A Review Paper

Current Management Options for Osteonecrosis of the Femoral Head: Part 1, Diagnosis and Nonoperative Management

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Abstract

Osteonecrosis of the femoral head is a multifactorial disease that can result in significant clinical morbidity and affects patients of any age, including young and active patients. Late sequelae of femoral head osteonecrosis include femoral head collapse and subsequent degeneration of the hip joint. A high index of suspicion and improved radiographic evaluation allow orthopedic surgeons to identify this disease at an earlier stage. Current management options for hip osteonecrosis have results that vary according to patient population and disease stage. Modifications of older techniques, as well as emerging technologies, have led to the development of management strategies that may be able to alter the course of femoral head osteonecrosis.

Approximately 20,000 new cases of femoral head osteonecrosis are diagnosed annually in the United States.[1,2] In addition, 5% to 18% of total hip arthroplasties (THAs) are performed to manage advanced osteonecrosis of the femoral head.[3-5] Although technologic advances in implant design, bearing surfaces, and surgical technique have increased the survivorship of THAs, prosthesis longevity is still a significant concern for young, active patients with femoral head osteonecrosis. Hence, substantial emphasis has been placed on early identification and management of this disease.

A high index of suspicion and improved radiographic evaluation allow identification of femoral head osteonecrosis at its early stages. An optimal management modality would foster healing without sacrificing the structural integrity of the bone or the health of the overlying articular cartilage, thus managing symptoms while preserving femoral head anatomy and maximizing posttreatment function. Although this ideal treatment has not been developed, recent advances in managing femoral head osteonecrosis may be able to prevent or delay progression of this disease and reduce its associated clinical morbidity.

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Etiology and Pathogenesis

Several clinical entities, both traumatic and atraumatic, have been associated with development of hip osteonecrosis (Table I). Although the exact pathophysiology is still unclear, the final common pathway of these conditions is disruption of the vascular supply to the femoral head. Once the vascular supply to the femoral head is compromised, cell death occurs. In addition, the edema associated with osteocyte death increases the local osseous compartment pressure and further inhibits vascular flow to the femoral head. In time, continued mechanical stress on the weak necrotic bone leads to stress fractures, and, without the ability to repair these defects, the bone eventually undergoes collapse. Once the bony architecture is altered, the congruity of joint articulation is disrupted, and additional degenerative changes ensue.

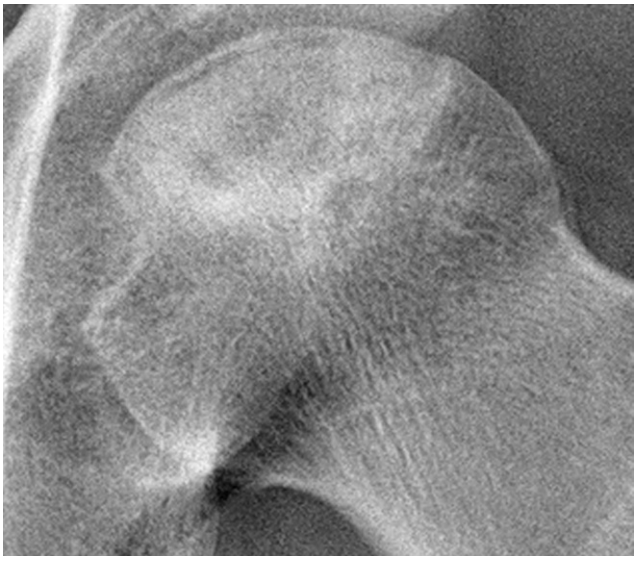

Figure 1. Anteroposterior radiograph of the hip showing a crescent sign before collapse of subchondral bone and flattening of femoral head.

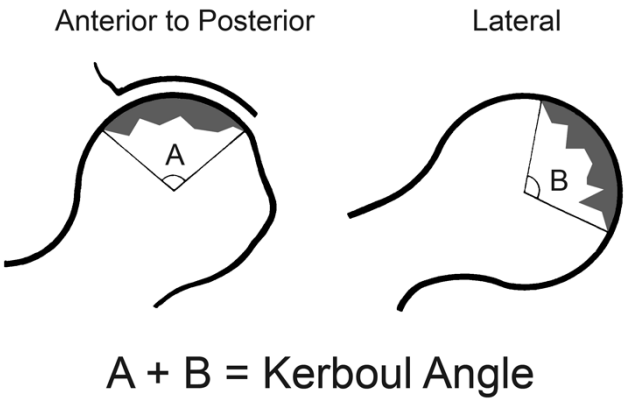

Figure 2. The Kerboul angle is the sum of the angles formed by the extent of femoral head lesion and the center of femoral head on anteroposterior (A) and lateral (B) radiographs of hip.[14] The modified Kerboul angle uses this concept of angular summation and applies it to the midcoronal and midsagittal magnetic resonance images.[18]

