Nontraumatic Osteonecrosis of the Femoral Head: Ten Years Later

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Current Concepts Review

Nontraumatic Osteonecrosis of the Femoral Head: Ten Years Later

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- The etiology of osteonecrosis of the hip may have a genetic basis. The interaction between certain risk factors and a genetic predisposition may determine whether this disease will develop in a particular individual.
- The rationale for use of joint-sparing procedures in the treatment of this disease is based on radiographic measurements and findings with other imaging modalities.
- Early diagnosis and intervention prior to collapse of the femoral head is key to a successful outcome of joint-preserving procedures.
- The results of joint-preserving procedures are less satisfactory than the results of total hip arthroplasty for femoral heads that have already collapsed.
- New pharmacological measures as well as the use of growth and differentiation factors for the prevention and treatment of this disease may eventually alter our treatment approach, but it is necessary to await results of clinical research with long-term follow-up of these patients.

It has been ten years since our previous Current Concepts Review on osteonecrosis of the femoral head was published[1]. Despite recent outstanding reviews on the subject[2-4], there continues to be a lack of consensus concerning the pathogenesis and treatment of this disease. Even the name *osteonecrosis* is now more accepted and more commonly used than the previous name, *avascular necrosis.* In this review, we will update concepts concerning etiologies and nonoperative and operative treatment methods that were discussed in the previous reviews. This article is based almost exclusively on peer-reviewed studies published from 1995 to the present, and it is intended to provide background for an evidence-based approach to treatment of this disease.

Over the past ten years, multiple studies have demonstrated excellent rates of success of total hip arthroplasties in patients with osteonecrosis[5-38]. The indications for joint-preserving procedures seem less clear as justification for their use requires further evidence of positive results from clinical studies. For patients in whom joint-preserving procedures are indicated, early diagnosis is essential. For the purpose of this review, the lesions will be broadly described as *precollapse* or *postcollapse* with occasional references to the size of the lesion, amount of head depression, or acetabular involvement.

Etiology, Pathogenesis, and Pathology

The pathophysiology of osteonecrosis of the femoral head has not been completely elucidated. Whereas some cases of the disease clearly have a direct cause (trauma, radiation, or Caisson disease), the pathophysiology is uncertain for most cases. Multiple investigators have postulated vascular impairment, altered bone-cell physiology, and other theories[1-4,7,39]. In addition, several comorbidities have been linked to this disease[1-4,7,40-43].

One of the most common risk factors for osteonecrosis of the femoral head is use of corticosteroids[41,44-61], but the extent of use that constitutes a risk is still under debate. Although many patients receiving corticosteroids have at least one other confounding factor, multivariate analysis has suggested that corticosteroid use, especially in high doses, is an independent variable. Dosages typically considered to be associated with the disease are >2 g of prednisone, or its equivalent, within a period of two to three months. Lower dosages are not typically related to osteonecrosis of the femoral head, and reports of an association with such doses are often anecdotal and involve patients with multiple risk factors, such as alcohol use or smoking[45,60,62-64]. Inoue et al.[41] reported that osteonecrosis of the femoral head developed in eighteen of 287 renal transplant recipients treated orally with ≥25.0 mg/day of

prednisolone. In a study of twenty-two patients diagnosed with osteonecrosis of the femoral head, Koo et al.[51] found that the total dose of corticosteroids used until osteonecrosis was detected with magnetic resonance imaging ranged from 1800 to 15,505 mg (mean, 5928 mg) of prednisolone or its equivalent. Various reports have described a corticosteroid dose-related risk of osteonecrosis of the femoral head in patients with severe acute respiratory syndrome (SARS)[47,50,55]. Griffith et al.[47] found that twelve (5%) of 254 patients with SARS had evidence of osteonecrosis of the femoral head and that the cumulative prednisolone-equivalent dose was the most important risk factor, with the risk being 0.6% for patients receiving a dose of <3 g and 13% for those receiving a dose of >3 g.

The risk period for the development of osteonecrosis of the femoral head following corticosteroid therapy has been more exactly defined. Using magnetic resonance imaging, Sakamoto et al.[56] prospectively evaluated the femoral heads in forty-eight patients (ninety-six hips) receiving high-dose corticosteroids for various autoimmune-related disorders. Abnormalities were found in thirty-one hips (32%). The initial necrotic changes were seen as well-demarcated, band-like zones at a mean of 3.6 months (maximum, twelve months) after initiation of the corticosteroid treatment. Fink et al.[59], in a prospective study of forty-three patients receiving corticosteroids while undergoing renal transplantation, observed that osteonecrosis of the femoral head occurred in six hip joints of four patients (9%) within three months after the transplantation. Magnetic resonance imaging performed twelve months after transplantation revealed no additional lesions. Koo et al.[51] found the period from the start of corticosteroid treatment to the diagnosis of osteonecrosis to range from one to sixteen months (mean, 5.3 months), with twenty-one of twenty-two patients diagnosed within twelve months. Thus, for the majority of patients receiving corticosteroids, the risk period for the development of osteonecrosis of the femoral head is twelve months or less.

Alcohol use is another important risk factor[44,62,63]. In a retrospective study comparing 118 patients with noncorticosteroid-associated osteonecrosis of the femoral head with 236 control patients, Hirota et al.[62] found a higher risk of osteonecrosis of the femoral head developing in occasional drinkers (<8 mL of alcohol once a week, but not daily) (relative odds = 3.2) and in regular drinkers (≥8 mL of alcohol daily) (relative odds = 13.1) than in controls. They also found a significant dose-response relationship ($p < 0.001$), with the relative odds for current drinkers being 2.8, 9.4, and 14.8 in association with ethanol intakes of <320, 320 to 799, and ≥800 g/wk, respectively. Matsuo et al.[63] compared 112 patients with osteonecrosis of the femoral head with 168 control patients and found an elevated risk for regular drinkers (>8 mL of alcohol every day) (relative risk = 7.8). They also reported a clear dose-response relationship, with relative risks of 3.3, 9.8, and 17.9 for current drinkers consuming <400, 400 to 1000, and ≥1000 mL/wk of alcohol, respectively.

