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Osteonecrosis literally means “bone death” (ossa [Latin] = bone; necrosis = killing or causing to die). Synonyms include avascular necrosis, ischemic necrosis of bone, aseptic necrosis, and subchondral avascular necrosis. Although the term osteonecrosis dissecans is sometimes used synonymously with osteonecrosis, strictly speaking, it is a consequence of osteonecrosis involving fragmentation of bone that leads to fracturing or cracking of bone. The concept of bone death was first described by Hippocrates, but the first clinical description of osteonecrosis was a case of sepsis-induced bone death described by Russell in 1794. The first description of the occurrence of bone death in the absence of infection was published almost a century later. The first report of osteonecrosis in a deep sea diver appeared in 1936. The pathogenesis of osteonecrosis is complex, and immune regulation of bone homeostasis may play a significant role, but ultimately, bone death occurs as a result of complete or partial disruption of the delivery of oxygen and/or nutrients to the bone and surrounding tissues. It is likely that multiple molecular mechanisms must be in play simultaneously for osteonecrosis to occur.

**EPIDEMIOLOGY**

The prevalence of osteonecrosis is unknown, but it is estimated that 10,000 to 20,000 new patients are diagnosed every year in the United States. Osteonecrosis occurs in 15% to 80% of patients with femoral neck fractures. Osteonecrosis is believed to be the cause of 10% of the 500,000 hip replacements performed in the United States each year. Osteonecrosis primarily affects men, with the notable exception of osteonecrosis associated with systemic lupus erythematosus, which has a significant female predominance. Osteonecrosis primarily occurs in the third to fifth decade of life, and consequently, long-term morbidity can be significant because most hip replacements have a finite period of viability.

Recently, osteonecrosis of the jaw (ONJ) has been increasingly reported as a consequence of bisphosphonate use. Other drugs and procedures, including dental implants have been associated with ONJ. In a Spanish study of a population center of 1.1 million, 70 cases of ONJ were identified, with patients in 25% and 75% of these cases receiving bisphosphonates orally and intravenously, respectively.

**ETIOLOGY**

Osteonecrosis has been linked to numerous conditions (Table 103-1). The strength of a causal relationship varies greatly, and in some cases only case reports have been published. The most common cause of nontraumatic osteonecrosis is corticosteroid use, which was first described in 1957. Although other adverse effects of corticosteroids are perhaps better known, osteonecrosis of the femoral head is one of the more serious complications. Clearly there exist individual susceptibility differences that are not predictive, and therefore it is important that steroids be prescribed only when indicated and only for the length of time required. As will be discussed, although it is safe for some people to take
large doses of steroids for long periods, avascular necrosis will develop in other patients who take smaller doses over shorter periods.

In a 1998 study in which the investigators reviewed associations in approximately 3000 cases of nontraumatic osteonecrosis, corticosteroid use was present in 34.7% of cases. Alcohol use was found in 21.7% of cases, and the remainder of the cases were idiopathic. Although the risk of developing osteonecrosis with corticosteroid use is small, because of the severity of the adverse event and the high morbidity associated with it, osteonecrosis is an important complication to consider when prescribing corticosteroids.

Studies have been performed to attempt to determine the duration of use and the dosages of corticosteroids necessary to precipitate osteonecrosis. Because several forms of corticosteroids exist with differing potencies and half-lives, and because dosages and duration of use vary between studies, any conclusions about a “safe” dose of corticosteroids are fraught with potential confounding variables and errors. In a study of 20 patients diagnosed with stage 1 osteonecrosis by MRI, the interval between the use of steroids and diagnosis ranged from 1 to 16 months. The cumulative dose of steroids in this study ranged from 1800 to 15,505 mg (mean, 5928 mg) of prednisolone or the equivalent. In other studies, cumulative doses of steroids associated with osteonecrosis ranged from 480 to 4320 mg of dexamethasone dose equivalence. In a 2010 article, Powell and colleagues collectively analyzed the available literature to derive maximum safe levels for duration, maximum daily dose, and average daily dose of corticosteroids. The study confirmed that many other confounding variables affect the development of osteonecrosis, making analysis of dose-response risk for an isolated association difficult. Nonetheless, corticosteroid-induced osteonecrosis is dependent on dosage, and the risk is higher with long-acting steroids and with parenteral usage.

Additional host-inherent risk factors also play a role in susceptibility. The incidence of osteonecrosis in a group of patients receiving glucocorticoid replacement therapy for primary or secondary adrenal insufficiency was 2.4%. In a study of patients undergoing renal transplantation, the 26 patients in whom osteonecrosis developed had taken a higher cumulative oral dose of prednisone after 1 and 3 months compared with 28 control patients undergoing renal transplantation in whom osteonecrosis did not develop. A separate study estimated the incidence of osteonecrosis in patients undergoing renal transplant to be 5%. No consistent evidence links the use of topical, inhaled, or nasal corticosteroids to osteonecrosis. The evidence for an association between osteonecrosis and intra-muscular or intra-articular corticosteroids is limited to case reports. Parenteral use poses a higher risk because of the rapid absorption and longer half-life of the drugs used. Bisphosphonate-induced osteonecrosis of the jaw is particularly interesting because the intended beneficial use of bisphosphonates with regard to bone diseases instead leads to a serious bone complication itself. Other associations include a link between cigarette smoking and osteonecrosis, with smokers having a threefold higher relative risk for the development of osteonecrosis, independent of all other factors. The association between osteonecrosis and alcohol consumption was first described in 1922. A study of patients with idiopathic osteonecrosis revealed that the risk of osteonecrosis increased with increasing daily consumption of alcohol. The subjects were divided into three groups on the basis of their alcohol consumption of less than 400 mL/week, 400 to 1000 mL/week, and greater than 1000 mL/week, and the relative risk of osteonecrosis for these groups, independent of corticosteroid use or smoking, was 3-fold, 10-fold, and 18-fold, respectively. It was also found that liver damage is not necessary for the development of osteonecrosis in patients who...
consume alcohol, although elevated liver enzymes may be present. The incidence of osteonecrosis in patients who received treatment for alcoholism was 5.3%. The femoral head was again the most common site (representing 82 of 92 lesions), with the other 10 lesions in the humeral head.

Musculoskeletal conditions can lead to osteonecrosis in children. Legg-Calvé-Perthes disease was first described in children between 3 and 12 years of age in 1910. Femoral head osteonecrosis is a feature of this disease and has been linked to trauma, congenital hip dislocation, and transient synovitis. Bilateral involvement is common, and associated clinical manifestations include abnormal growth and stature, delayed skeletal maturation, disproportionate skeletal growth, congenital anomalies, and abnormal hormone levels. Osteonecrosis can develop in children with acute lymphoblastic leukemia as well, but this phenomenon may be a result of steroid use. An additional risk factor for patients with acute lymphoblastic leukemia has been found to be high body mass index.

Osteonecrosis has also been associated with metabolic disorders and pregnancy. Diagnosis is often delayed in mothers until months after delivery. Women who experience osteonecrosis during pregnancy tend to have a small body frame and a large weight gain.

Hematologic conditions have been associated with osteonecrosis. The long-term morbidity of osteonecrosis in patients with sickle cell anemia is dismal. Common issues include decreased mobility, abnormal gait, and leg-length discrepancy. Osteonecrosis in patients with hemophilia has been reported, but no statistically reliable causal link has been established.

Dysbaric osteonecrosis has been reported in construction workers exposed to high pressure environments, such as the Elbe tunnel, and may have been a feature of the first report of Caisson disease. The prevalence of dysbaric osteonecrosis is 4.2% in divers and 17% in workers exposed to compressed air. Patients with dysbaric osteonecrosis may have more than one lesion; in addition to the femoral head, common sites include the tibia and the humeral head and shaft. The condition is not related to decompression sickness, and although proper decompression procedures can reduce the incidence of “the bends,” they do not have any effect on the development of osteonecrosis, which can occur months or years after the last exposure to high-pressure environments.

Osteonecrosis has also been associated with a number of infectious diseases, including severe acute respiratory syndrome (SARS). Many patients who contracted SARS in the early 2000s received treatment with corticosteroids, and osteonecrosis subsequently developed in some of these patients. The incidence of osteonecrosis appears to be higher in this group of patients than in patients with other conditions who were treated with corticosteroids. Chan and colleagues reported that osteonecrosis developed in five children with SARS who were treated with corticosteroids.

### CLINICAL FEATURES

**Osteonecrosis**

The primary presenting symptom in osteonecrosis is pain, although many patients may be asymptomatic in the early phases of the disease. In osteonecrosis of the femoral hip, the pain is located in the hip joint but may radiate to the groin, anterior thigh, or knee. The severity of the pain can vary, depending on the size of the infarct and whether the onset of disease is insidious or sudden. When sudden and severe disruption of blood flow occurs in trauma, and when large infarcts occur in the presence of Gaucher’s disease, dysbarism, or hemoglobinopathy, pain can be intense and sudden. In other conditions with a more insidious onset, the pain can follow a gradual and slow incremental progression. The pain of osteonecrosis is usually increased with use of the joint, but in individuals with advanced disease, the pain can be persistent at rest. Limitation of range of motion is progressive and is usually a late symptom, except when it results from accompanying pain. The risk of developing osteonecrosis of the contralateral hip when one side is affected ranges from 31% to 55%.