Epidemiologic studies have shown that more than 90% of atraumatic osteonecrosis cases occur secondary to use of alcohol and corticosteroids. These chemicals are thought to interrupt blood flow through intravascular coagulation and alterations in lipid metabolism leading to the production of fat emboli. Other studies have implicated other extrinsic and intrinsic factors affecting coagulation as the primary culprits in the pathogenesis of osteonecrosis. In one study, the blood samples of 37 of 45 patients (82.2%) with femoral head osteonecrosis showed evidence of at least 1 coagulopathy.[6] In addition, when compared with normal controls, patients with femoral head osteonecrosis were 14 times more likely to have elevated hypofibrinolytic plasminogen activator inhibitor activity and 3.4 times more likely to have elevated anticardiolipin antibody levels. In another study, factor V Leiden and mutations in the prothrombin gene occurred 3.6 times as often in patients with femoral head osteonecrosis compared to controls.[7]

Other studies have indicated a significant role for genetics in the development of osteonecrosis, particularly in cases attributed to corticosteroid use and alcohol abuse. Genetic polymorphisms in the genes encoding enzymes responsible for intracellular steroid transport and metabolism, including the ATP-binding cassette, sub-family B (MDR/TAP), member 1 gene, *ABCB1* (formerly know as the multidrug resistance 1 gene, *MDR1*), and cytochrome p450 3A gene, *CYP3A4*, have been shown to influence the likelihood of disease by as much as 9-fold.[8-10] In addition, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (eg, simvastatin, pravastatin) and phenobarbital have been shown to increase the activity of the cytochrome p450 3A gene and reduce osteonecrosis in rabbits.[11,12]

Table I. Risk Factors for Development of Osteonecrosis of the Femoral Head

Corticosteroid use
Alcohol abuse
Femoral neck fracture
Slipped capital femoral epiphysis
Hip dislocation
Sickle cell disease or sickle cell trait
Caisson disease (dysbaric osteonecrosis)
Systemic lupus erythematosus
Hypercortisolism (Cushing disease)
Coagulopathies (including malignancy)
Organ transplantation (immunosuppression)
Prior radiation therapy
Gaucher disease
Chronic pancreatitis
Smoking
Chronic renal failure
Pregnancy

Regardless of the etiology of osteonecrosis, the pathologic findings tend to be similar. Histologic examination in the early stages of femoral head osteonecrosis demonstrate bone marrow necrosis and dead osteocytes leading to empty lacunae within the bone. Creeping substitution follows: osteoclasts resorb the areas of bony necrosis and osteoblasts lay new bone down over the acellular trabeculae. Genes involved in bone remodeling, including *BMP2, BMP7,* and *RUNX2,* are elevated in the necrotic bone.[13] For small lesions, this process successfully replaces the necrotic region with normal bone. However, for large lesions, vascular in-growth develops at the periphery of the lesion, and new bone is deposited with increasing thickness and density at the periphery. There is limited vascular penetration through this dense periphery of bone, thus inhibiting repair of the more central portions of the lesion and leaving an area of weakened acellular bone prone to fracture and subsequent collapse. Collapse of the necrotic bony segment, heralded radiographically as the crescent sign, is followed by collapse of the subchondral bone and articular cartilage as well as flattening of the femoral head (Figure 1). This alteration in femoral head morphology creates abnormal stresses across the hip joint and leads to femoral and acetabular degenerative changes, including joint space narrowing, subchondral sclerosis, formation of subchondral cysts, and marginal osteophytes.

Diagnosis and Classification

The most common problem report of patients with osteonecrosis of the femoral head is pain, often localized to the groin. The pain may also localize to the ipsilateral buttock or knee. Typically, this pain is described as deep and throbbing, and is exacerbated by activity or weight-bearing. On examination, both active and passive hip range of motion may be limited because of the pain. Passive internal rotation is often the most limited and painful. As 40% to 80% of cases are bilateral, evaluation of patients with osteonecrosis should focus on both hips.