Smoking has been implicated as a risk factor for osteonecrosis of the femoral head[62-64]. Hirota et al.[62] found an increased risk for current smokers (relative odds = 4.7); however, a cumulative effect of smoking was evident only in association with twenty pack-years or more. Matsuo et al.[63] also found an increased risk for current smokers (relative risk = 3.9). Various studies have demonstrated that smoking inhibits osteogenesis or fracture-healing[64-66].

Osteonecrosis of the femoral head is believed to be a multifactorial disease that is associated in some cases with both a genetic predilection and exposure to certain risk factors. These risk factors include corticosteroid use, alcohol intake, smoking, and various chronic diseases (renal disease, hematological disease, inflammatory bowel disease, post-organ transplantation, hypertension, and gout)[1-4,39-44,52-54,57,58,62,63].

Patients with inherited coagulation disorders may be at risk for the development of osteonecrosis of the femoral head. Studies have shown an association with thrombophilia (an increased likelihood of blood clots) and hypofibrinolysis (a decreased ability to lyse blood clots)[3,4,39,40,42,43,67-80]. We analyzed nine coagulation factors and found at least one coagulation factor abnormality in thirty-seven (82%) of forty-five patients with osteonecrosis of the femoral head compared with 30% of controls ($p < 0.0001$)[74]. Two or more abnormalities were identified in twenty-one patients (47%) compared with 2.5% of controls ($p < 0.0001$). Glueck et al.[70] found a high prevalence of plasminogen activator inhibitor-1 coagulation abnormalities in a study of fifty-nine patients with osteonecrosis of the femoral head. Because some of these coagulation alterations may be the result of autosomal dominant disorders, it may be possible to screen individuals at risk.

Liu et al.[81] identified three families with an autosomal dominant inheritance of osteonecrosis of the femoral head and mapped the chromosomal position of a collagen type-II gene (COL2A1 gene) mutation. Osteonecrosis of the femoral head has also been associated with certain genetic polymorphisms such as alcohol-metabolizing enzymes and the drug-transport protein P-glycoprotein[48,78,82-86]. The importance of these findings is that genetic screening of families with osteonecrosis of the femoral head could be used to identify carriers before the onset of clinical symptoms. This might allow the initiation of measures that could delay disease progression and may have implications for pharmacological treatment. In addition, the pathological condition associated with the defect could be treated, thereby possibly eliminating the risk factor. For example, a patient with familial hyperlipidemia could be treated with lipid-lowering agents and be regularly screened with magnetic resonance imaging to enable an early diagnosis, which could lead to the most optimal treatment.

Corticosteroids and alcohol may also have an effect on osteoblast differentiation[48,49,84,87]. While laboratory studies by Wang et al.[57,58] showed that corticosteroids may direct bone-marrow stromal cells into the adipocytic pathway as opposed to the osteoblastic pathway, a clinical study has also shown decreased osteogenic differentiation in cells harvested from patients with corticosteroid or alcohol-associated osteonecrosis of the femoral head[87].

Patients infected with human immunodeficiency virus

(HIV) are at increased risk for the development of osteonecrosis of the femoral head[88-96]. It is unclear whether the virus itself is responsible or the treatments (with antiretroviral drugs such as protease inhibitors, corticosteroids, or other chemotherapeutic agents) are the pathogenic agents. In a study of eight patients with HIV infection, Blacksin et al.[88] found that osteonecrosis of the femoral head did not appear to be directly related to HIV, but rather to the use of corticosteroid treatment. Miller et al.[94] found osteonecrosis of the femoral head in fifteen (4.4%) of 339 HIV-infected adults and no hip lesions in 118 age and gender-matched HIV-negative volunteers. The hip lesions occurred more frequently in individuals who used corticosteroids, lipid-lowering agents, or testosterone. Several studies have implicated antiretroviral therapy as the most important pathogenic agent[89,91,92,95]. In contradistinction to these studies, Ries et al.[96] identified four patients with HIV and osteonecrosis of the femoral head who had no other known risk factors, a finding that suggests that HIV infection itself may be a unique risk factor.

Although osteonecrosis of the femoral head is a rare complication of pregnancy, several cases have been documented in the literature[97-100]. These patients typically have no other risk factors. Montella et al.[98] reported on thirteen patients (seventeen hips) in whom osteonecrosis of the femoral head developed during pregnancy or in the first postpartum month. The patients were mostly primigravid (eleven of thirteen patients), with "a small body frame and a relatively large weight gain." Many of these cases were initially misdiagnosed as transient osteoporosis of the hip.

Factors Affecting Treatment

Radiographic Staging

Treatment algorithms for osteonecrosis of the femoral head are based on staging of the lesion. Numerous staging systems have been utilized to describe the radiographic extent of the disease. Each system has limitations, and no single system has been universally accepted for use alone as a guide to treatment.

Most authors have reported routinely utilizing four essential radiographic findings when formulating a treatment plan. These findings, which have been corroborated in peer-reviewed studies of outcomes of various treatment methods[3,4,74,101-111], include (1) evidence that the lesion is either precollapse or postcollapse, (2) the size of the necrotic segment, (3) the amount of femoral head depression, and (4) acetabular involvement with signs of osteoarthritis.

Integrity of femoral head: Collapse of the femoral head is a consequence of mechanical failure. While large areas of collapse can be recognized as a change in the contour of the femoral head, the so-called crescent sign is an earlier indicator of this failure (Fig. 1). When collapse is present, it is probable that the patient will eventually require a total hip replacement.

Size of lesion: Many studies have shown that the size of the lesion, regardless of the treatment method, is predictive of outcome[101]. The size of a radiographically evident lesion can be estimated on the basis of combined necrotic angle measurements[112]. When a patient has early disease, the lesion is not radiographically evident or the margins may be poorly defined. These lesions can be detected only with magnetic resonance imaging (Fig. 2). Steinberg et al.[111] described a method for assessing the amount of femoral head involvement by these lesions with magnetic resonance imaging. Cherian et al.[113] used radiographs and magnetic resonance imaging to evaluate thirty-nine hips in twenty-five patients who had Stage-I or II disease according to the grading system of the Association Research Circulation Osseous (ARCO). They found that various methods for measuring the sizes of lesions (calculation of an index of necrotic extent and estimation of the percent involvement) could be used with confidence as they were highly reliable and reproducible. Their analysis of the grades assigned independently on two separate occasions by three observers with different medical specialty backgrounds and experience resulted in correlation coefficients that demonstrated substantial agreement for all sizes of lesions.