In addition to the femoral head, osteonecrosis can affect other sites such as the humeral head, femoral condyles, and proximal tibiae, the wrists and ankles, the bones of the hands and feet, the vertebrae, the jaw, and bony structures of the face. Osteonecrosis of the humeral head is the second most common location; pain is usually present in the shoulder and is associated with reduced range of motion and weakness. Pain in the ankle is the main presenting symptom in nontraumatic osteonecrosis of the talus, and in some cases, the disease has already progressed to Ficat and Arlet stage 3 by the time pain presents.

Kienböck’s disease involves osteonecrosis of the lunate. Patients present with pain in the radiolunate joint, along with weakness and limitation of motion. Kienböck’s disease appears to be related to manual labor. Soccer players have been reported to develop osteonecrosis of the foot, and football players may be prone to the development of osteonecrosis of the hip.

### Staging Osteonecrosis

The Ficat and Arlet method of staging osteonecrosis consists of four stages. Stages 1 and 2 are reversible, whereas stage 3 (subchondral collapse) and stage 4 (joint space narrowing and destruction of cartilage) are irreversible. The Marcus staging system consists of six stages, with the first two reversible and the subsequent four stages irreversible. The modified Steinberg staging system is based on the Marcus system and also consists of six stages. Each stage is further divided into three subclasses on the basis of the extent of femoral head involvement. In subclass A, involvement is less than 25%; in subclass B, 26% to 50% of the femoral head is involved; and in subclass C, greater than 50% of the femoral head is involved.

Table 103-2 shows the Modified Steinberg system for staging osteonecrosis. The Association of Research Circulation Osseous (ARCO) has proposed a modification to the Ficat and Arlet system, adding a stage 0 for patients with negative findings of imaging studies but who are at risk for the development of osteonecrosis. In addition, stages 1 and 3 are further stratified to take into account lesion size, location, and extent of collapse. In 2001 the Japanese Ministry of Health, Labor, and Welfare proposed revising criteria for the diagnosis and staging of osteonecrosis of the femoral head. Diagnostic criteria included (1) collapse of the
femoral head without joint space narrowing or acetalubrred abnormality as seen on a plain radiograph, (2) demarcating sclerosis in the femoral head without joint space narrowing or acetalubrred abnormality, (3) “cold in hot” areas on bone scans, (4) a low-intensity band on T1-weighted MRI, and (5) histologic findings of trabecular and marrow necrosis. If a patient fulfills two of the five criteria, the diagnosis is established. The working group also proposed four types of lesions based on extensiveness and defined stages of disease according to diagnostic imaging.

Bone Marrow Edema

Bone marrow edema is a common observation in people with osteonecrosis and is frequently accompanied by vascular congestion. Bone marrow edema is not specific for osteonecrosis and may be seen in many musculoskeletal disorders, including osteomyelitis, osteoarthritis, occult intraosseous fracture, stress fracture, osteoporosis, and sickle cell crisis.

A specific syndrome known as bone marrow edema syndrome was initially thought to be a precursor to osteonecrosis, but it is now believed to be a separate entity. Bone marrow edema is a transitory, self-limiting condition typically seen in middle-aged men or in women in their third trimester of pregnancy. Patients report pain, limited range of motion, and an abnormal gait. Osteopenia is detected with conventional radiographs, and MRI confirms this diagnosis with a low signal on T1-weighted images and a high signal on T2-weighted images. The three phases of bone marrow edema syndrome include an initial phase lasting about 1 month, followed by a plateau phase lasting 1 or 2 months, and finally a regression phase lasting an additional 4 to 6 months. Subchondral fractures do not occur. Biopsy specimens obtained in the initial phase show diffuse interstitial edema, fragmentation of fatty marrow cells, and increased formation of new bone.

A study of 24 cases of bone marrow edema syndrome of the knee showed that although migrating bone marrow edema occurred in a third of patients at 5-year follow-up, the patients were asymptomatic and MRI signal alterations had resolved. Biopsy specimens of affected bone were obtained using arthroscopic surgery and core decompression, and histologic findings revealed areas of bone marrow edema and vital trabeculae covered by osteoblasts and osteoid seams. None of the cases progressed to osteonecrosis.

**TABLE 103-2** Modified Steinberg Staging Systems for Osteonecrosis

| Stage | Radiographic Appearance | Reversible |
|-------|-------------------------|------------|
| I     | Normal radiographs, but abnormal bone scan or MRI | Yes |
| II    | Lucent and sclerotic changes | Yes |
| III   | Subchondral fracture without flattening | No |
| IV    | Subchondral fracture with flattening or segmental depression of the femoral head | No |
| V     | Joint space narrowing or acetalubrred changes | No |
| VI    | Advanced degenerative changes | No |

**Bisphosphonates, Denosumab, and Osteonecrosis of the Jaw**

Bisphosphonate is a class of drug used to treat osteoporosis and diseases in which bone is not formed adequately. Two forms of bisphosphonates are available, and osteonecrosis appears to occur in association with bisphosphonates that contain nitrogen. The mechanism of action of bisphosphonate-induced ONJ appears to parallel that of glucocorticoids, with derangement in lipid metabolism, bone homeostasis, and apoptosis of bone cells all playing a role. It is interesting that the jawbone seems to be the most vulnerable bone in bisphosphonate-induced disease, as opposed to the femoral head in most other associations or causes of osteonecrosis. This phenomenon may be a result of the high bone turnover rate in the jaw or because bisphosphonates exert their action not only on bone but also on many elements of the surrounding tissue, including fibroblasts and blood vessels.

ONJ increasingly has been recognized as a significant disease, and in addition to bisphosphonate use, other causes have been reported in recent years. Many of these findings are from case reports, but epidemiologic studies are beginning to appear in the literature. For example, a case of ONJ was reported in association with the use of raloxifene. Raloxifene is a nonsteroidal benzothiophene that is used as an estrogen receptor modulator to treat osteoporosis in postmenopausal women and to reduce the risk of breast cancer. Denosumab, a monoclonal antibody against receptor activator of nuclear factor-κB ligand (RANKL) that is used in the treatment of osteoporosis, has also been implicated in ONJ. In addition to case reports, animal studies also suggest that anti-RANKL interferes with the normal bone resorptive functions of osteoclasts after dental trauma, which may play a role in the pathogenesis of ONJ.

German investigators analyzed 1229 cases of ONJ between 2004 and 2012 for risk factors. The indication for bisphosphonate use was primarily cancer, and it was found that ONJ developed earlier in men than in women. Most of the patients (81%) were taking zoledronate at the onset of ONJ.

**PATHOGENESIS**

**Anatomic Considerations in Trauma-Related Osteonecrosis**

The femoral head is the most common site of osteonecrosis. An understanding of the anatomy of the femoral head may help explain why that is the case.

Three arterial networks supply the femoral head and neck. The extracapsular arterial ring consists of the lateral femoral circumflex artery and the medial femoral circumflex artery, which arise from the profunda femoris. The medial femoral circumflex artery and its branches supply most of the blood to the head and neck of the femur. The lateral femoral artery winds anterolaterally, and the medial femoral artery winds posteromedially around the neck of the femur; they ultimately anastomose with each other at the superolateral aspect of the femoral head. The lateral femoral circumflex artery and the medial femoral circumflex artery further anastomose with the superior and inferior gluteal...
branches of the internal iliac artery, providing collateral circulation between the femoral artery and the internal iliac artery. Small vessels known as retinacular arteries, which are ascending cervical branches of the extracapsular ring, form an intra-articular ring at the level of the cartilage. Epiphyseal arterial branches arise from this ring and penetrate the head and neck of the femur, including the epiphyses. The artery of the ligament of the head of the femur is a branch of the obturator artery and may be the sole supplier of blood to the proximal fragment of the head.

Some of these anatomic features may render the femoral head particularly vulnerable to ischemia. The retinacular arteries are believed to supply 80% of the femoral epiphysis. Compromise of this critical vascular system may lead to osteonecrosis originating in the anterosuperior aspect of the femoral head, as indicated by angiographic studies in early osteonecrosis in which these arteries are not visualized. A schematic of the blood supply to the femoral head is shown in Figure 103-1.

Histologically, after an infarct, a rim of osteoarthritic proliferation begins to form at the margins of the infarcted area. If the necrotic lesion is within the weight-bearing region of the femoral head, subchondral fractures occur. With repeated microfractures and continued weight bearing, the original fracture cannot heal completely and new fractures appear. The secondary fracture propagates along the junction between subchondral bone and the necrotic segment. As time goes on, the femoral head becomes flattened and eventually collapses. A nonspherical head articulating with the acetabulum produces friction, erosion, and loss of cartilage. The cycle repeats itself, and the structure of the joint deteriorates, leading to degenerative changes and eventual total joint destruction.92-94

**Nontraumatic Osteonecrosis**

Disruption of the blood supply to the femoral head can occur through a number of different mechanisms. In traumatic osteonecrosis of the femoral head, the cause of this disruption is often viewed as completely mechanical. However, as in the case of nontraumatic osteonecrosis (to be discussed in the following text), an additional component to the disruption may exist that is related to the immunologic and inflammatory changes that occur in damaged bone tissue and surrounding soft tissues.