Initial radiographic evaluation should include anteroposterior (AP) and frog-leg lateral radiographs, which should be scrutinized for any femoral head changes, including the crescent sign, which may indicate impending structural collapse. In addition, lesion size (based on

Table II. Ficat-Arlet Classification of Femoral Head Osteonecrosis[15]

Stage	Clinical and Radiographic Findings
0. Preclinical	—Osteonecrosis is suspected because disease is present in contralateral femoral head —No symptoms —Plain radiography is normal —Magnetic resonance imaging is nondiagnostic
I. Preradiologic/ Early resorptive	—Patients may have mild pain related to affected hip that may be associated with limited range of motion, especially abduction and internal rotation —Plain radiography is normal —Magnetic resonance imaging/bone scan is diagnostic
II. Reparative	—Symptoms persist or worsen —Plain radiography shows areas of demineralization, sclerosis, and cystic changes —Crescent sign representing subchondral fracture is evident, especially on frog-leg lateral view
III. Early collapse	—Symptoms progress, often leading to difficulty in activity and limitation in hip range of motion —Segmental articular collapse is evident on plain radiography —Joint space is normal or increased secondary to head collapse
IV. Progressive degenerative	—Symptoms persist or progress —Progressive deformation of femoral head and loss of joint space associated with degenerative changes on acetabular side

Kerboul angle), osteophyte formation, joint congruity, and remaining joint space should be characterized (Figure 2).[14] Information obtained from plain radiographs can then be used to stage femoral head osteonecrosis according to the Ficat-Arlet classification (Table II).[15]

The development of magnetic resonance imaging (MRI) has allowed osteonecrosis to be identified in patients who may be minimally symptomatic and show no significant changes on plain radiographs. MRI has a high sensitivity and specificity for diagnosing preradiographic osteonecrosis through its ability to detect the signal changes associated with osteocyte death and marrow fat cell replacement. Typical MRI findings include a high-intensity region of bone marrow edema accompanied by a peripheral band of low signal intensity on both T_1- and T_2-weighted images separating the osteonecrosis from the surrounding normal bone marrow. The Association Research Circulation Osseous (ARCO) classification system takes into account abnormal findings on MRI and plain radiographs but has not proved to be superior to the Ficat-Arlet classification (Table III).[16,17] A modified combined Kerboul angle using midcoronal and midsagittal MRI predicted femoral head collapse in 37 hips with osteonecrosis of the femoral head.[18] None of the femoral heads with a combined angle of 190° or less collapsed; 50% of femoral heads with a combined angle of 190° to 240° collapsed; and all femoral heads with a combined angle of 240° or more collapsed.

Table III. Association Research Circulation Osseous (ARCO) Classification of Femoral Head Osteonecrosis[16]

Stage	Findings	Modalities	Location Description	Quantification
0	None	Radiography CT Scintigraphy MRI	None	None
1	Radiography and CT are normal, but MRI or scintigraphy is positive	Scintigraphy MRI	Medial Central Lateral	Areas of involvement: A (<15%), B (15%-30%), C (>30%)
2	Sclerosis, osteolysis, or focal osteoporosis	Radiography CT Scintigraphy MRI	Medial Central Lateral	Areas of involvement: A (<15%), B (15%-30%), C (>30%)
3	Crescent sign and/or flattening of articular surface	Radiography CT	Medial Central Lateral	Areas of involvement: A (<15%), B (15%-30%), C (>30%) Surface collapse: A (<2 mm), B (2-4 mm), C (>4 mm)
4	Osteoarthritis with acetabular changes	Radiography	None	None

