Introduction

James Russell first described osteonecrosis in 1794, and a full description of the entity followed in 1930 by Phemister et al\textsuperscript{1,2}. Since then many researchers have been trying to determine the pathogenesis of osteonecrosis, but this seems only to have succeeded in creating more questions. Why does a disease with so many diverse etiologies seem to end in one common pathological entity? Why do some patients enter this pathway to destruction while others remain unaffected? Is there some genetic predisposition we are yet to discover? There is no animal model that is suitable for the study of the human form of osteonecrosis. Many experiments conducted in steroid treated rabbits and rats have produced severe lipidemia, fatty livers, loss of body weight, severe malnutrition, decreased blood flow in the femoral head, fat embolism of multiple organs including bone, but no bone necrosis.\textsuperscript{3}

The treatment of osteonecrosis is considerably more successful at early stages of the disease. The early diagnosis of osteonecrosis depends upon the identification of individuals at risk. Understanding the pathogenic factors leading to osteonecrosis enables the early investigation of at-risk individuals and facilitates prompt diagnosis\textsuperscript{4}. A number of hypotheses concerning the pathogenesis of osteonecrosis exist with the most commonly accepted hypothesis by Jones\textsuperscript{5,6,7}.

Osteonecrosis is defined as cell death of bony tissue (marrow and mineralized tissue) due to ischaemia. It represents the final common pathway of several disease entities, which result in impaired blood supply to the bone tissue, causing necrosis of the bone. Jones\textsuperscript{5} has demonstrated the final common pathway for non-traumatic osteonecrosis to be a coagulopathy within the intraosseous microcirculation leading to both intraosseous venous thrombosis and retrograde arterial occlusion. In contrast, a sick cell syndrome hypothesis has been proposed\textsuperscript{3} suggesting that there is little evidence to support the hypothesis that an interruption of the blood supply to bone is involved directly, rather, the pathologic features may result from a direct metabolic effect on the cells.

Bone as a tissue has a remarkable biological capacity to repair and reconstitute itself. Necrosis of the bony portions of a joint should not in any way affect the normal metabolism and functioning of the articular cartilage. The chondrocytes should initiate a series of cellular responses that ultimately “heal” the dead portion of the bone replacing it with new living bone. Therefore there is no reason to expect that the development of osteonecrosis should result in any discernible biological sequelae or clinical, but it does.\textsuperscript{8}

Etiology\textsuperscript{7}

- Idiopathic (40% of all reported cases)
- Alcoholism (20% of all reported cases)
- Antiphospholipid antibody syndrome
- Dysbaric disorders
- Endotoxic (Schwartzman) reactions secondary to systemic bacteraemia
- Gaucher’s disease
- Haemoglobinopathies including sickle cell disease
- Hypercoagulable states
  - Protein C and Protein S deficiency
  - Antiphospholipid antibodies
  - Lupus anticoagulant
- Hypercortisolism
  - Endogenous (Cushing’s syndrome)
  - Exogenous (37% of all reported cases)
- Hyperlipidemia
- Hypersensitivity reactions
  - Allograft organ rejection
  - Anaphylactic reactions
- Inflammatory conditions
  - Systemic Lupus Erythematosus
  - Inflammatory bowel disease
- Malignancy
  - Metastatic carcinoma
  - Acute promyelocytic or lymphoid leukaemia
- Pregnancy
- Radiation therapy
- Traumatic
  - Femoral head dislocation
  - Intracapsular neck of femur fracture
- Viral infections
  - HIV
  - Hepatitis
  - Cytomegalovirus
  - Rubella
  - Varicella
  - Measles

**Vascular Anatomy**

The circulation and arrangement of blood vessels in long bones have been disputed for many years. The most widely accepted patterns of intraosseous circulation are those proposed by Brooks in 1971. Bones have multiple arterial inlets and venous outlets, with long bones having four arterial inputs. The nutrient artery supplies blood to the diaphyseal cortex and marrow, the metaphyseal artery supplies to the metaphyseal cortex and marrow and the epiphyseal artery supplies the epiphysis. The periosteal arteries probably do not provide significant arterial input. Nutrient, metaphyseal and epiphyseal vessels enter the bone through foramina in the cortex and anastamose to supply marrow, cancellous bone, and cortex in a centrifugal direction. The epiphyses of long bones are covered with avascular joint cartilage, as a result, the dual blood supply (periosteal system and the nutrient, metaphyseal and epiphyseal system) does not exist in these areas. Instead, the functional end arteries comprise those ascending in the epiphyseal cancellous bone toward the articular surface. As a result, the epiphysis and the articular surfaces are particularly susceptible to circulatory insufficiency.

