentine line demarcating the infarct facilitates diagnosis [34, 35, 40].

F. Severity of ONFH

Aiming at the precise determination of the stage of the disease and therefore at the possibility of elementary prediction of its natural history and its treatment, more than 16 different staging systems have been proposed in the literature for evaluating ONFH, mainly based on the MRI and X-ray findings. The Arlet-Ficat (1960 and revised at 1985-commonly used), the ARCO (1991 and revised at 2019), the Japanese Orthopaedic Association (1987), the Pittsburgh classification (1984-Steinberg), the Kerboul (1974) staging systems combine findings both on plain radiographs and on the MRI as well as the proportion of the femoral head affected (Table 2).

Although all these classification systems lack high intra-observer and inter-observer reliability and validity can adequately differentiate the pre-collapse lesion which requires conservative treatment or minimal surgical approach [34, 41, 42, 43, 44]. Generally, if more than 30% of the femoral head is involved a greater risk (95%) for hip collapse within two years exist (Fig.4a &b).

G. Prognosis:

It depends on the location in relation to the weight bearing surfaces, the extent of the lesion, the presence of subchondral fracture and different morphologies of the necrotic-viable interface in osteonecrosis of the femoral head. The grater the extent of the infarct the worse the prognosis as more unfavourable outcome occurs (Fig. 4). Lesions extending beyond the lip of the acetabulum present the worst prognosis and major risk of future collapse. Recent or continuing collapse of the affected segment, together with aggravation of pain and extensive bone marrow oedema of the proximal femur are signs of rapid degenerative changes and deterioration of the hip joint function. Additionally, in a recent study by Kwon HM et al. has been proposed that a high pelvic incidence was associated with a greater likelihood of femoral head collapse in patients with nontraumatic ONFH. Clinical signs and symptoms correlated with the radiographic evaluation are necessary for the assessment of the severity and selection of the appropriate treatment [34, 45, 46, 47, 48].

H. Treatment options

I. Non-operative with partial weight bearing and activity modification, is indicated only in the early stages for very small lesions (<10%) and requires constant re-evaluation for the disease progression. However, it has no role in treatment of late-stage osteonecrosis and show limited success in preventing disease progression, even in early stages. Several additional measures to the nonsurgical treatment

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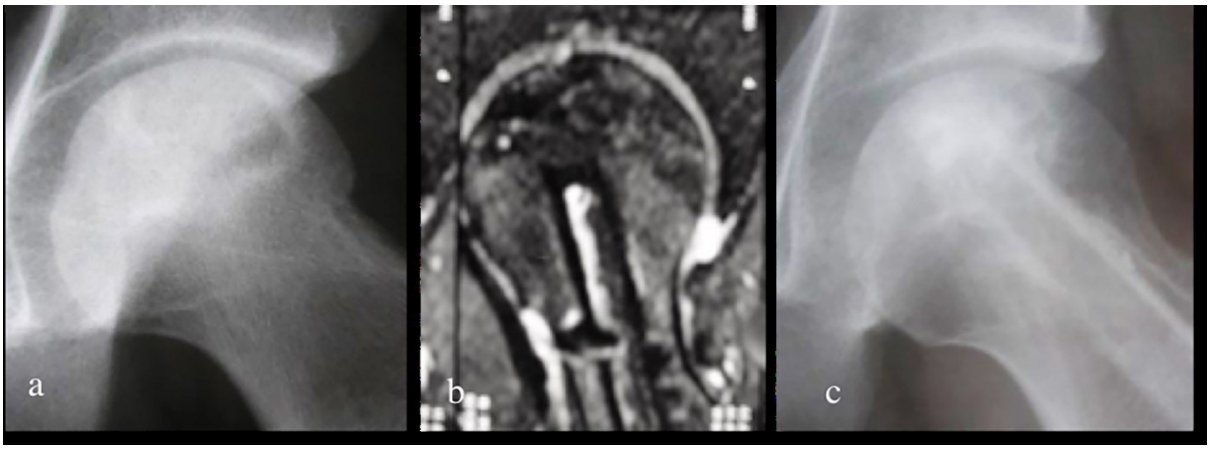

Figure 5. *Surgical treatment of FH ON with the implantation of vascularised fibula graft. (a) Preoperative radiograph. (b) and (c) Postoperative MRI and radiograph depicting the implanted fibula.*

have been suggested, such as shock wave therapy, pulsed electromagnetic fields, hyperbaric oxygen and pharmacological agents (anticoagulants, lipid-lowering factors, bisphosphonates**,** growth factors, antioxidants, and vasoactive substances) but there are not enough data in the literature to support their proven effect in preserving the hip joint. Patients are encouraged to abstain from or decrease alcohol consumption and smoking. [2, 9, 25]

II. Surgical management: except for the very small lesions where the natural history of the disease may last for years without an operation, larger lesions will eventually collapse and lead to joint replacement. In the early stages, prior to articular surface collapse, a variety of surgical procedures have been described for the preservation of the hip joint.

II.a. Salvage procedures: include core decompression after, various bone grafting technics and rotational osteotomies. Core decompression is carried out either with multiple drilling within the lesion with smooth pins (4-5 mm) drillings into the lesion, relieving intra-osseous pressure and inducing micro fractures to initiate a healing response. It is indicated for small sclerotic lesions in the early stages and its main drawback is the potential weakening of the adjacent intact cancellous bone [49, 50]. Efficacy has improved over the past 20 years, and this may be due to improved patient selection or the use of new surgical techniques such as multiple percutaneous drilling.