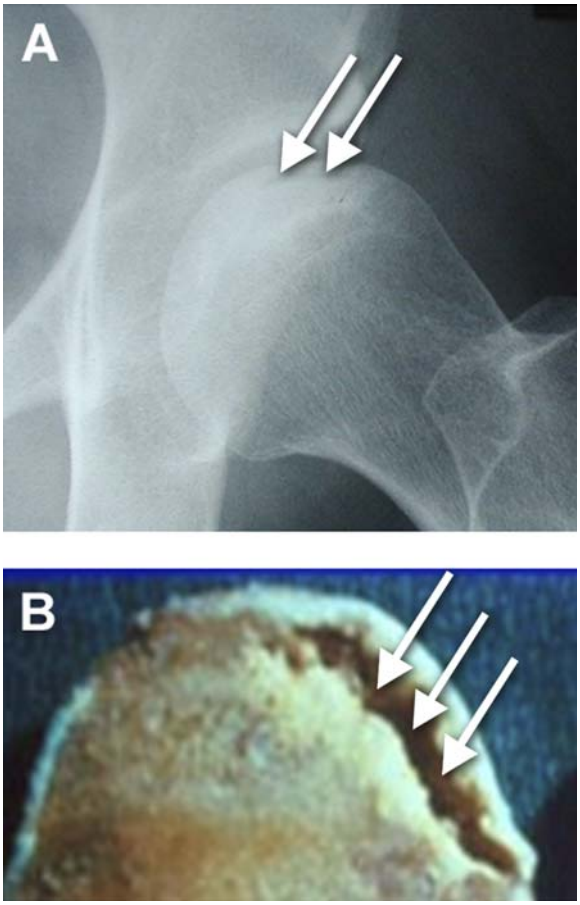

Fig. 1

A: Sagittal radiograph of a femoral head, delineating a crescent sign (arrows) that is the result of a subchondral fracture and indicates biomechanical compromise. *B:* Sagittally sliced gross section of a femoral head obtained at surgery, delineating a crescent sign (arrows).

Femoral head depression: A change in the femoral head contour of >2 mm has been shown to confer a worse prognosis. In a cross-sectional study of fifty-two patients (sixty-eight

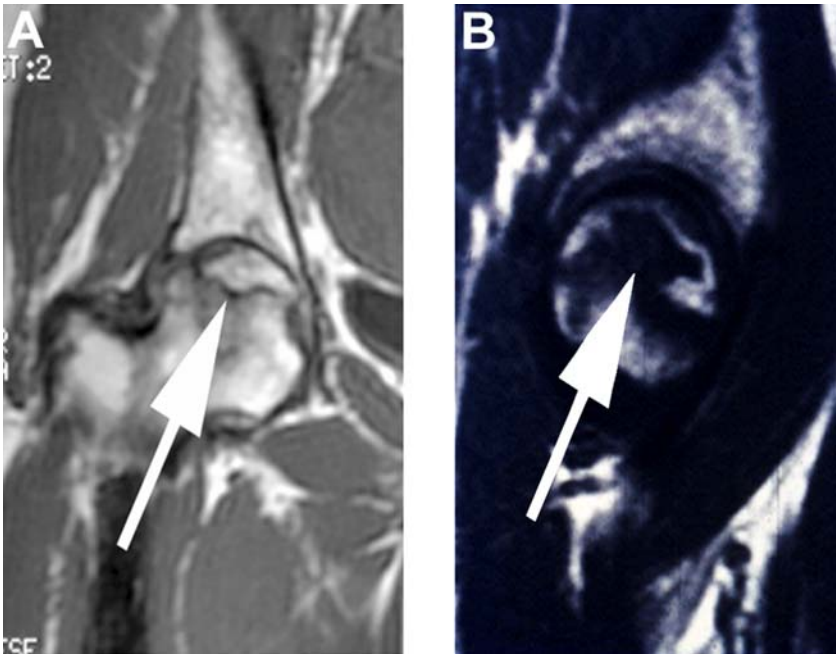

Fig. 2

T1-weighted magnetic resonance images showing a small *(A)* and a large *(B)* osteonecrotic lesion of the femoral head. The arrows denote the lesions.

hips) who had had a core decompression for the treatment of Ficat and Arlet Stage-III disease[114] and had been followed for a mean of twelve years (range, four to eighteen years)[109], eighteen (41%) of forty-four hips with Steinberg Stage-III disease[111] (no head depression and the presence of a crescent sign) required a total hip replacement whereas twenty-two (92%) of twenty-four hips with Steinberg Stage-IV disease (head depression) underwent arthroplasty. Soucacos et al.[115] reported that, in a study of 184 hips (152 patients) followed for one to ten years (mean, 4.7 years) after vascularized fibular grafting, the best results were found in hips with Steinberg Stage-II disease (no head depression), 95% of which had remained stable. In contrast, only 39% of the hips with femoral head depression had remained stable.

Acetabular involvement: It is important to recognize acetabular involvement, as treatments directed at saving the femoral head will be unsuccessful when the disease has progressed to involve the acetabular socket[1,2,116-118]. Moreover, there may be evidence of degeneration of the acetabulum even when radiographs show normal findings and joint-space narrowing is absent[119].

Intraoperative Assessment

Although most procedures used for the early treatment of osteonecrosis of the femoral head are selected on the basis of preoperative assessment, intraoperative findings are valuable for confirming staging and they may play a role in treatment choice. For example, one might have planned a bone-grafting procedure on the basis of the radiographic findings, but an intraoperative finding of substantial damage to the cartilage of the femoral head would indicate that a total hip replacement would be more appropriate. Arthroscopy can also be utilized to evaluate lesions[120-124]. Ruch et al. used arthroscopy to study fifty-two hips in forty-six patients with osteonecrosis of the femoral head that had been staged prospectively with radiographs and magnetic resonance imaging[123]. In eighteen hips in which loss of integrity of the femoral head had been noted on plain radiographs, arthroscopy of the hip revealed osteochondral degeneration not detected by magnetic resonance imaging. McCarthy et al. used arthroscopy to study seven patients and concluded that this procedure could enhance the accuracy of staging[122].