The immunologic changes occurring in nontraumatic osteonecrosis may help explain why corticosteroids are particularly dangerous to the integrity of the blood supply of the femoral hip. Some investigators have likened osteonecrosis to "coronary disease" of the hip95,96 and propose that the same mechanisms that cause ischemia of the myocardium may also cause ischemia of the femoral head (Table 103-3).

**Mechanical and Vascular Considerations**

In Legg-Calvé-Perthes disease, obstruction to venous drainage elevates intrasosseous pressure and consequently increases intra-articular pressures. In a study of patients with Legg-Calvé-Perthes disease, bone scintigraphy using technetium 99m methylene diphosphonate (Tc 99m MDP) was used to measure arterial and venous flow in the diseased hip. Although arterial flow was normal, venous drainage was significantly disrupted.97 This disturbance was reproduced in a dog model in which injection of silicone was used to obstruct venous flow distal to the hip.98 Ischemia resulted from the obstruction to venous drainage, leading to a cessation of endochondral ossification in the preosseous epiphyseal cartilage and the physeal plate. Widening of the joint space ensued, followed by revascularization of the epiphysis and deposition of new, immature bone. A weakened or
unstable femoral epiphyseal plate resulted, and the subchondral bone became prone to segmental collapse and fracture.109

The pathologic mechanism of dysbaric osteonecrosis is unclear. The most intuitive explanation is that formation of gas bubbles causes arterial occlusion and ischemia. However, the true mechanism may not be quite so simple. Multiple other factors might contribute to the disease, including thromboembolic events such as platelet aggregation, erythrocyte clumping, lipid coalescence, intraosseous vessel compression as a result of extravascular gas bubbles, formation of fibrin thrombi, and narrowing of arterial lumina as a result of myointimal thickening caused by gas bubbles. The interaction between gas and blood can lead to the formation of vessel-occluding substances. All of these events can lead to redistribution of blood flow.

The increased vulnerability of bone to compression disorders has been explained by several factors, including the relative rigidity of bone and its inability to absorb increased gas pressure, inherent poor vascularization, and gas supersaturation of fatty marrow.100 A sheep model of dysbaric osteonecrosis has been developed. Exposure to compressed air at pressures of 2.6 to 2.9 atmospheres for 24 hours results in extensive bone and marrow necrosis. The authors proposed that the initial event involving elevated intramedullary pressures leads to the formation of nitrogen gas bubbles in the fatty marrow of the long bones. Radiography shows medullary opacities and endosteal thickening. Later, neovascularization of previously ischemic fatty marrow occurs, followed by new bone formation. Osteonecrosis occurs in subchondral cortical bone with marrow fibrosis and osteocyte loss.101

Changes in the vasculature through injury or inflammation from other diseases may in turn lead to a compromise in blood flow. Examples include structural damage to arteriolar walls, degeneration of the tunica media, smooth muscle cell necrosis, and disruption of the internal elastic lamina. These changes can lead to eventual hemorrhagic infarction, which was observed in a study of 24 core biopsy specimens from osteonecrotic femoral heads. The changes did not occur in 11 femoral heads affected by osteoarthritis.102

**Osteoimmunology**

Although bone marrow is a critical component of the immune system, the bone matrix itself has often been perceived to be merely static scaffolding that functions as a support for the musculoskeletal system. In fact, it is now known that bone matrix is a dynamic tissue that is constantly replacing itself. It is estimated that about 10% of a person’s bone is replaced every year. Diseases such as osteopetrosis and osteoporosis are a result of a dysfunction in the balance between bone deposition and bone resorption. The factors that regulate this homeostasis include cells of the bone matrix, immune cells, signaling molecules, cytokines and chemokines, and vitamins and hormones. Some of these regulatory factors may be present on both bone cells and immune cells, often serving different functions, thereby providing a link between the immune system and bone. Osteonecrosis, in fact, may be a result of such an imbalance in bone homeostasis. Immune factors may affect surrounding soft tissue as well, contributing to the development of osteonecrosis. The study of immune regulation of bone in osteonecrosis encompasses many of the previously proposed mechanisms of osteonecrosis, including apoptosis, oxidative stress, and genetic predisposition.

Immune factors involved in bone homeostasis include receptor activator of NF-κB (RANK) and its ligand (RANKL), IL-1, IL-6, IL-10, TGF-β, TNF, CD80, CD86, CD40, macrophage colony-stimulating factor (M-CSF), nuclear factor of activated T cell cytoplasmic (NFATc), and vitamin D (see Table 103-4 for roles and function). Many of these factors can be categorized into one of two categories—those with the overall effect of inducing osteoclastogenesis, and those that inhibit osteoclastogenesis. In addition, factors involved in cell survival and apoptosis such as Blimp-1 and Bcl-6 may also play a role. RANKL is expressed on osteoblasts and is critical for the differentiation and proliferation of osteoclasts. Because transcription of factors involved in the regulation of bone homeostasis is often influenced by glucocorticoids, this mechanism may begin to explain why steroids may be associated with osteonecrosis. The role of the innate immune system has recently come into play as well because investigators reported an upregulation in Toll-like receptor 4 signaling pathways in animal models of osteonecrosis, leading to activation of osteoclasts.103,104

The action of glucocorticoids is mediated by the glucocorticoid receptor, which is present on many cell types, including osteoclasts, osteoblasts, osteocytes, and cartilage. Binding of glucocorticoids to its receptor leads to the anti-inflammatory activity known to be a function of steroids. One mechanism by which this anti-inflammatory effect is mediated is through transcription of genes that inhibit the synthesis of inflammatory mediators.

**Osteoblast/Osteoclast Balance**

Any disturbance in the normal homeostasis between bone deposition and bone resorption can lead to bone disease. Moreover, defective bone deposition or bone resorption in which new bone is formed in an aberrant manner can lead to disease. Alcohol can affect the ability of mesenchymal stem cells to differentiate into osteogenic lineages. During hip replacement surgery, the bone narrow in the proximal head of femurs was isolated in 33 patients with either femoral neck fractures or alcohol-induced osteonecrosis. The cells from femurs of patients with alcohol-induced osteonecrosis showed a reduced ability to differentiate into osteoblasts.105 A subsequent study compared mesenchymal stem cells from patients with hip osteoarthritis, idiopathic osteonecrosis, and nontraumatic osteonecrosis associated with steroid or alcohol use. In idiopathic and alcohol-induced osteonecrosis, the ability of mesenchymal stem cells to differentiate into osteoblasts was decreased, but in steroid-induced osteonecrosis, it was elevated, although not to a statistically significant level. The adipogenic differentiation ability was similar in all four groups.106

In rats fed a diet of alcohol and glucose, lower bone mineral content and density were detected compared with control subjects. In hamsters, alcohol led to thinning of the trabeculae of the distal part of the femur. Cytologic effects included mitochondrial swelling in osteoblasts and
osteocytes. Partial osteonecrosis of the femoral head was detected in Merino sheep that were injected with ethanol. In humans, alcohol causes increased plasma calcium levels, decreased osteocalcin and circulating parathyroid hormone levels, reduced serum calcitriol, reduced bone volume, and an increased number of osteoclasts.

Alterations in osteoblast function may also contribute to the pathogenesis of osteonecrosis. In one study, osteoblasts were obtained from bone biopsy specimens from the intertrochanteric region of the femur and the iliac crest of 13 patients with osteonecrosis and 8 patients with hip osteoarthritis. Cell replication was measured on the basis of proliferation rate in secondary culture. Levels of alkaline phosphatase activity, collagen synthesis, and sensitivity to 1,25-dihydroxyvitamin D$_3$ were measured. The results indicated that although differentiation was not affected, the proliferation rate of osteoblastic cells was reduced in samples obtained from the patients with osteonecrosis compared with patients who had osteoarthritic hips.$^{107}$

### Apoptosis and Osteonecrosis

Glucocorticoids can also act via their action on apoptosis of immune and bone cells. When prednisolone was administered to mice for 27 days, increased metaphyseal apoptotic activity of both osteoblasts and osteoclasts was noted.$^{108}$ The result was decreased bone turnover, density, and formation, increased formation of cancellous bone, and decreased trabecular width. The decreased bone turnover can be explained by the reduced osteoclast survival, and the reduction in trabecular width can be explained by a decrease in osteoblasts. An accumulation of apoptotic elements was also found in the region of the “fracture crescent” in the femurs of patients treated with glucocorticoids. On the
other hand, glucocorticoids may also increase osteoclast survival, leading to increased bone loss. Clearly, the effect of osteoclast survival on bone disease is more complicated than at first glance, and it involves the interaction of the osteoclast with the osteoblast. Because osteoblasts are also responsible for osteoclast differentiation under the right circumstances, a significant feedback system exists that maintains bone homeostasis.