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

Table IV. Nonoperative Treatment Modalities for Femoral Head Osteonecrosis

Treatment	Literature	Study Design	Outcome	Recommendation
Activity modification & physical therapy	Mont et al[5]	Meta-analysis of 21 studies (819 hips)	22% satisfactory results; 80% required joint replacement or other salvage operation	Not recommended
	Neumayr et al[19]	Randomized clinical trial of 46 sickle cell hips with follow-up of 3 years	Hip function was equivalent after physical therapy alone or core decompression with physical therapy	
	Hernigou et al[20]	Prospective evaluation of 121 sickle cell hips with mean follow-up of 14 years	75% had intractable pain and required surgery	
Bisphosphonates	Astrand & Aspenberg[21]	Systemic administration of alendronate in rats	Inhibited bone resorption	Recommended for Ficat I & II; potential adverse effects (see review[33])
	Agarwala et al[22]	Prospective study of 100 femoral heads (Ficat I-IV) at 1 year	Reduced pain, improved function, and delayed progression of femoral head osteonecrosis	
	Lai et al[23]	Randomized clinical trial of alendronate vs placebo in 40 patients (Steinberg II & III) with follow-up of 28 months	Alendronate significantly reduced rate of femoral head collapse (6.9% vs 76%) and improved HHS score (from 65.6 to 74.4)	
	Nishii et al[24]	Prospective comparison of 20 hips managed with daily alendronate and 13 untreated control hips	Compared with control group, alendronate group had lower rate of femoral head collapse, less hip pain, and larger decrease in markers of bone resorption	
	Ramachandran et al[25]	Prospective case series of 17 adolescents treated with intravenous bisphosphonates for 20 months with follow-up of 2 years	82% pain-free and excellent clinical and patient-reported outcomes 2 years after therapy	
	Peled et al[26]	24 rats after surgical vascular interruption of femoral head treated with or without alendronate	No histologic femoral head collapse 42 days after intervention	
	Agarwala et al[27]	Retrospective review of 395 hips managed with alendronate for 3 years with mean follow-up of 4 years	Significant alteration of natural history of osteonecrosis with radiographic progression of collapse in 45% and survival of 90% for Ficat I & II hips at 4 years	
Extracorporeal shockwave therapy	Ludwig et al[28]	Prospective study of 22 patients with early-stage (precollapse) osteonecrosis with follow-up of 1 year	Successful outcomes (improved HHS; decreased pain; stable, partially healed, or fully healed lesions on MRI) in 14 patients (64%)	Further research needed before routine use can be recommended; causes transient local ecchymosis in about half of patients
	Wang et al[29]	Randomized clinical trial of ECST vs core decompression and bone grafting in patients with early osteonecrosis with follow-up of 25 months (79% vs 29%); and transient local ecchymosis and swelling in 14 hips (48%)	Compared with core decompression group, ECST group had significant reductions in pain and significant improvement in HHS; higher self-rated improvement in symptoms (79% vs 29%); and transient local ecchymosis and swelling in 14 hips (48%)	
	Massari et al[30]	Retrospective review of 76 hips managed with pulsed electromagnetic field stimulation 8 h/d for 5 months	94% (50/53) of Ficat I & II hips were preserved; 52% (12/23) of Ficat III hips later underwent THA; 26% showed evidence of continued femoral head collapse; 53% of patients experienced pain relief	
	Wang et al[31]	Randomized clinical trial of 60 hips managed with ECST and alendronate vs ECST alone with follow-up of 1 year	No significant improvement in clinical outcome, THA rate, or lesion progression	
Hyperbaric oxygen therapy	Reis et al[32]	12 patients (Steinberg I) treated with hyperbaric oxygen therapy for 100 days	10 patients (81%) had normal MRI with healed lesion; at 2 years, these 10 patients remained free of major symptoms and were able to return to active employment	Further research needed before routine use can be recommended

Abbreviations: ECST, extracorporeal shockwave therapy; HHS, Harris Hip Scale; MRI, magnetic resonance imaging; THA, total hip arthroplasty.

Nonoperative Management

Activity Modification and Physical Therapy

Altering weight-bearing status to preserve the shape of the femoral head while it is undergoing remodeling has been attempted in numerous studies, but most have failed to show a significant clinical benefit for this approach. A meta-analysis of 21 studies demonstrated that, with nonoperative management, only 22% of patients had satisfactory outcomes and 80% required THA or another salvage procedure.[5] On the other hand, results of a small randomized clinical trial evaluating physical therapy alone and core decompression with physical therapy in 38 patients with osteonecrosis of the femoral head from sickle cell disease demonstrated no statistical difference in clinical outcome after core decompression and physical therapy and after physical therapy alone (Table IV).[19] However, this study is not necessarily generalizable to all cases of osteonecrosis of the femoral head and had a prohibitively small sample size as well as a high attrition rate.[34] In addition, untreated osteonecrosis of the femoral head from sickle cell disease has a predictable progression to pain and femoral head collapse in long-term follow-up.[20] Given the data in the orthopedic literature, activity modification or physical therapy alone is not recommended and requires more investigation despite its relative success in managing osteonecrosis of the femoral head in sickle cell disease.