Sometimes procedures (core decompression and bone-grafting) are performed without assessment of the femoral head cartilage intraoperatively. Other tests might be considered for further evaluation of such cases. For example, if one is considering core decompression for what is believed to be a precollapse lesion, a computed tomography scan or tomogram could be used to determine whether there is actually femoral head collapse[125].

Patient-Specific Factors

It is essential to consider patient age, activity level, general health, comorbidities, and life expectancy when planning treatment. Physical examination assessing the amount of pain, limp, and limitation of hip motion may also be utilized to determine the severity of joint involvement. Systemic disease or a short life expectancy may preclude a major surgical procedure. Similar lesions may not be treated in the same way in two patients with different ages and activity levels. For example, a hip with femoral head collapse and no acetabular involvement might be best treated with a bone graft in a healthy twenty-one-year-old but

the same pathological condition would be best treated with a total hip replacement in a seventy-six-year-old. Patients who are medically compromised may be more appropriately treated with one definitive procedure (total hip replacement) rather than with procedures that may be only temporizing. It might be intuitive to think that patients with certain diagnoses and risk factors (corticosteroid treatment or systemic lupus erythematosus, for example) would have worse outcomes of treatment. However, treatment success rates have been more closely correlated with the structural integrity of the femoral head than with demographic factors.

The duration of symptoms has been found to influence the outcomes of preservative treatment. In a previous study of forty-five Ficat and Arlet Stage-I and II hips in which core decompression was done by drilling multiple times with a percutaneous small-diameter pin, one of us (M.A.M.) and colleagues[126] reported a mean preoperative duration of symptoms of six months for patients who had a successful outcome compared with eleven months for those who had a poor outcome. Beaule et al.[127] observed a better prognosis for patients who had experienced symptoms for less than twelve months before treatment with limited femoral head resurfacing than for patients who had had symptoms for more than twelve months before such treatment.

Diagnostic Methods

If standard anteroposterior and frog-leg lateral radiographs show obvious osteonecrosis of the femoral head, it is not necessary to perform magnetic resonance imaging. However, magnetic resonance imaging is the best diagnostic method for cases that are radiographically occult or not obvious on radiographs as it has been found to be 99% sensitive and 98% specific for this disease[128-134]. Protocols have allowed rapid screening to reduce the cost and time of magnetic resonance imaging, making sequential, temporal screenings feasible. When limited, rapidly performed magnetic resonance imaging and full screening with magnetic resonance imaging were both used to diagnose lesions and to determine their size, the two studies showed agreement for 177 (98.9%) of 179 hips[132]. May and Disler[134] found that the results of a rapid screening protocol (an imaging time of less than one minute) were similar to those of the routine protocol (an imaging time of more than seven minutes) for patients who had had findings suspicious for radiographically occult osteonecrosis of the femoral head.

Bone-scanning has been reported to be insensitive for the diagnosis of osteonecrosis of the femoral head[135-140]. Scheiber et al.[139] compared planar three-phase bone scans that had been made with a high-resolution parallel-hole collimator with magnetic resonance images of 120 patients with nontraumatic hip pain and twenty-three individuals in a control group. All patients had undergone the magnetic resonance imaging scan within two months of the bone scan. Of thirty hips with a normal appearing scan, twenty-two were found to have osteonecrosis of the femoral head on the magnetic resonance image. The authors concluded that bone-scanning is not indicated for the diagnosis of possible involvement of the contralateral hip in patients with osteonecrosis of the femoral head. Figure 3 illustrates the lack of sensitivity of bone-scanning for diagnosing osteonecrosis of the femoral head.

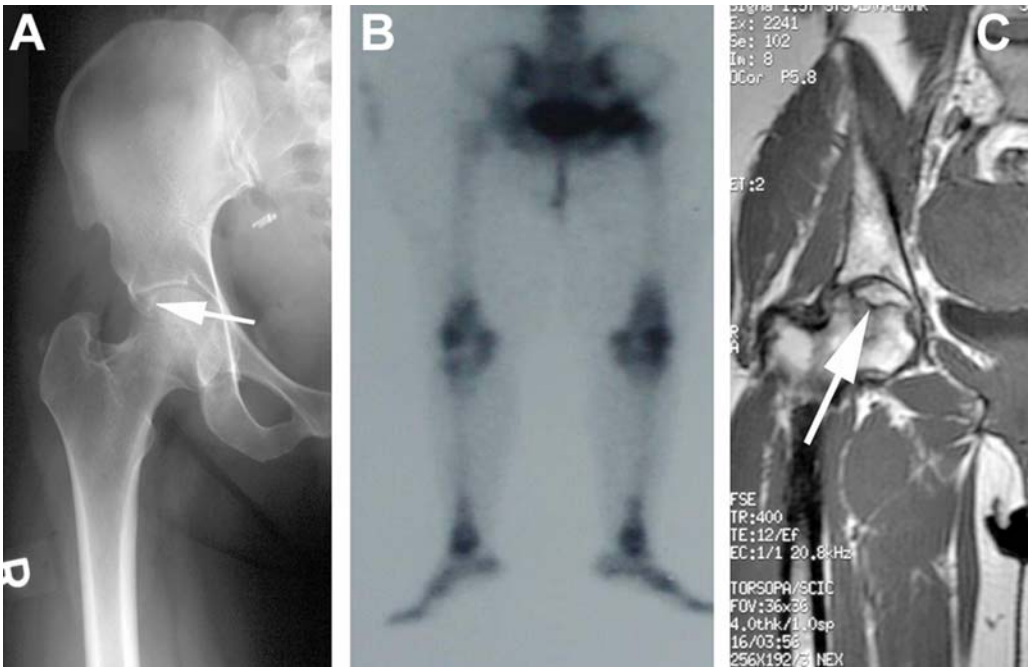

Fig. 3

Bone-scanning lacks sensitivity for diagnosing osteonecrotic lesions of the femoral head. *A:* Early signs of an osteonecrotic lesion (arrow) are shown on the plain radiograph. *B:* A normal or "cold" bone scan of both hips. *C:* Evidence of a subchondral osteonecrotic lesion (arrow) is seen on the magnetic resonance image.