Osteocyte death is also a feature of osteonecrosis. In a rat model, ischemia caused an induction in the expression of stress proteins, oxygen-regulated protein (ORP150), and hemoxygenase 1 (HO1). Induction of ischemia in these rates caused DNA fragmentation and the presence of apoptotic bodies in chondrocytes, bone marrow cells, and osteocytes.109 Both alcohol and corticosteroids can induce osteocyte apoptosis, possibly via aberrations in lipid metabolism.

**Lipids and Osteonecrosis**

Rabbits that were fed alcohol were found to have fatty infiltration of the liver and adipogenesis in the bone marrow. Increases in fat cell hypertrophy and proliferation, as well as a decrease in hematopoiesis in the subchondral head, were observed. Osteocytes contained triglyceride deposits, and an increase in empty osteocyte lacunae was noted. Alcohol also primarily triggered differentiation of bone marrow stromal cells into adipocytes in a dose-dependent manner. Intra-cellular lipid deposits led to the death of osteocytes.

In corticosteroid-induced osteonecrosis, the alteration in lipid metabolism parallels that of alcohol-induced osteonecrosis. In both cases, fatty infiltration of osteocytes has been postulated to occur.110-112 Table 103-5 lists lipid-altering effects of corticosteroids and alcohol. In addition, interosseous venous stasis affects the interosseous microcirculation, which can lead to hemodynamic and structural changes in the femoral head. The resulting decrease in blood flow leads to osteonecrosis. In chickens treated with steroids, fatty infiltration of the liver and fat cell hypertrophy and proliferation in the femoral head occurred concurrently 1 week after the initiation of steroids. As in the case of alcohol-induced osteonecrosis, adipocytes contained triglyceride vesicles. In rabbits treated with steroids, it was found that interosseous pressure was increased and the size of bone marrow fat cells was larger than in control rabbits.113 A histologic study of acetabular and proximal femoral bone in osteonecrosis of the femoral head revealed that osteonecrosis is more extensive in corticosteroid-induced compared with alcohol-induced or idiopathic osteonecrosis.114 The reason for this phenomenon is unknown.

In ONJ, bisphosphonates inhibit protein prenylation via inhibition of the enzyme farnesyl diprophosphate synthase. The normal lipid metabolism of pathways that regulate cytoskeletal integrity and osteoclastogenesis such as Rho, Rac, and Ras is disrupted, which is one of the mechanisms by which bisphosphonates exert their intended action, but their ability to disrupt normal regulation of bone metabolism may instead lead to osteonecrosis.

**Coagulation and Osteonecrosis**

The hyperlipidemia, increased serum free fatty acids, and increased prostaglandins that are associated with alcohol-induced osteonecrosis may potentially trigger vascular inflammation and coagulation. Other triggers for intravascular coagulation include atherosclerosis and arteriolar fibroid degeneration. Jones115 proposed that the progression of osteonecrosis from stage 1A to 1B is linked to an inability to clear procoagulants from blood or tissue. He proposed that decreased clearance of procoagulants leads to persistent levels of tissue thromboplastin and thus to arteriolar thrombosis, vascular stasis, free fatty acid–induced endothelial damage, and hypercoagulability. Studies have shown that patients with osteonecrosis had a much higher frequency of having at least one or two abnormal coagulant levels compared with normal control subjects. Of patients with osteonecrosis, 82% had at least one and 47% had at least two abnormal procoagulant levels. In normal control subjects, only 30% had one abnormal procoagulant level and only 2.5% had two or more abnormal levels. The procoagulants measured included free protein S, protein C, lipoprotein A, homocysteine, plasminogen activator inhibitor, stimulated tissue plasminogen activator, anti-cardiolipin antibodies (IgM and IgG), and resistance to activated protein C.116

In addition, both thrombophilia and hypofibrinolysis have been associated with osteonecrosis. Hypofibrinolysis leads to an increased likelihood of clot formation, and thrombophilia results in a decreased ability to lyse clots. Hypofibrinolysis is yet another mechanism by which corticosteroids lead to osteonecrosis—high-dose steroids lead to increased plasma plasminogen activator inhibitor, decreased tissue plasminogen activator activity, and inhibition of the fibrinolytic pathway, thus leading to a higher risk for clot formation. There is an early indication that coagulation abnormalities may play a significant role in corticosteroid-induced osteonecrosis in patients with SARS.117,118

**Oxidative Stress and Osteonecrosis**

Alcohol consumption is associated with reduced superoxide dismutase activity. Alcohol has deleterious effects on muscle, including increased oxygen free radical–related damage, reduced myocardial contractility, defective mitochondrial function, and increased tissue enzymes.119 When rabbits were injected with methylprednisolone, elevations in 8-hydroxy-2′deoxyguanosine, a marker of DNA oxidative injury, were observed.120,121 These elevations coincided with the development of osteonecrosis. A polymorphism in nitric oxide synthase (NOS), which will be subsequently described, was also associated with the development of

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**TABLE 103-5** Lipid-Altering Effects of Steroids and Alcohol

| Fatty liver | Swelling and necrosis of fat cells | Lipid-filled osteocytes |
| Adipogenesis of marrow stromal cells | Fatty infiltration of bone marrow |
| Fat emboli | | |
osteonecrosis. The relationship between osteonecrosis and oxidative injury leads one to wonder if corticosteroid-induced osteonecrosis can be prevented or lessened in severity by simultaneous or prophylactic administration of antioxidants.

**Radiation and Osteonecrosis**

An association between radiation exposure and osteonecrosis was reported as early as 1950. The earliest reports involved primarily ONJ. Most of the evidence for radiation as a cause of osteonecrosis is derived from case reports. One of the more recent larger studies involved a case-control study to investigate risk factors for ONJ, in which 191 patients with ONJ and 573 control subjects were enrolled from 119 dental practices. The odds ratio for radiation exposure was 24.1 (4.9 to 118.4). However, when patients with cancer were excluded, the association between ONJ and radiation exposure no longer existed as an independent risk factor.

Exposure to radiation may result in damage to vascularity of bone and lead to osteonecrosis in a dose-dependent manner. In particular, osteonecrosis after radiation for neoplasms is well documented and particularly affects the femoral head and the mandible. Concomitant administration of chemotherapy can accentuate the risk of osteonecrosis in patients who are receiving radiation, particularly elderly women.

Interestingly, an animal model of osteonecrosis induced by high-intensity focused ultrasound (HIFU) was developed to determine if HIFU could be used to generate osteonecrosis for animal studies. In this model, high-power acoustic energy up to 1000 W/cm² focused directly at bone was able to induce osteonecrosis of the femoral head in a canine model via the creation of a thermal injury. Typical diagnostic ultrasound transducers generally deliver intensities ranging between 0.1 to 100 W/cm², although HIFU has been used for use in cancer and can reach 100 to 10,000 W/cm². This finding raises the possibility of ultrasound-induced osteonecrosis in humans in real-life clinical settings, although this possibility is far from substantiated.

The proposed mechanism by which ultrasound can induce osteonecrosis is through thermal damage induced by osteocyte damage and vascular thrombosis.

**Nitric Oxide Synthase and Osteonecrosis**

Glucocorticoids can cause derangements in vascular responsiveness to vasoactive substances such as nitric oxide. Endothelial NOS (eNOS) stimulates the production of nitric oxide. Nitric oxide regulates vascular “tension” by acting as a vasodilator, inhibiting mononuclear adhesion to endothelial cells and preventing platelet aggregation. A defect in this activity can lead to increased vascular resistance and disruption to downstream blood flow, resulting in osteonecrosis.

**Multihit Hypothesis**

Other proposed mechanisms of osteonecrosis involve endothelial cell injury, abnormal angiogenesis and repair mechanisms, the effects of vasoactive substances, antioxidative stress, and disruption to downstream blood flow, resulting in osteonecrosis. The role of the microorganism environment itself versus the host innate immune response to this environment are still to be elucidated.

In yet another study investigating the microbacterial environment in patients with BRONJ, Wei and colleagues found that the predominant species in osteonecrosis lesions in patients with BRONJ included Streptococcus (29%), Eubacterium (9%), and Pseudoramibacter (8%) compared with the control group, in whom the most common species found were Parvonomas (17%), Streptococcus (15%), and Fusobacterium (15%). Wei and colleagues also found that in patients with BRONJ, hematoxylin-eosin staining revealed that the bacteria were layered and packed into the scalloped edges of BRONJ bone, suggesting the role of biofilms as a potential risk factor for the development of BRONJ.
Scanning electron microscope images have shown the presence of biofilms in BRONJ lesions. It should also be noted that bacteria are not the only pathogens found in BRONJ lesions; fungi, especially Candida and Actinomyces, have also been found in lesions of patients with ONJ.