Although the role of an impaired blood supply to the femoral head in the pathogenesis of osteonecrosis has not been confirmed, Atsumi and Kuroki have found an abnormal blood supply in patients with corticosteroid induced osteonecrosis. They found that in most cases the blood supply of the superior retinacular arteries from the extraosseous site was impaired. Other studies in corticosteroid induced osteonecrosis have found that the draining veins of the femoral head in steroid treated patients were stenotic or obliterated. In a study by Spencer et al., they demonstrated a gross diminution in both the number of vessels and the caliber of vessels in the femoral head arteries of renal patients receiving steroids. “It was of great interest that in these three patients, arterioles in the femoral head filled, although in
decreased numbers compared with controls. In one of the patients in the study group, distinct multiple filling defects in the arteries and arterioles were a unique finding. Subsequent histology indicated that there were degenerative changes in the arteries of the femoral head and hip capsule of this patient.” (figure 1 and figure 2)

Figure 1
A roentgenograph showing the normal pattern of arteries and arterioles in the femoral head. A= lateral epiphyseal arteries, B= medial epiphyseal artery, C= superior metaphyseal artery and D= inferior metaphyseal artery. (taken from Spencer JD, Brookes M. Avascular necrosis and the blood supply of the femoral head. *Clin Orthop* 1988;235:127)

Figure 2
A roentgenograph of a central coronal section of the femoral head, showing a reduced number of arteries and arterioles. (Spencer JD, Brookes M. Avascular necrosis and the blood supply of the femoral head. *Clin Orthop* 1988;235:127)

Pathogenesis

Although many theories and multiple causes for osteonecrosis have been suggested, until recently little has been known about its pathophysiology or the pathogenic mechanisms involved in its various forms. Today it is most appropriate to consider osteonecrosis as a multifactorial group of disorders that lead, possibly by a common pathway, to bone necrosis.

Trauma

Traumatic conditions, such as fracture, dislocation or surgery, can result in osteonecrosis as a result of vascular disruption leading to ischaemia. Vascular disruption may occur either as the vascular supply enters the bone through smaller arterioles and capillaries or in the intramedullary canal. The association of transcervical fractures of the femur with avascular necrosis of the capital fragment was recognized many years ago. Nevertheless, several basic questions, such as the incidence of avascular necrosis, the extent and pattern of bone death and revascularisation and also the role played by avascular necrosis in non-union of these fractures, remain unanswered12.
Spontaneous osteonecrosis of the knee is a condition of unknown etiology in which there is development of an area of osteonecrosis on the weight-bearing surface of the medial femoral condyle. Trauma is thought to play a role. Spontaneous osteonecrosis has occurred following knee arthroscopy as well as cruciate ligament reconstruction, especially the posterior cruciate ligament.\textsuperscript{14,15} Meniscal tears and arthroscopy has been indicated in the development of osteonecrosis, but which of the two is the initiating factor is still undecided. Muscolo \textit{et al.}\textsuperscript{13} report a series of 5 patients over 60 years of age with symptomatic medial meniscal tear, confirmed on MRI, who developed spontaneous osteonecrosis of the knee without any arthroscopic intervention.

**Coagulation abnormalities**

Jones\textsuperscript{5,6} has postulated that intravascular coagulation activated by a variety of underlying diseases may be the missing link that joins several seemingly unrelated risk factors and leads to the final ischaemic insult producing intraosseous thrombosis and bone necrosis. Studies by Korompilias \textit{et al.}\textsuperscript{7} have shown an 83% prevalence of thrombophilic disorders or hypofibrinolysis in patients with osteonecrosis. Patients were found to have a deficiency in natural anticoagulant proteins C and S, activated protein C resistance (APCR), antiphospholipid antibodies (APLA), antiphospholipid antibodies (aCLA), lupus anticoagulant (LA) or hypofibrinolytic lipoprotein a (Lpa). Protein C and protein S deficiencies lead to increased procoagulant activity because of decreased inactivation of prothrombotic factors Va and VIIIa.