Nonoperative Treatment

Most methods of nonoperative treatment have involved restricted weight-bearing (with various modalities such as a cane, crutch, walker, or two crutches) on the basis of the belief that this slows the progression of the disease so that ultimately, femoral head-preserving procedures can be performed. However, >80% of affected hips progress to femoral head collapse and arthritis by four years after the diagnosis[141]. Disease diagnosed in the early stages (before femoral head collapse) may be amenable to newer nonoperative treatment modalities, but the exact stages at which specific interventions may be successful have not been established.

Published reports now appear to justify nonoperative treatment of small precollapse lesions that are asymptomatic, which may have a better natural history[142-146]. These lesions are often diagnosed in the contralateral hip after evaluation of a symptomatic hip. Jergesen and Khan found that fourteen of nineteen asymptomatic hips with untreated osteonecrosis of the femoral head had progression of the disease; nine had it within five years and five, more than five years after the diagnosis[143]. In a prospective study of forty asymptomatic hips with a small early-stage lesion that was not treated, Hernigou et al.[144] reported that thirty-five (88%) became symptomatic and twenty-nine (73%) demonstrated collapse at a minimum of ten years (mean, eleven years) after the diagnosis.

There is evidence that certain small lesions may spontaneously heal. Cheng et al.[147] prospectively studied thirty hips and found that three had spontaneous resolution. Factors that appeared to be related to resolution were early, asymptomatic disease and a small lesion. In a study by Yoshida et al.[61], twenty-four asymptomatic, radiographically normal hips that were found to have osteonecrosis of the femoral head on magnetic resonance imaging in thirteen patients with systemic lupus erythematosus were followed with magnetic resonance imaging for twelve to ninety-five months (mean, fifty-one months). Fifteen hips improved (>15% reduction in the volume of necrosis) during the observation period, and all hips in which the volume of the necrotic area had been <25% showed a time-dependent decrease in the size of the lesion.

A meta-analysis of the outcomes of protected weight-bearing in 819 patients demonstrated a failure rate of >80% at a mean of thirty-four months[141]. As the majority of patients required a total hip replacement in a short period of time, the authors concluded that conservative treatment of osteonecrosis of the femoral head is not appropriate.

The use of pharmacological agents for the treatment of osteonecrosis of the femoral head has received considerable attention in recent years. The aim of these agents, which include lipid-lowering drugs, anticoagulants, vasodilators, and bisphosphonates, is to address specific physiological risk factors for osteonecrosis such as lipid emboli, adipocyte hypertrophy, venous thrombosis, increased intraosseous pressure, and resorption of bone.

Patients with systemic lupus erythematosus and high serum cholesterol and lipid levels have been treated with lipid-lowering agents[46,148]. This treatment is based on laboratory studies by Wang et al.[57,58], who analyzed the ability of lovastatin to prevent corticosteroid-induced adipogenesis in vitro as well as its effects on adipogenesis and osteonecrosis of the femoral head in vivo in chickens. These studies suggested that, in patients with systemic lupus erythematosus, osteonecrosis of the femoral head may develop as a result of a physiological diversion of mesenchymal stem cells toward an adipocytic as opposed to an osteoblastic lineage. Consequently, treatment with lovastatin may prevent osteonecrosis by preventing the effects of the disease on the diversion of normal osteoblastic cellular differentiation. Pritchett reported that, at a mean of 7.5 years (minimum, five years), osteonecrosis of the femoral head had developed in only three (1%) of 284 patients who were taking high-dose corticosteroids as well as various statin drugs (lipid-clearing agents that dramatically reduce lipid levels)[148]. That prevalence is much lower than the 3% to 20% prevalence reported for patients receiving high-dose corticosteroids without statins[3,43,44]. Thus, statins might offer protection against this disease when corticosteroid treatment is necessary.

Glueck et al.[71] used the anabolic steroid stanozolol (6 mg/day) to treat four patients who had hypofibrinolysis associated with a high level of plasminogen activator activity and one patient who had a high level of lipoprotein in the serum. All five patients showed a decrease of symptoms at one year following treatment. In another study, Glueck et al.[72] used enoxaparin (60 mg/day for twelve weeks) to treat patients who had thrombophilic or hypofibrinolytic disorders and early stages of osteonecrosis of the femoral head. At two years, thirty-one (89%) of thirty-five hips had not required surgery and still had Ficat and Arlet Stage-I or Stage-II disease as assessed radiographically.

The effects of the prostacyclin derivative iloprost, used as a vasodilator, have been studied in patients with osteonecrosis of the femoral head and bone marrow edema syndrome[149,150]. Seventeen patients with early-stage osteonecrosis of the femoral head all had clinical and radiographic improvements at one year after treatment with this agent.

Bisphosphonates have shown promise in small case series[151-154]. These agents, which inhibit osteoclast activity and thus curtail bone resorption, could theoretically slow progression of the disease on the basis of the hypothesis that increased resorption contributes to collapse of the femoral head. Three recent studies of rats[155], canines[156], and pigs[157] have shown a reduction in the prevalence of femoral head collapse after treatment with bisphosphonates. Recent clinical reports have suggested that alendronate can be potentially beneficial for patients with osteonecrosis of the femoral head. At an average of one year (range, three months to five years) after treatment of sixty patients (100 hips) with this agent (10 mg/day), Agarwala et al.[151] found clinical improvement, with a reduction in patient disability scores and only six patients (ten hips) requiring surgery. Similar findings were recently reported by Lai et al.[154], in a study of forty patients with Steinberg Stage-II or III osteonecrosis of the femoral head who were either treated with alendronate (70 mg/day for twenty-five weeks) or assigned to a control group. At a minimum of twenty-four

months, only two of the twenty-nine hips in the alendronate group had loss of femoral head integrity compared with nineteen of the twenty-five hips in the control group ($p < 0.001$). One hip in the alendronate group and sixteen hips in the control group underwent total hip arthroplasty ($p < 0.001$).