Genetic and Epigenetic Considerations

The degree to which genetics and the environment play a role in the pathogenesis of osteonecrosis is the subject of an ongoing investigation. Certainly, single nucleotide polymorphisms have been noted in a number of genes that may be associated with osteonecrosis. It has been argued that eNOS is an important player in the development of osteonecrosis. Nitric oxide may have beneficial effects on three systems involved in osteonecrosis—namely skeletal, vascular, and thrombotic. Each of these systems may be targets for proposed mechanisms of pathogenesis of osteonecrosis. A comparative analysis of the 26-base pair repeat polymorphism in intron 4 and the Ghe298Aasp polymorphism in exon 7 of the eNOS gene in patients with idiopathic, steroid-induced, and alcohol-induced osteonecrosis and normal control subjects was performed. The frequency of the homozygous 4a allele was found to be higher in patients with idiopathic osteonecrosis compared with control subjects. The frequency of the 4a/b allele was found to be higher in all types of osteonecrosis when compared with control subjects. The 4a allele is known to be associated with reduced synthesis of eNOS, suggesting that nitric oxide may play a protective role with regard to the development of osteonecrosis.

Forty-one percent of patients with osteonecrosis compared with only 20% of control subjects were homozygous for the 4G/4G mutation in the plasminogen activator inhibitor-1 (PAI-1) gene. This mutation causes increased hypofibrinolytic plasminogen activator inhibitor activity, resulting in decreased stimulated plasminogen activator activity. This observation lends support to the theory that procoagulants may play a significant role in the pathogenesis of osteonecrosis. A polymorphism in the PAI-1 gene has also been reported to be predictive of osteonecrosis in children with acute lymphoblastic leukemia.

Genetic variations in the type and levels of lipoprotein(A) have been linked to osteonecrosis. Apolipoprotein(A) (Apo[A]) is involved in lipid metabolism and the coagulation systems, and the Apo(A) low-molecular-weight phenotype is associated with an increased risk of osteonecrosis. Polymorphisms in the promoter for vascular endothelial growth factor (VEGF) and in the receptor for IL-23 were associated with osteonecrosis in the Korean population, reflecting the significance of the association of osteonecrosis with vascular disorders and autoimmune diseases, respectively.

Epigenetic modulation of gene expression has recently been recognized to affect more than half of all human genes. Several pathways exist for epigenetic transformation, including DNA methylation and demethylation, histone modifications such as acetylation and deacetylation, and microRNAs. MicroRNAs are short 21- to 23-nucleotide RNA molecules that bind to messenger RNA of the promoter region of genes and serve a regulatory function. Over-expression of certain microRNAs therefore may affect the expression of genes coding for various mediators of disease, such as cytokines or growth factors. In 2012, Yamasaki and colleagues demonstrated that microRNA-210 is upregulated in the cells surrounding osteonecrotic bone. Furthermore, microRNA-210 is known to play a role in angiogenesis. Accompanying the upregulation of microRNA-210 in patients with osteonecrosis were also increased expression of VEGF and matrix metalloproteinase (MMP)-2 and -7 when compared with patients who had osteoarthritis.

Other microRNAs such as microRNA-29a and microRNA-548d-5p have also been shown to play a role in regulation of bone resorption and osteogenesis. MicroRNA-17-5p, which is known to play a role in cancer cell proliferation and invasion, was evaluated to test whether it also plays a role in osteoblast differentiation. The investigators found that expression of this microRNA was lower in patients with osteonecrosis compared with patients who had osteoarthritis. This finding was accompanied by a facilitation in the differentiation of HMSC-bm cells, which is thought to be mediated by the action of microRNA-17-5p on expression of β-catenin and a subsequent increase in COLIA1. MicroRNA profiles identified 27 microRNAs that were differentially expressed in patients with osteonecrosis of the femoral head. Fifteen were overexpressed, and 12 were underexpressed in patients with osteonecrosis when compared with either patients who had systemic lupus erythematosus or healthy control subjects. The differentiating nature of microRNA profiles may play a future role as disease biomarkers.

Small interfering RNAs (siRNAs) have been shown to play a potential role in disease management. It is known that glucocorticoids may act in osteonecrosis by virtue of their ability to induce overexpression of the peroxisome proliferator-activated receptor γ (PPARγ) gene, leading to adipogenesis, which has already been discussed as a potential mechanism for osteonecrosis. In a rabbit model for steroid-induced osteonecrosis, siRNAs targeting PPARγ were able to reduce levels of PPARγ expression and increase levels of Runx2 and osteocalcin in rabbits treated with dexamethasone plus a recombinant adeno-virus shuttle vector carrying an siRNA targeting PPARγ, compared with rabbits treated with dexamethasone alone. Treatment with dexamethasone plus the recombinant adeno-virus shuttle vector led to amelioration of the narrow necrosis, adipocyte hypertrophy and proliferation, diminished hematopoiesis, thinner and sparse trabeculae, and an increased number of empty osteocyte lacunae in the femoral head seen in rabbits that only received dexamethasone or in combination with an irrelevant shuttle vector. These studies, although in their early stages, offer hope for novel treatments based on pathogenesis and the physiologic and cellular derangements that are risk factors for the development of osteonecrosis.

DIAGNOSIS

History and Physical Examination

The diagnosis of osteonecrosis is generally made via the history, because many patients may not present until hip pain develops. By the time the patient is clinically symptomatic, the disease may be quite advanced. Therefore a
Physical examination includes palpating the lateral aspect of the hip for tenderness and identifying limp, leg-length discrepancy, the presence of masses, abnormal gait, muscle strength, and range of motion. The Harris hip score is frequently used to evaluate hip function and is also useful in monitoring the effectiveness of treatment (Figure 103-2). The Harris hip score is a multidimensional observational assessment based on eight items that address pain, high index of suspicion is necessary for all patients taking oral or parenteral steroids. The following information should be elicited: any history of trauma; underlying disease; alcohol use; tobacco use; current medications; past medications; history of joint anomalies; presence of pain or limitation of motion; involvement in sports, especially high-impact sports; occupational history; gestational history; and the presence of liver disease or lipid abnormalities.

### Hip Joint Evaluation Form

| Date of assessment: | Name: | Medical record #: | DOB: |
|---------------------|-------|--------------------|------|

#### Pain
- **Distance walked**
  - o Totally disabled, crippled, pain in bed, bedridden
  - o Marked pain, serious limitation of activities
  - o Moderate pain, tolerable but makes concessions to pain. Some limitation of ordinary activity or work. May require occasional pain medication stronger than aspirin
  - o Mild pain, no effect on average activities, rarely moderate pain with unusual activity, may take aspirin
  - o Slight pain, occasional, no compromise in activity
  - o None, or ignores it

- **Activities-shoes, socks**
  - o Bed and chair only
  - o Two or three blocks
  - o Six blocks
  - o Unlimited

- **Public transportation**
  - o Unable to fit or tie
  - o With difficulty
  - o With ease

- **Limp**
  - o Unable to use
  - o Able to use

#### Support
- **Stairs**
  - o Unable to do stairs in any manner
  - o Normally using a railing
  - o Normally without using a railing

- **Sitting**
  - o Unable to sit comfortably on any chair
  - o On a high chair for 30 minutes
  - o Comfortably, ordinary chair for one hour

- **Limb-length discrepancy**
  - o Severe or unable to walk
  - o Moderate
  - o Slight
  - o None

#### Motions
- **Hip flexion:**
- **Adduction:**
- **Abduction:**
- **Internal rotation:**
- **External rotation:**

#### Comments:
- **Distance walked:**
  - o Totally disabled, crippled, pain in bed, bedridden
  - o Marked pain, serious limitation of activities
  - o Moderate pain, tolerable but makes concessions to pain. Some limitation of ordinary activity or work. May require occasional pain medication stronger than aspirin
  - o Mild pain, no effect on average activities, rarely moderate pain with unusual activity, may take aspirin
  - o Slight pain, occasional, no compromise in activity
  - o None, or ignores it

- **Activities-shoes, socks**
  - o Bed and chair only
  - o Two or three blocks
  - o Six blocks
  - o Unlimited

- **Public transportation**
  - o Unable to fit or tie
  - o With difficulty
  - o With ease

- **Limp**
  - o Unable to use
  - o Able to use

- **Support**
  - o Two crutches or not able to walk
  - o Two canes
  - o One crutch
  - o Cane most of the time
  - o Cane for long walks
  - o None

- **Stairs**
  - o Unable to do stairs in any manner
  - o Normally using a railing
  - o Normally without using a railing

- **Sitting**
  - o Unable to sit comfortably on any chair
  - o On a high chair for 30 minutes
  - o Comfortably, ordinary chair for one hour

- **Limb-length discrepancy**
  - o Severe or unable to walk
  - o Moderate
  - o Slight
  - o None

- **Comments:**

#### Figure 103-2
Harris hip score evaluation form.
walking function, daily activity, and range of motion. Scores range from 0 (maximum disability) to 100 (no disability).