Current evidence suggests that intravascular coagulation, an intermediary mechanism, is the most likely final common pathway by which intraosseous fat embolism causes nontraumatic osteonecrosis\textsuperscript{5}. Fatty osteocytic necrosis appears to progress to the classic picture of ischaemic degeneration of necrotic osteocytes and adipocytes when the ischaemic threshold is exceeded by absolute subchondral fat overload with insufficient local clearance of procoagulants, especially tissue thromboplastin. The result is vascular stasis, hypercoagulability, endothelial damage (by free fatty acids) and intravascular coagulation, especially if there is coexistent subchondral vasoconstriction and impaired secondary fibrinolysis (figure 3). Since fat embolism is related to diffuse intravascular coagulation in the Shwartzman phenomenon (a necrotic reaction produced by endotoxins) osteonecrosis could be expected to occur in post-meningococcemiac children with diffuse intravascular coagulation (figure 4).

![Figure 3](image-url)

\textit{Figure 3}

Immunological factors

Osteonecrosis has been associated with several autoimmune diseases most notably Systemic Lupus Erythematosus (SLE) and Rheumatoid arthritis. In most cases, vasculitis and the use of corticosteroids have been described as pathogenic mechanisms. Osteonecrosis is a common manifestation in SLE and was first reported in 1960 by Dubis and Cozen. It occurs in 5% to 40% of all documented SLE cases. Anticardiolipin antibodies and lupus anticoagulant, found in 73% of SLE patients, have been associated with vessel thromboses of all sizes and at multiple organ sites.

Corticosteroids

Corticosteroid use has been suggested as a major predisposing factor for osteonecrosis in SLE. The duration of steroid therapy, the total cumulative dosage and high daily dosages have all been independently implicated. Jones states that beyond a certain threshold there is a corticoid osteonecrosis response phenomenon, in his experience the threshold is about 2000mg of prednisone (or equivalent) administered continuously. Although the correlation between corticosteroids and osteonecrosis has been well established, the pathogenesis remains controversial.

Two hypotheses have been proposed in an attempt to explain the mechanism by which changes in fat metabolism after corticosteroid administration can lead to osteonecrosis. The first suggests that altered fat metabolism causes an increase in the size of intraosseous adipocytes leading to increased intraosseous pressure which compromises perfusion (through activation of the coagulation pathway) and results in ischaemia. The second proposed mechanism is that altered fat metabolism results in increased serum lipid levels with subsequent occlusion of subchondral vessels by fat emboli. In a study by Wang on chickens, he found evidence of osteonecrosis in steroid treated chickens, whereas sections from the animals treated with steroids and lovastatin (lipid lowering agent) showed less adipogenesis and no bone death.

Drescher et al described endothelin-1-induced vasoconstriction of the epiphyseal arteries in patients on corticosteroid treatment; this may lead to a reduction of blood flow and local ischaemia.

Alcohol

The pathogenesis of osteonecrosis in relation to alcohol use seems to be similar to that of corticosteroid use, with fat emboli produced by the liver occluding vessels in the subchondral bone. It was previously assumed that osteonecrosis was caused by the active metabolites of ethanol. The direct cytotoxicity of lipid peroxidation, caused by alcohol and its metabolites, might further insult ischemic osteocytes, resulting in an irreversible state of the injury, leading to cell death, and finally osteonecrosis. Changes in the bone marrow after alcohol abuse can
also lead to venous stasis, increased intraosseous pressure, decreased perfusion and bone death. There is still controversy regarding length and quantity of alcohol abuse that results in osteonecrosis, with Jones stating that the alcohol threshold for alcohol-associated osteonecrosis being a consumption of 150 litres of 100% ethanol at 400ml or more of absolute ethanol a week. The results his study showed elevated serum lipid peroxides and reduced superoxide dismutase activity in animals treated with alcohol.