Various external, biophysical, nonoperative modalities have been utilized to treat osteonecrosis of the femoral head. These include electromagnetic stimulation, extracorporeal shock-wave therapy[158-160], and hyperbaric oxygen[161-164]. The effectiveness of electromagnetic stimulation for treatment of osteonecrosis of the femoral head was evaluated in the 1980s and 1990s, with some studies showing early promising results[114,165]; however, the evidence was not conclusive enough for approval by the Food and Drug Administration. Extracorporeal shock-wave therapy has been utilized in Europe for treatment of early-stage disease. Wang et al.[160] compared the results of such therapy in twenty-three patients (twenty-nine hips) with the results in a group treated with nonvascularized fibular grafting. At a mean of twenty-five months, 79% of the shock-wave group had improved Harris hip scores compared with 29% of the group treated with nonvascularized fibular grafting. The use of hyperbaric oxygen has had mixed results and is associated with high cost and an extensive time commitment for patients. In one study, hyperbaric oxygen prevented femoral head collapse in a vascular deprivation-induced osteonecrosis model in rats[161]. In another study, by Reis et al.[162], sixteen hips in twelve patients who had early-stage osteonecrosis of the femoral head were treated with hyperbaric oxygen for 100 days. Thirteen of the sixteen hips had disappearance of abnormalities on magnetic resonance imaging.

Operative Treatment

Core Decompression

In a meta-analysis of the outcomes of core decompression in 1206 hips treated in twenty-four studies published prior to 1995, the best results were observed following the treatment of early-stage lesions[141]: 84% of patients with Ficat and Arlet Stage-I disease and 65% of patients with Stage-II disease had a successful result. Similar results for precollapse disease were found in studies published since 1996 (see Appendix)[103,105,107,109,126,165-191]. In 2000, Castro and Barrack identified twenty-two studies of core decompressions and compared them with eight studies in which the patients had been treated nonoperatively[167]. Chi-square analysis showed the success rate of core decompression to be significantly higher than that of conservative treatment for hips with early-stage disease ($p < 0.05$). The authors concluded that large, multicenter, prospective, double-blinded studies of patients randomized to either treatment method and then stratified by the stage, cause, and bilaterality of the disease were needed.

One of us (M.A.M.) and colleagues described a core technique that involves drilling multiple times with a small (3.2-mm-diameter) pin[126]. At a mean of two years (range, twenty to thirty-nine months) postoperatively, the clinical outcome was successful (a Harris hip score of >80 points and no additional surgery) for thirty-two (71%) of forty-five hips and for twenty-four (80%) of thirty Ficat and Arlet Stage-I hips. The procedure was technically straightforward, and there were no operative complications. The technique was based on previous work by Kim et al., who reported a lower rate of radiographically determined femoral head collapse (14.3%) at three years compared with the rate following traditional core decompression techniques (45%; $p = 0.03$)[172].

Scully et al.[184] compared core decompression (ninety-eight hips; seventy-two patients) with vascularized fibular grafting (614 hips; 480 patients). None of the eleven hips that had Ficat and Arlet Stage-I disease needed a total hip replacement after being treated with either regimen, whereas 65% (twenty-eight) of forty-three Stage-II hips treated with core decompression and 89% (ninety-nine) of 111 Stage-II hips treated with vascularized fibular grafting had survived at fifty months. The rate of survival of the hips with Ficat and Arlet Stage-III disease was superior following vascularized fibular grafting ($p < 0.0001$). The authors concluded that the increased morbidity associated with vascularized fibular grafting is justified by the associated delay in, or prevention of, articular collapse in hips that have large Ficat and Arlet Stage-II lesions or Stage-III disease. Since the results of the two procedures were similar for the hips with Stage-I or early Stage-II disease, core decompression, which is technically easy and associated with low morbidity, might be preferable at those stages. In summary, core decompression has the best results in hips with a small or medium-sized lesion, regardless of associated risk factors. For an excellent review of core decompression, readers are referred to the recent report by Lieberman[191].

Osteotomy

Osteotomies are used to move the segment of necrotic bone away from the weight-bearing region. There are two general types of osteotomies: angular intertrochanteric (varus and valgus) and rotational transtrochanteric[20,108,192-214]. Rotational osteotomies allow large degrees of translation of the osteonecrotic segment, as vthey employ a rotational femoral bone flap based on a vascular pedicle (the medial femoral circumflex artery). While rotational osteotomies may have a role in the management of selected patients, they can be difficult to perform and they have a high potential for morbidity, including nonunion. Total hip replacements performed after an osteotomy are often technically more difficult than those done in patients with osteonecrosis of the femoral head who have never had an osteotomy. Several reports have described increased operative time, increased blood loss, technical difficulties, and high infection rates in association with hip replacements after osteotomy[193,215,216].

The results of seven studies of angular osteotomies, published since 1995, are summarized in the Appendix. Ancillary bone-grafting was also used in some of the studies[198,208,217]. Results were variable, with success rates ranging from 40% to 96% at three to twenty-six years postoperatively. The angular osteotomies usually had the best results in young active patients who were not taking corticosteroids, had unilateral involvement with a good preoperative range of hip motion, and

had a small lesion without femoral head collapse.

The results of nine studies of rotational osteotomies are also summarized in the Appendix. These procedures are technically more demanding than angular osteotomies. For excellent reviews of the indications, techniques, and results of osteotomies, readers are referred to recent reports by one of us (D.S.H.)[116] as well as by Shannon and Trousdale[193].

Nonvascularized Bone-Grafting

Nonvascularized bone-grafting has numerous theoretical advantages for the treatment of precollapse and early postcollapse lesions when the articular cartilage is relatively undamaged. The procedure provides decompression of the femoral head, removal of necrotic bone, and structural support and scaffolding to allow repair and remodeling of subchondral bone[176,217-228]. Presently, there are three distinct approaches for introducing bone graft: (1) placement of cortical graft through a core track made in the femoral neck and head; (2) grafting performed through a so-called trapdoor[220-222] made through the articular cartilage of the femoral head (the trapdoor exposes the underlying lesion, necrotic bone is removed, and the cavity is filled with cancellous and/or cortical bone graft); and (3) grafting through a window made in the femoral neck at the base of the head (the necrotic area is removed, and bone graft is placed in the defect).