**Diagnostic Imaging**

When the diagnosis of osteonecrosis is suspected clinically, it can be confirmed by imaging studies. In the early stages of osteonecrosis, plain radiographs may be completely normal. The earliest radiographic sign of osteonecrosis is the presence of a radiolucent crescent-shaped rim along the contour of the femoral head (the crescent sign) (Figure 103-3). This appearance on radiographs is the result of structural collapse of a necrotic segment of subchondral trabecular bone. At this stage, the disease is already irreversible. Later, radiographs will begin to show sclerotic changes (Figure 103-4). The appearance of radiographic “density” is secondary to compression of bone trabeculae after microfracture of the nonviable bone, calcification of detritic marrow, and repair of the necrotic area by deposition of new bone, the so-called “creeping substitution.” Flattening of the articular surface of bone is a sign of further bone collapse (Figure 103-5). To show best the radiographic appearance of osteonecrosis in the femoral head and to better visualize the extent of the necrotic lesion, anteroposterior and frog-leg lateral radiographs of the hip should be obtained.

Skeletal scintigraphy (i.e., a radionuclide bone scan) using technetium-labeled diphosphonates has also been
used to diagnose osteonecrosis. The use of this technique in the early diagnosis of this condition depends on the increase of osteoblastic activity and blood flow in the early stages of osteonecrosis. In an advanced stage of disease, the appearance may be one of increased activity in a subchondral distribution as a result of osteoblastic activity at the reactive interface around the necrotic segment; however, the center of the osteonecrotic lesion may show much less radionuclide uptake (Figure 103-6) or even a complete lack of activity, reflecting decreased metabolism in the necrotic focus as a result of interruption of the blood supply.7

In addition to bone scintigraphy, single-photon emission computed tomography maximizes sensitivity. A study comparing conventional radiography, MRI, computed tomography (CT), and a Tc 99m MDP three-phase bone scan in diagnosing bisphosphonate-associated osteonecrosis of the jaw showed that CT and MRI best defined the extent of the disease but that a bone scan best identified disease at an early stage. A bone scan could be an excellent screening tool for the diagnosis of osteonecrosis before further characterization of the lesions using CT or MRI.159

CT allows more detailed examination of the femoral head. A star-shaped structure, formed by weight-bearing bone trabeculae, gives the appearance of an asterisk on a CT scan (the asterisk sign).160-162 This asterisk undergoes a characteristic change in ischemic bone necrosis of the femoral head, and this change was considered important for early detection of osteonecrosis. At a later stage, the collapse of necrotic bone can be well visualized (Figure 103-7).

Currently, MRI is the gold standard for imaging of osteonecrosis. Most of the staging systems for osteonecrosis are now based on MRI appearance (Table 103-6). MRI of osteonecrosis can show changes earlier than conventional radiography or CT. It can also detect bone marrow edema, a feature sometimes seen in the early phases of osteonecrosis that is not visible on conventional radiography or CT.

The typical MRI findings in osteonecrosis are intermediate or low signal intensity on T1-weighted images and high signal intensity on T2-weighted and other water-sensitive sequences (Figure 103-8). As the disease progresses, the subchondral necrotic lesion is surrounded by a low signal line on T1-weighted images and a high signal line is seen on T2-weighted images, central to the low signal line, producing the “double-line” sign (Figure 103-9). In advanced osteonecrosis, the necrotic segment exhibits low signal intensity on both T1-weighted and T2-weighted images (Figure 103-10). MRI is performed in the sagittal, coronal, and axial planes and includes T1- and T2-weighted sequences. Although excellent correlation exists between histologic findings and MRI appearance (see Table 103-6),
### TABLE 103-6  MRI Changes and Their Correlation with Histology in Osteonecrosis

| Type of Appearance | Category of Observations | Histology | MRI Appearance |
|--------------------|--------------------------|-----------|----------------|
| A                  | Fat-like                 | Premature fatty marrow development in the femoral neck or intertrochanteric region | Normal fat signal; sclerotic margin may be seen; circumscribing lesion |
| B                  | Blood-like               | Bone resorption; replacement by vascular granulation tissue | High signal intensity of inner border; low signal intensity of the surrounding rim |
| C                  | Fluid-like               | Bone marrow edema | Diffusely decreased signal on T1-weighted images; high signal on T2-weighted images |
| D                  | Fibrotic                 | Sclerosis as a result of reinforcement of existing trabeculae at the margin of live bone (repair tissue interface) | Decreased signal on T1- and T2-weighted images |

**Figure 103-8**  
A, On a T1-weighted coronal MRI of the left hip, the osteonecrotic segment in the subchondral portion of the femoral head shows low signal intensity. B, On a T2-weighted coronal image, the necrotic bone exhibits high signal intensity, surrounded by a sclerotic low signal rim. The low signal intensity rim surrounds a high signal intensity rim, representing the double-line sign (see also Figure 103-9). Note that the signal intensity of the necrotic area is heterogeneous in both the T1- and T2-weighted sequences.

**Figure 103-9**  
A coronal T2-weighted MRI scan of the right femoral head shows the double-line sign (arrow), which is characteristic for osteonecrosis: low signal at the periphery of the lesion and a high signal band located more centrally.

In most cases the necrotic area is composed of a variety of tissue, including areas of fibrosis and necrosis mixed with areas of blood and edema, depending on the age of the infarct. Therefore the MRI signal of the necrotic area is often very heterogeneous (see Figure 103-8), and as a result, this classification is of little clinical value. The low signal intensity band in the periphery of the osteonecrotic area correlates with a sclerotic band seen on radiographs and CT and often has a serpiginous appearance. When the osteonecrosis involves a long bone, this serpiginous band or line has been termed “smoke in a chimney.”

MRI is an important tool in determining the extent of femoral head involvement in osteonecrosis. Three techniques are used to evaluate the extent of this involvement. The first is estimating head involvement. This method was first proposed by Steinberg and colleagues\(^\text{163}\) in 1984, and it is defined by the appearance of abnormal signals on T1-weighted images. The degree of head involvement was classified into three categories: less than 15%, 15% to 30%, and greater than 30%. The second method used to evaluate the extent of involvement is the index of necrotic extent, which is determined by measuring the angle created by the extent of subchondral involvement. Lesion size was estimated using a “necrotic arc angle,” defined by the angle of...
The ability to find consistent and reliable markers of disease is always a welcome tool for diagnosis, determination of the extent of the disease, or even determination of the risk of acquiring the disease. The measurement of serum and urine carboxy-terminal cross-linking telopeptide of type I collagen (CTX-1), a marker of bone resorption, has been proposed as a method of evaluating the risk of ONJ as a result of bisphosphonate usage, although they are not commonly measured in the clinical setting. A serum osteocalcin level, which is easier to obtain, is another marker for bisphosphonate-related ONJ that has been suggested as a risk predictor because levels were significantly lower in the osteonecrosis group compared with a control group.164

OUTCOME

The natural history of osteonecrosis depends on the size of the infarcted segment, the site of occurrence, and the clinical and radiologic staging of the disease. At the onset of the disease, range of motion may be well preserved but gradually deteriorates over time. In the early stages of the disease, when it is still reversible, patients may be asymptomatic; many patients therefore present with advanced disease.

## Markers of Disease

The ability to find consistent and reliable markers of disease is always a welcome tool for diagnosis, determination of the extent of the disease, or even determination of the risk of acquiring the disease. The measurement of serum and urine carboxy-terminal cross-linking telopeptide of type I collagen (CTX-1), a marker of bone resorption, has been proposed as a method of evaluating the risk of ONJ as a result of bisphosphonate usage, although they are not commonly measured in the clinical setting. A serum osteocalcin level, which is easier to obtain, is another marker for bisphosphonate-related ONJ that has been suggested as a risk predictor because levels were significantly lower in the osteonecrosis group compared with a control group.164

### OUTCOME

The natural history of osteonecrosis depends on the size of the infarcted segment, the site of occurrence, and the clinical and radiologic staging of the disease. At the onset of the disease, range of motion may be well preserved but gradually deteriorates over time. In the early stages of the disease, when it is still reversible, patients may be asymptomatic; many patients therefore present with advanced disease.
Figure 103-11 Diagnostic algorithm for osteonecrosis.

Figure 103-12 Coronal T1-weighted (A) and coronal T2-weighted (B) MRI scans of the wrist of a patient with Kienböck’s disease. Note the low signal intensity of the lunate in both pulse sequences without bone collapse, indicating the intermediate stage of osteonecrosis of the lunate.
Although spontaneous resolution of femoral head osteonecrosis can occur, it is rare and occurs only when the lesion size is small. A study of the prognosis of osteonecrosis of the femoral head as a function of symptoms (pain) and radiographic findings showed that in patients who were asymptomatic and had normal radiographs, progression of the disease was slow, with only 1 of 23 hips progressing to pain and radiographic changes after 5 years. When radiographic changes are already present, disease progresses to pain in 14 of 19 patients after 5 years. In a study of stage 1 osteonecrotic lesions of the hip diagnosed with MRI, 40 patients were followed up for an average of 11 years. All patients had stage 1 lesions on the contralateral hip. Overall, 35 of the 40 stage 1 hips became symptomatic, and 29 hips showed collapse. The mean interval between diagnosis and collapse was 92 months, whereas the mean interval between symptoms and diagnosis was 80 months. Most stage 1 hips eventually progress to a more advanced stage, requiring surgery, and thus these hips should be monitored closely.