A variety of bone grafting techniques have been introduced combined with core decompression, to substitute the cored out necrotic bone, thus providing mechanical support and reconstituting the subchondral area with new bone-callus formation to prevent collapse. There are many studies since 2010 aimed to determine the effectiveness of bone marrow aspirate concentrate (BMAC), platelet-rich plasma (PRP), bone morphogenetic proteins (BMP) or their combination with CD in early stages of AVN hip, prior to collapse of femoral head [51, 52, 53, 54].

Implantation of one 11 mm or multiple 4 mm porous Tantalum rods is an alternative option, to provide mechanical support of the affected subchondral bone in carefully selected precollapse patients, but the results of many studies have not been optimal. Because of the increased complication rates in patients who undergo THA following tantalum rod failure, this treatment modality has fallen out of favour [2, 55]. The most advantageous grafting procedure is the implantation of a vascularised bone graft, as it combines the benefits of necrotic bone excision and core decompression with adequate mechanical support of the subchondral bone, together with the osteoinductive, osteoconductive and osteo-regenerative properties of an autologous bone graft, in addition to re-vascularisation of the affected area (Fig. 5). Autologous free vascularized fibula implantation has been proven very successful for intermediate size lesions prior to articular surface collapse [56, 57].

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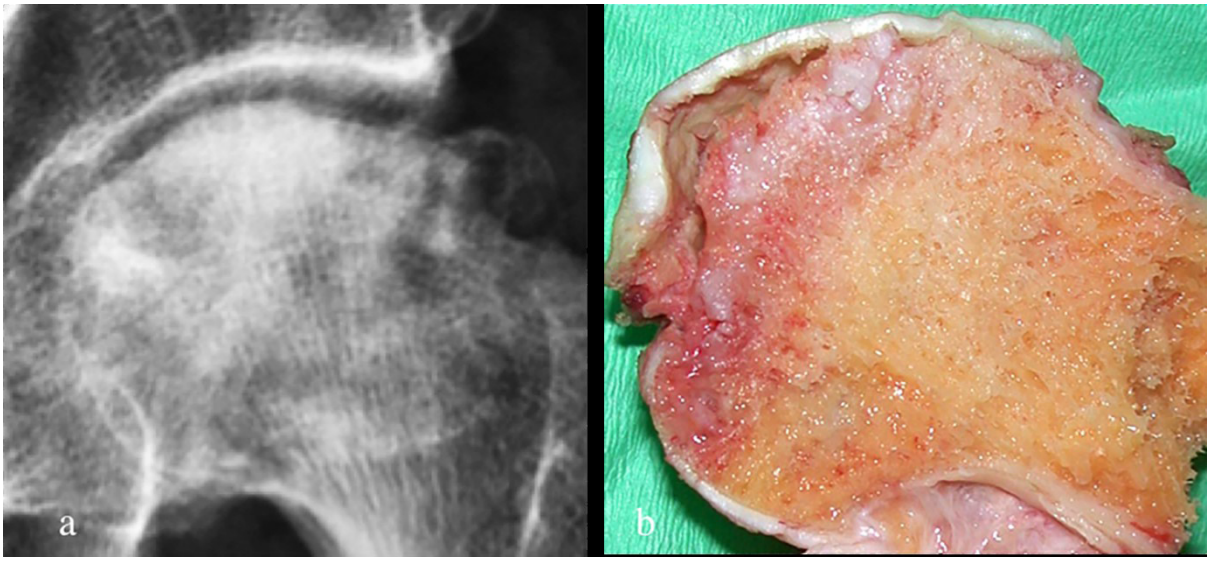

Figure 6. *Progressive joint degeneration in late stages of FHOn. (a): Preoperative radiographic appearance of femoral head advanced collapse due to On. (b): Pathologic appearance of the bisected, excised, femoral head.*

In addition, the vascularized iliac bone flap grafting technique yields significant improvement for restoration of the biomechanical support of the collapsed femoral head and reconstruction of the blood supply to the osteonecrotic area [58].

Nonvascularized fibular grafts, cortical strut grafts, or cancellous bone chips are viable options for the treatment of ONFH. Techniques for the implantation of these grafts include the Phemister technique, the trapdoor, and the lightbulb technique [2, 29]. Intertrochanteric or rotational osteotomies of the proximal part of the femur for the transposition of the effected segment away from the weight bearing area, also consist a hip salvage procedure. The long-term results, however, remain controversial [59, 60].

II.b. Hip replacement procedures: although non desirable in the younger ages, in late stages or in elderly patients with established degenerative changes of the hip, joint replacement surgery is the treatment of choice (Fig. 6). Total hip arthroplasty provides pain relief and early functional improvement but durability of the prosthesis is the main drawback as osteonecrosis affects mainly young energetic patients in their productive life years. The long-term survivorship of the THA is comparable to that for osteoarthritis in general, except for the cases with haemoglobinopathies, renal failure in dialysis and autoimmune diseases, which may present higher rates of early failure, and infections. Hip resurfacing arthroplasty is another option, but it has not been proven equally successful to THA [61, 62, 63].

I. Take home message

Osteonecrosis is a pathology commonly seen in younger adults, in which collapse of the femoral head and early onset of joint degeneration may eventually necessitate hip arthroplasty when non-operative measures and joint-sparing procedures fail. Patients on chemotherapy or with auto-immune diseases receiving high dose steroids are considered at risk, for the functionally debilitating ONFH, and an MRI of the hips is recommended for screening and early-stage detection. The same is valid for those with two or more aetiology associated risk factors. Higher age, higher BMI, and higher stages with large lesions of osteonecrosis are determinants of likelihood of conversion of joint-sparing procedures to THA. These factors can be useful during patient selection for joint-sparing procedures.

Conflict of interest disclosure:
The authors declared no conflicts of interest.

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