The results of these bone-grafting techniques are summarized in the Appendix. In well-selected patients, success rates have ranged from 24% to 100% at two to fifteen years postoperatively. Rosenwasser et al.[228] described a "light bulb" procedure in which diseased bone was curetted out through a trapdoor in the femoral neck and was replaced by cancellous autograft. The authors found an 87% rate of successful results in a study of fifteen hips at a mean of twelve years. One of us (M.A.M.) and colleagues[223] performed a similar procedure in twenty-one hips (nineteen patients), with diseased bone replaced by a bone-graft substitute (a combination of demineralized bone matrix, processed allograft bone chips, and a thermoplastic carrier). At a mean of four years (range, three to 4.5 years), eighteen (86%) of the twenty-one hips showed a clinically successful result (a Harris hip score of >80 points and no additional procedures).

Rijnen et al.[227] used a lateral approach, as is employed in a traditional core decompression, to remove osteonecrotic bone from femoral head lesions and impacted allogeneic and autogenous cancellous bone grafts to regain femoral head sphericity. Of twenty-eight consecutive hips (twenty-seven patients) with extensive lesions that were prospectively followed for a mean of forty-two months (range, twenty-four to 119 months), eight (29%) were converted to a total hip replacement. Of the twenty reconstructed hips that survived, eighteen (90%) had a clinically successful result (minimal or no pain) and 70% showed no signs of progression radiographically.

Lieberman et al. reported on the use of bone morphogenetic proteins for the treatment of osteonecrosis of the femoral head[176]. Partially purified human bone morphogenetic protein was combined with allogeneic antigen-extracted autolyzed human bone and was introduced into the femoral head through a core track in fifteen patients (seventeen hips). At a mean of fifty-three months (range, twenty-six to ninety-four months), fourteen hips showed a clinically successful result, with a Harris hip score of >80 points and no patient requiring conversion to a total hip replacement.

Vascularized Bone-Grafting

The rationale for vascularized bone-grafting is that it allows decompression, provides structural support, and restores a vascular supply that had been deficient or nonexistent for a long period of time. There have been multiple published reports on the use of vascularized fibular and iliac grafts[106,113,171,184,198,200,208,226,229-251]. The results of these procedures are summarized in the Appendix.

Urbaniak et al.[246] treated 103 osteonecrotic hips with a vascularized fibular graft and followed them for a minimum of five years. The best results were seen after the treatment of small and medium precollapse lesions. Of seventy-five patients who responded to a questionnaire, 81% expressed satisfaction with the result of the procedure. Eleven percent (two) of nineteen hips with a precollapse lesion, 23% (five) of twenty-two hips with a postcollapse lesion without depression, and 39% (twenty-four) of sixty-two hips with a more advanced lesion were converted to a total hip replacement.

Berend et al.[101] analyzed 224 collapsed osteonecrotic hips (in 188 patients) treated with vascularized fibular grafts and found a survival rate of 64.5% at a mean of 4.3 years (range, two to twelve years). They reported that an increased relative risk of conversion to total hip replacement was associated with an increased lesion size and the amount of collapse.

In summary, vascularized bone-grafting can lead to excellent results in hips with early-stage disease. The procedure may be effective, compared with core decompression, for larger lesions just before head collapse. Once the head has collapsed, the results are less predictable. For an excellent review of the indications, techniques, and results of vascularized fibular grafting, readers are referred to the report of Urbaniak and Harvey[247].

Other Operative Methods for Treating Stage-III and IV Disease

Multipotential stem cells: The augmentation of various treatment methods with mesenchymal cells may be of benefit for patients with osteonecrosis of the femoral head[252-255]. Gangji et al. randomized thirteen patients (eighteen hips) with precollapse disease to be treated with either a 3-mm core decompression or a core decompression with implantation of autologous bone-marrow mononuclear cells[252]. After twenty-four months, the group treated with the bone-marrow graft had a significant reduction in pain ($p = 0.021$) and joint symptoms compared with the other group. Five of the eight hips treated with core decompression only had radiographic evidence of deterioration, whereas only one of the ten hips treated with the bone-marrow graft had such deterioration ($p = 0.016$). Hernigou and Beaujean followed 189 hips in 116 patients for five to ten years after core decompression and grafting combined with implantation of autologous bone marrow obtained from the iliac crest[254].

TABLE I Decision-Making Hierarchy for the Treatment of Patients with Osteonecrosis of the Femoral Head

Stage	Treatment
I (no radiographic changes)	Core decompression, percutaneous drilling
II (precollapse)	Core decompression, percutaneous drilling, bone-grafting, osteotomies
III (crescent sign [subchondral fracture collapse])	Bone-grafting, hemiresurfacing, total hip arthroplasty
IV (joint deformity, acetabular involvement)	Total hip arthroplasty, possibly metal-on-metal total hip resurfacing arthroplasty

Success (avoidance of total hip replacement) was achieved in 136 (94%) of 145 hips that had been operated on before collapse but in only nineteen (43%) of forty-four hips that had been operated on after collapse.

Cementation of the femoral head[256-260]*:* Treatment by removing the dead bone from the femoral head (sequestrectomy) and replacing it with bone cement was first reported in 1993 by Hernigou et al., who studied the results in patients with sickle cell anemia[256]. Sixteen hips were injected with cement to elevate the cartilage and allow immediate full weight-bearing. At a mean of five years (range, three to seven years), fourteen of the sixteen hips were stabilized (i.e., they had minimum pain and no radiographic signs of progression). Wood et al. treated nineteen patients (twenty hips) with open reduction augmented with methylmethacrylate cement and followed them for six months to two years[258]. Three patients had a conversion to a total hip replacement. The long-term results of this procedure are unknown.

Joint Arthroplasty

Total joint replacement: Total hip replacement is indicated once the femoral head has collapsed and the hip joint has degenerated such that the articulation is compromised. Total joint replacement will not be addressed in this paper, as it is too extensive a topic and deserves a separate review. Large precollapse lesions and postcollapse disease pose a difficult problem. Procedures aimed at joint preservation do not have predictable results in hips with such lesions; however, because patients with osteonecrosis of the femoral head are generally young, total hip arthroplasty is often an unfavorable option. Surgical alternatives for these patients may include limited femoral resurfacing and bipolar hemiarthroplasty.