TREATMENT

Surgery

Most cases of osteonecrosis ultimately require surgical intervention. Sometimes surgical procedures can be used in conjunction with nonsurgical approaches, as will be discussed. The more advanced the disease, the more extensive the surgery that is required.

The various surgical procedures used in the treatment of osteonecrosis include core decompression, structural bone grafting, vascularized fibula grafting, osteotomy, resurfacing arthroplasty, hemiarthroplasty, and total hip replacement. Table 103-8 shows the typical success rates for each of these procedures.

Arthroscopy is a valuable tool used in the treatment of osteonecrosis. It has been used to determine the position of the core decompression tract to the necrotic part of the femoral or humeral head, and arthroscopic débridement has been used in the treatment of osteonecrosis of the capitellum of the humerus in adolescents, in individuals with Kienböck’s disease, and in individuals with osteonecrosis of the scaphoid.

Core decompression, which involves the removal of a core of bone from the femoral neck and head, is indicated in less advanced stages of osteonecrosis (Figure 103-14). The core acts as a vent to reduce intraosseous pressure and intramedullary pressure, reversing ischemia and improving symptoms. Other benefits of core decompression include stimulation of angiogenesis, which leads to improved vascularization during the repair process. The effectiveness of core decompression in the treatment of nontraumatic osteonecrosis was illustrated in 34 patients with 54 affected hips. The mean age at presentation was 38 years. The patients were monitored for a mean duration of 120 months after surgery. Success was defined as absence of symptoms, no further progression of disease, and no further surgery. Clinical improvement was established in 26 hips (48%), and radiographic success was established in 20 hips (37%).

Computer-assisted core decompression has been used to provide greater precision in directing the core into the ischemic area and to minimize the duration of radiation exposure to patients. Because early diagnosis improves outcome and the incidence of developing osteonecrosis in a contralateral hip is high, core decompression is frequently performed on both hips simultaneously. This approach adds little risk compared with unilateral core decompression, with the benefit of better outcomes as a result of early surgical treatment of the contralateral hip.

In structural bone grafting, or bone impaction grafting, the bone graft is inserted into the necrotic segment through the core tract. The bone graft acts in similar fashion to a stent, providing support to overlying subchondral bone. The goal is to prevent collapse. This combination of
### TABLE 103-8 Surgical Treatment of Osteonecrosis

| Surgical Procedure       | Rationale                                           | Stages of Osteonecrosis | Outcome                                      | Comments                                         |
|--------------------------|-----------------------------------------------------|-------------------------|----------------------------------------------|-------------------------------------------------|
| Core decompression       | Reduction of intraosseous and intramedullary pressure | Early stages            | 37% radiographic success, 48% clinical success | Success rate depends on disease stage           |
| Structural bone grafting | Provide support to overlying subchondral bone       | 1 or 2                  | Poor in advanced disease                     | 100% failure rate in stages 3 and 4            |
| Vascularized fibula grafting | Increase blood flow to graft                  | 2 to 4                  | 96% success in stage 2, 90% in stage 3, and 57% in stage 4 |                     |
| Osteotomy                | Shifting position of osteonecrotic segment out of weight-bearing region | 2 and 3                | Not available                                |                                                 |
| Resurfacing arthroplasty | Preservation of bone and joint mechanics with a metallic or ceramic shell over the femoral head | Later stages            | Mean 7-year success rate is 90%             | An alternative to total hip arthroscopy in later stages of disease |
| Hemiarthroplasty         | Replacement of the femoral head, preservation of the anatomic acetabulum | Later stages            | The failure rate for unilateral hemiarthroplasties is 50%-60% at 3 years; for bilateral hemiarthroplasties, the failure rate is 44% | Various techniques are available, some with a better outcome |
| Total hip replacement    | Complete replacement of the hip joint              | Late stages             | 17.4% required revision after 10 years       | Eventually most patients will require several hip replacements |

#### Figure 103-14
An anteroposterior radiograph (A) and a T1-weighted MRI scan (B) in a patient who underwent core decompression demonstrate the decompression tunnel extending from the subtrochanteric area into the area of the osteonecrosis in the femoral head.

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Procedures is frequently used in treating stage 1 or 2 osteonecrotic femoral heads. Allogeneic and autologous bone grafts, mostly harvested from the tibia or fibula, are used. When this technique was attempted in patients with stages 3 and 4 lesions, the outcome was generally poor (100% failure after 2 to 4 years), with progression to collapse and further surgical procedures.  Another study investigated outcomes after structural augmentation with autogenous bone grafts in stage 1 and 2 disease in 31 patients (33 hips); all patients had significantly reduced pain, along with an improvement in Harris hip scores from 76 before surgery to 91 after surgery.

Vascularized structural bone grafting also uses the core tract to insert a corticocancellous bone graft into the femoral neck and head along with its vascular pedicle. The vascular pedicle is anastomosed to a nearby vessel, adding a source of blood to the graft. The results of vascularized fibular grafting in the treatment of hips with osteonecrosis showed a survival of 61% of hips at 5-year follow-up and 42% at a median of 8 years. In another study, 197 patients with 226 osteonecrotic hips were treated with a combination of autologous cancellous bone impaction and pedicled iliac bone block transfer. The anastomosis was to the ascending branch of the lateral femoral circumflex artery. Fourteen
hips required conversion to total hip arthroplasty because of collapse, severe pain, or both. Of the remaining 212 hips, 92% were considered a clinical success and 76% were considered radiographically successful. The success rate declined from stage 2 to stage 4 hips (96% for stage 2 hips, 90% for stage 3 hips, and 57% for stage 4 hips). Free vascularized fibula grafting has been compared favorably with other modes of surgical treatment.\textsuperscript{122}

Osteotomy of the femur involves shifting the position of the osteonecrotic segment by making a cut in the proximal femur so that the osteonecrotic segment is rotated or flexed out of the weight-bearing region of the acetabulum and then replacing the weight-bearing region with viable bone. Healing of the necrotic region can proceed without the stress of weight bearing. Several different osteotomy techniques have been attempted to salvage hips with stage 2 or 3 osteonecrosis.

Resurfacing arthroplasty uses a metallic or ceramic shell placed over a femoral head that has been debrided of the necrotic area. The potential advantages of resurfacing arthroplasty include preservation of joint mechanics, bone conservation, more physiologic loading of the bone, a lower incidence of perioperative complications, and easier follow-up compared with total hip arthroplasty in case of failure.\textsuperscript{174} Complications of this procedure include femoral neck fractures, a secondary osteonecrosis when the procedure is performed for other reasons,\textsuperscript{175} and increased metal ion levels.\textsuperscript{176} Resurfacing arthroplasty has been recommended for patients with later-stage osteonecrosis, including those with femoral head collapse.\textsuperscript{177} A retrospective study compared the results of limited femoral head resurfacing and total hip arthroplasty in 30 consecutive patients with Steinberg stage 3 or 4 disease. The survival rate at a 7-year mean follow-up period for the resurfacing group was 90%, whereas the survival rate at a mean 8-year follow-up for the total hip arthroplasty group was 93%.\textsuperscript{178} A recent level 3 therapeutic study showed that hip resurfacing success rates at a 5-year follow-up were comparable with those of total hip arthroplasty in patients with osteonecrosis who were younger than 25 years.\textsuperscript{179}

In hemiarthroplasty, only part of the hip joint is replaced. The original acetabulum is preserved, but the femoral head is replaced with a prosthesis. Two types of prostheses are used—a unipolar prosthesis and a bipolar prosthesis. In a unipolar prosthesis, the articulation is between the artificial femoral head and the acetabulum. In the bipolar prosthesis (presently the most frequently used), the articulation is within the prosthesis itself. Failure rates for hemiarthroplasties in individuals with osteonecrosis are 50% to 60% at 3 years for unipolar prostheses and 44% for bipolar prostheses. Another study evaluated the success rate of Charnley/Bicentric hemiarthroplasty in the treatment of Ficat and Arlet stage 3 osteonecrosis of the femoral head. Failures included three hips that needed to be revised to cementless total hip replacement, two hips with radiographic changes of loosening and imminent failure, and one hip with progressive loss of joint space and secondary degenerative changes. The success rate was 84.2% after a mean of 56 months.