Bisphosphonates

Bisphosphonates (eg, etidronate, pamidronate, alendronate, ibandronate, risedronate, zoledronate) are a class of compounds that inhibit the ability of osteoclasts to resorb bone, increase osteoclast apoptosis, and reduce osteoblast and osteocyte apoptosis. The overall effect of bisphosphonates is to reduce the rate of bone remodeling and turnover. Bisphosphonates have been approved by the US Food and Drug Administration to treat patients with osteoporosis. Resorption of bony matrix and the structural collapse that subsequently occurs in osteonecrosis may also be prevented by these compounds. Systemic use of bisphosphonates may be effective as management during early stages of osteonecrosis (Table IV). A retrospective evaluation of 395 hips managed with alendronate for 3 years demonstrated improved function, reduction in collapse rate, and delayed THA at 4-year follow-up.[27] Results were similar for adolescents after 2-year follow-up.[25] Animal studies support this observation, as rats with surgically interrupted femoral head circulation managed with alendronate showed no histologic evidence of femoral head collapse 42 days after surgery, whereas controls showed marked femoral head collapse over the same time course.[26] Authors of a randomized clinical trial found that, in 40 patients with osteonecrosis, alendronate (vs placebo) significantly reduced the rate of femoral head collapse from 76% to 7% within 2 years.[23]

Bisphosphonate therapy is not without adverse effects. The most notorious and fortunately rare adverse effect is mandibular osteonecrosis. More common adverse effects are upper gastrointestinal upset, flu-like symptoms, nephrotoxicity, secondary hypoparathyroidism, musculoskeletal pain, medication-induced fracture, atrial fibrillation, ophthalmic complications, and dermatologic complications. These were comprehensively reviewed by Papapetrou.[33]

Extracorporeal Shockwave Therapy

Extracorporeal shockwave therapy (ECST) was originally used to disrupt calcific deposits within the renal, biliary, and salivary tracts. Subsequent animal studies demonstrated that extracorporeal shockwaves applied at certain energy levels stimulated osteogenesis.[35] In a bovine fracture model, extracorporeal shockwaves recruited osteoblasts in a dose-dependent manner.[36] Histopathologic analysis of femoral heads extracted from 14 patients with femoral head osteonecrosis—half underwent ECST before THA, half did not—showed significant changes in expression of several genes involved in angiogenesis and bone remodeling after ECST.[31] Hence, this technology has been applied to several musculoskeletal conditions, including osteonecrosis.[31,36-38] A few studies, including a randomized controlled trial, have shown that ECST resulted in higher Harris Hip Scores (HHS) and less pain (Table IV) and possibly prevented femoral head collapse.[28-30] Adding alendronate to ECST, however, apparently did not improve the short-term clinical outcome of ECST alone.[31] In summary, ECST is an inexpensive and noninvasive treatment modality that may be useful in managing early-stage osteonecrosis, but further investigation is needed.

Hyperbaric Oxygen Therapy

Administration of hyperbaric oxygen has been reported to increase the level of tissue oxygenation, which can in turn lead to fibroblast proliferation, collagen synthesis, and angiogenesis.[32,39] In addition, hyperbaric oxygen therapy has been shown to decrease tissue edema, potentially lowering intraosseous pressure within the femoral head and improving microcirculation.[40] In a recent study, 12 patients with early-stage femoral head osteonecrosis underwent hyperbaric oxygen therapy for 100 days. Ten patients (83%) demonstrated a healed femoral lesion on follow-up evaluation at 2 years. These patients remained free of major symptoms and were able to return to active employment.[32] Nonetheless, few studies have been conducted on this modality and additional clinical experience is needed (Table IV).

Summary

The management of osteonecrosis remains controversial, especially for young and active patients. Clearly, early management should focus on preventing structural col-

lapse. Improved diagnostic tools have made early disease detection possible, and many treatment modalities (nonoperative and operative, to follow in Part II) have favorably altered the natural progression of femoral head osteonecrosis. Some results have varied according to patient population, treating center, and disease stage. However, recent modifications of management techniques as well as new management strategies hold the potential to significantly improve clinical outcomes.

Authors' Disclosure Statement

Dr. Di Cesare reports being a paid consultant to Zimmer, Inc. on digital templating program and porous tantalum implants. The other authors report no actual or potential conflict of interest in relation to this article.

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This paper will be judged for the Resident Writer's Award.