Limited femoral resurfacing arthroplasty: In this procedure, the damaged cartilage on the femoral side is removed and bone stock is preserved[127,261-274]. The viable acetabular cartilage is retained. The potential advantages of resurfacing over total hip replacement are lower dislocation rates, preservation of bone stock, and the ability to perform conversion to total hip arthroplasty if necessary. A study of hips treated for postcollapse disease showed that, at a mean of seven years, overall survivorship after hemiresurfacing (twenty-seven of thirty hips) was similar to that after standard total hip replacement (twenty-eight of thirty hips)[271]. A higher percentage of patients treated with resurfacing maintained a high activity level (60% [eighteen hips] compared with 27% [eight hips] in the group treated with total hip replacement). However, more patients in the resurfacing group had persistent groin pain (20% [six hips] compared with 7% [two hips] in the other group). In a study of thirty-seven hips followed for a mean of 6.5 years (range, two to eighteen years), Beaule et al. reported a good or excellent result (according to the Harris hip score) in 79% and 62% of the hips at five and ten years, respectively[127].

Various studies on limited femoral resurfacing published since 1995 have demonstrated satisfactory results for up to ten years and beyond[127,261,264,270-273]. Recently, a few studies showed less predictable outcomes of these procedures. In a review of the results of twenty-nine consecutive femoral head resurfacing procedures in twenty-eight patients[261], Adili and Trousdale reported that seventeen patients (eighteen hips, 62%) stated that they felt better than they had before the surgery. The overall hip survivorship was 75.9% at three years, and eight hips (27.6%) were converted to a total hip replace-

TABLE II Recommendations for Treatment for Osteonecrosis of the Femoral Head

	Grade of Recommendation*
Nonoperative	
Lipid-lowering agents	I
Anticoagulants	I
Iloprost	I
Bisphosphonates	I
Shock-wave therapy	I
Hyperbaric oxygen	I
Pulsed electromagnetic fields	I
Operative	
Core decompression (early-stage disease)	A
Osteotomy	B
Nonvascularized bone-grafting	B
Vascularized bone-grafting	A
Multipotential stem cells	I
Cementation	I
Limited femoral resurfacing	B

*A = good evidence (Level-I studies with consistent findings) for or against recommending intervention, B = fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention, C = poor-quality evidence (Level-IV or V studies with consistent findings) for or against recommending intervention, and I = insufficient evidence to make a recommendation.

TABLE III Methods Not Recommended for Treatment of Osteonecrosis of the Femoral Head

	Grade of Recommendation Against Use of Treatment*
Nonoperative	
Non-weight-bearing	A
Restricted weight-bearing	A
Operative	
Core decompression (late-stage disease)	A
Bipolar arthroplasty	B
Rotational osteotomy (United States)	A

*A = good evidence (Level-I studies with consistent findings) for or against recommending intervention, B = fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention, C = poor-quality evidence (Level-IV or V studies with consistent findings) for or against recommending intervention, and I = insufficient evidence to make a recommendation.

ment. In a study of fifty-nine patients (fifty-nine hips) followed for a mean of 4.5 years[266], Cuckler et al. reported eighteen failures—i.e., conversion to total hip replacement or considerable groin pain requiring medication.

We recommend the following criteria for choosing candidates for limited femoral head resurfacing: (1) Ficat and Arlet Stage-III disease, (2) a combined necrotic angle of >200° or >30% involvement, (3) femoral head collapse of >2 mm, and (4) no evidence of damage to the acetabular cartilage.

Bipolar hemiarthroplasty: Bipolar hemiarthroplasty has the same indications as hemiresurfacing arthroplasty. The procedure has yielded variable success rates in the treatment of osteonecrosis of the femoral head[13,275-281]. In a series of twenty-two patients, Grevitt and Spencer[276] reported a good or excellent clinical outcome (defined as no need for total hip replacement) in twenty-one patients at a mean of forty months (range, twenty-four to seventy-one months). Chan and Shih[13] compared the outcomes of cementless total hip replacement with those of hemiarthroplasty in a series of twenty-eight patients with bilateral disease. At a mean of 6.4 years (range, four to twelve years), a satisfactory outcome (defined as no need for additional surgery) was found in twenty-four of the twenty-eight hips treated with the hemiarthroplasty compared with twenty-three of the twenty-eight hips treated with the standard total hip replacement. Other studies have shown high complication rates following bipolar hemiarthroplasties in patients with osteonecrosis of the femoral head. Sanjay and Moreau[279] reported seventeen complications in twenty-one patients at a mean of 4.6 years (range, 2.1 to seven years) postoperatively. Takaoka et al.[280] found a 42% rate of radiographic failure and/or acetabular degeneration in forty-7eight hips (thirty-five patients) at a mean of 11.4 years postoperatively. At a mean of twelve years following implantation of twenty-nine uncemented press-fit bipolar endoprostheses, Yamano et al.[281] found femoral loosening in six hips, acetabular protrusio in five, and osteolysis in eleven. Bipolar hemiarthroplasty has a high failure and complication rate and is associated with a high prevalence of polyethylene wear[279-281]. As a consequence, there has been an overall decrease in the utilization of these devices.

Treatment Recommendations and Future Methods

A decision-making hierarchy that we used for the treatment of patients with osteonecrosis of the femoral head is presented in Table I. It is based on radiographic findings and the philosophy of performing the least invasive treatment appropriate for the extent of the disease. This hierarchy is necessary because the surgeon can use an extensive procedure such as a total hip replacement for any stage. The table should serve as a guide, and it is subject to surgeon interpretation.

The use of biological agents (bone morphogenetic proteins and vascular growth factors) to preserve the femoral head and avoid joint replacement is currently under investigation[282-285]. In the future, these agents might be used to augment some of the femoral head-preserving procedures mentioned in this paper. Future treatment of osteonecrosis of the femoral head appears promising as recombinant factors become more available to enhance bone and cartilage healing.

Tables II and III present treatments recommended and not recommended for osteonecrosis of the femoral head on the basis of the quality (level of evidence) of studies of those treatments.

Appendix

eA Tables showing the results of core decompression, angular and rotational osteotomy, nonvascularized bone-grafting, and vascularized bone-grafting, as reported in the literature, are available with the electronic versions of this article, on our web site at jbjs.org (go to the article citation and click on "Supplementary Material") and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM).

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