Total hip arthroplasty is complete replacement of the hip joint with a prosthesis, including the femoral head and the acetabulum. In a study of 55 consecutive hip arthroplasty procedures, cementless total hip arthroplasty was shown to provide favorable results in advanced-stage osteonecrosis of the femoral head. Although 10 of the 48 hips available for follow-up after a minimum of 5 years required revision, all of these patients had Ficat and Arlet stage 3 or 4 disease. A study of 53 hips in 41 patients treated with cemented total hip replacement showed that at a minimum of 10 years of follow-up, 17.4% required revision. Compared with cemented total hip replacements performed for other conditions, osteonecrosis had a greater risk for loosening of acetabular and femoral components. A survivorship analysis of cemented total hip replacements in renal transplant patients with osteonecrosis of the femoral head showed excellent survival after 10 years (98.8%). After 20 years, the survival rate decreased to 63.8%.

In individuals with ONJ, the most common surgical procedure is resection of the affected bone.\textsuperscript{180} Conservative treatment has also been used but has a higher recurrence rate. A larger extent of surgical excision and a higher number of surgical debridements were associated with a lower recurrence rate. Other modes of surgical therapy for ONJ include bone-contouring procedures, fluorescence-guided bone-contouring procedures,\textsuperscript{181} and segmental osteotomies, but these procedures are generally reserved for more severe cases. Nonsurgical treatments, including hyperbaric oxygen therapy\textsuperscript{182} and low-intensity laser therapy, are controversial but have been used to treat ONJ.

**Nonsurgical Approaches**

The key to the successful treatment of osteonecrosis is early detection. Because many patients with osteonecrosis are relatively young, and because treatment of late-stage osteonecrosis is associated with high failure rates, earlier detection may be associated with a greater chance of preservation of the hip. The choice of conservative nonsurgical versus more aggressive surgical options depends on the clinical and pathologic staging of the disease. Figure 103-15 is an algorithm for the treatment of osteonecrosis.

Nonsurgical treatment of osteonecrosis of the femoral head includes refraining from weight bearing on the affected joint, use of analgesic and anti-inflammatory medications, and physiotherapy. Conservative medical treatment is effective only in the early stages for symptomatic relief. Nonsurgical management does not seem to alter the natural course of the disease. Electrical stimulation has been used in the treatment of osteonecrosis, in conjunction with core decompression. Electrical stimulation enhances osteogenesis and neovascularization. It also alters the balance between osteoblast and osteoclast activity, resulting in increased bone deposition and decreased bone resorption. Delivery of electrical stimulation can be performed by direct current (DC), pulsed electromagnetic field, and capacitance coupling. The success of electrical stimulation in the treatment of osteonecrosis has been rather mediocre. A study was performed of 11 hips in 8 patients with Ficat stage 2 osteonecrosis who underwent core decompression and placement of an electric stimulating coil within the core in the anterosuperior segment of the femoral head.\textsuperscript{183} Of these 11 hips, 5 required a repeat operation, and 6 had progressive deterioration 13 months after initial placement of the coil. In addition, there was little histologic evidence that the coil did indeed
Twenty-three patients with 29 affected hips were assigned to the shock wave group, and the remaining patients and hips were treated surgically. The patients in the shock wave group were given treatment of 6000 pulses of shock waves at 28 kV to the affected hip. The patients were evaluated radiographically and by their reports of symptoms (pain), Harris hip scores, and quality of life (daily work activity assessment). Shock wave therapy produced better results than did the nonvascularized bone grafting procedure, with comparatively less progression of disease. In 35 patients with 47 osteonecrotic hips, the use of shock wave therapy led to improvements in serum nitric oxide levels, angiogenic factors such as VEGF, and osteogenic factors such as bone morphogenetic protein (BMP)-2 and osteocalcin. Levels of inflammatory markers were reduced. It is interesting to note that although these changes did not persist beyond several months, the clinical and radiographic improvement, present in 83% of hips, was present after 12 months.

Conservative treatment of osteonecrosis of the talus is not promising, and the affected ankles generally continue to progress, requiring either core decompression or arthrodesis. Conservative treatment of bisphosphonate-induced ONJ includes cessation of bisphosphonate usage or surgical

Extracorporeal shock wave therapy has been used in the treatment of osteonecrosis of the femoral head. A study of 48 patients and 57 hips compared extracorporeal shock wave therapy with core decompression and bone grafting. Generate new bone deposition around itself. The efficacy of this method of treatment is unproven.

On the other hand, another study compared the effectiveness of conservative nonsurgical treatment with core decompression with or without DC electrical stimulation. The clinical symptom scores and the rate of progression to arthroplasty were best in the group with core decompression and DC electrical stimulation and worst in the nonoperative group. Capacitive coupling can be performed with or without core decompression and grafting. Forty patients with stage 1 to 3 osteonecrosis underwent core decompression and grafting; half of the patients wore active capacitive coupling units with electrodes over the femoral head for 6 months. The control group was 55 patients with osteonecrosis who were treated conservatively. Follow-ups at 2 and 4 years showed that core decompression with or without capacitive coupling provided a better clinical and radiologic outcome than did conservative treatment. Capacitive coupling did not improve the results further when used with core decompression and grafting.

Extracorporeal shock wave therapy has been used in the treatment of osteonecrosis of the femoral head. A study of 48 patients and 57 hips compared extracorporeal shock wave therapy with core decompression and bone grafting.
débridement. Good oral hygiene, regular dental assessment, and avoidance of dental procedures during bisphosphonate usage can prevent the onset of osteonecrosis.

**RECENT DEVELOPMENTS**

**Prevention Versus Treatment**

A recent study evaluated the role of antioxidants in the treatment of osteonecrosis. Japanese white rabbits were divided into two groups and fed either a normal diet or a normal diet supplemented with α-tocopherol. Osteonecrosis developed in 14 of 20 rabbits in the control group but in only 5 of 21 rabbits in the experimental group. This finding suggests that oxidative stress may play a role in the pathogenesis of osteonecrosis and that a role may exist for antioxidants such as vitamin E. The authors of this study believe that ACTH enhances osteoblast support and stimulates the production of VEGF, which stimulates the generation of new blood vessels. The result is an increase in blood flow to the vulnerable areas of bone, preventing cell death and reducing the likelihood of osteonecrosis.

**Mesenchymal Stem Cells**

Corticosteroids interfere with the balance of adipogenesis and osteogenesis in the differentiation of mesenchymal stem cells. Corticosteroids shunt uncommitted osteoprogenitor cells in the bone marrow into the adipocytic pathway, leading to reduced osteoblast formation. Corticosteroids have also been shown to reduce VEGF, which leads to a reduction in new blood vessel formation and potentially can lead to bone death. Alcohol has a similar effect on the differentiation of progenitor cells.

The balance between adipogenesis and osteogenesis has been targeted as a potential site for the treatment of osteonecrosis. Multipotential mesenchymal stem cells from femoral bone marrow near osteonecrosis sites are able to express messenger RNA aggrecan and type II collagen. Both are deposited into the bone matrix. These features are characteristic of chondrogenic differentiation. The mesenchymal stem cells can be differentiated into osteocytic lineage in vitro.

A pilot study evaluating the effectiveness of implantation of autologous bone marrow cells in the treatment of osteonecrosis used core decompression to implant stem cells into the necrotic lesions of the femoral head. The patients were divided into two groups—one that received core decompression alone as treatment for osteonecrosis and another that received autologous bone marrow cell implantation along with core decompression. The patients were followed up for 24 months, and at that time, 5 of 8 hips in the control group, but only 1 of 10 in the treatment group, advanced to stage 3 osteonecrosis. In addition, greater improvement in pain and joint symptoms occurred in the treatment group, and the treatment seemed to be safe. Because of the small number of patients involved, further studies are necessary to confirm these results.

Twenty-eight patients with 44 necrotic hips were treated with percutaneous decompression and autologous bone marrow mononuclear cell infusion. Patients were followed up for a minimum of 2 years and evaluated for clinical and radiographic progression of the disease. Overall slowing in the progression of the disease stage appeared to occur. The mean Harris hip score improved from 58 to 86.

In 2014, Houdek and colleagues reviewed the literature and published a report in which they concluded that using core decompression in conjunction with mesenchymal stem cell infusion in the form of bone marrow leads to improved pain and functionality and halts progression of osteonecrosis of the femoral head, potentially obviating the need for future invasive procedures such as total hip replacement.

**CONCLUSION**

Osteonecrosis is a potentially debilitating condition with significant morbidity despite medical interventions or surgery. Corticosteroid use is the most common cause of osteonecrosis, and corticosteroid-induced osteonecrosis can be reproduced in animal models. The pathogenesis of osteonecrosis is multifaceted and is still not completely understood. Why is it that corticosteroid-induced osteonecrosis is more common in patients with certain underlying diseases and not in others? Does osteonecrosis have a genetic or epigenetic basis, and is there a familial predisposition? Common pathogenic mechanisms known to be involved in osteonecrosis include osteoblast/osteoclast survival and apoptosis, lipid metabolism, and coagulation abnormalities. However, it is still unclear how these mechanisms interrelate. To better appreciate the risk factors involved in osteonecrosis, a more complete understanding of the pathogenesis is necessary. Until then, the physician should always maintain a high index of suspicion for osteonecrosis whenever known risk factors are present, especially use of corticosteroids and alcohol.

Full references for this chapter can be found on ExpertConsult.com.

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