**Haemoglobinopathies**

Several haemoglobinopathies, especially sickle-cell disease, are common causes of osteonecrosis. The pathogenesis is primarily related to emboli formation, but deformed erythrocytes may also cause microinfarts in the subchondral bone. A higher haematocrit leads to higher blood viscosity and further increases the risk of osteonecrosis. In addition, bone marrow hyperplasia caused by chronic haemolytic anemia can increase bone marrow pressure leading to osteonecrosis.

**Caisson disease (dysbarism/decompression sickness)**

The pathogenic mechanism seems to be embolic, with air bubbles causing occlusion and ischaemia, although rapidly expanding nitrogen can cause secondary injury to adipocytes within the marrow and cause vessel collapse. Sudden intraosseous fat overload could also be precipitated by dysbaric phenomena. Of those factors known to increase the incidence of dysbaric osteonecrosis, increased rate of decompression may be the most important. A single rapid decompression can not only cause fat embolism, but also diffuse intravascular coagulation or osteonecrosis. Intravascular fat and tissue thromboplastin accelerate diffuse intravascular coagulation after decompression sickness. There is a decrease in antithrombin III activity, prolongation of the prothrombin time, increased fibrin degradation products, and accelerated platelet and fibrinogen turnover leading to osteonecrosis.

**Gaucher’s disease**

The accumulation of lipid-laden Gaucher cells in the bone marrow can increase intraosseous pressure, influence coagulation and occlusion of intraosseous vessels leading to osteonecrosis.

**Human immunovirus**

Osteonecrosis in HIV-infected patients was first reported in 1990. Miller et al found an alarmingly high prevalence (4.4%) of osteonecrosis in their HIV-patient study group. Risk factors identified included the use of corticosteroids, testosterone and, paradoxically, lipid lowering agents. The treatment of HIV infection with protease inhibitors may play a role in the pathogenesis. Protease inhibitors may cause osteonecrosis through a tendency to cause hyperlipidemia. Alternatively, protease inhibitors may inhibit the metabolism of drugs (e.g. corticosteroids) that are metabolised by the cytochrome p450 system decreasing their safe therapeutic ranges.

**Bone marrow oedema syndrome**

Jones hypothesised that, “In bone marrow oedema syndrome there is initially subtotal ischemia, especially in the intraosseous locations with compromised collateral circulation. Ischemic hypoxia temporarily injures those cells within the marrow and trabeculae, but there is insignificant cellular necrosis, because there is nearly complete fibrinolysis of the intraosseous (and extraosseous) thrombi within a few minutes to two hours after the acute ischemic event. Therefore the marrow cells, osteoblasts and osteocytes will eventually recover from this reversible ischemic event. I suspect that most bone marrow oedema syndrome patients probably have rapid plasma activation by a relatively competent fibrinolytic system. However, there is probably incomplete fibrinolysis in those bone marrow oedema syndrome cases in the grey zone between classic bone marrow oedema syndrome and osteonecrosis, who may have significant hypofibrinolysis.”
Bisphosphonates

Bisphosphonates are now widely prescribed to orthopaedic and rheumatological patients, for osteoporosis, Paget’s disease and various bone tumours. The list of potential uses is constantly expanding. What we are less aware of is the potential of bisphosphonates to cause osteonecrosis. Already there are documented cases of osteonecrosis of the jaw, but as yet other bones seem unaffected. Bisphosphonates inhibit bone resorption and thus bone renewal by suppressing the recruitment and activity of osteoclasts thus shortening their life span. Recently three bisphosphonates, Pamidronate (Aredia; Novartis Pharmaceuticals, East Haven, NJ), Zoledronate (Zometa; Novartis Pharmaceuticals), and Alendronate (Fosamax; Merck Co, West Point, VA) have been linked to painful refractory bone exposures in the jaws. Osteonecrosis of the jaw is hypothesized to occur as a direct result of microtrauma on bone that is both hypovascular and hypodynamic and thus less able to meet an increased demand for repair and remodeling. The jaw is particularly prone to osteonecrosis as it is regularly exposed to physiologic stress (e.g. mastication), iatrogenic damage (e.g. tooth extraction or denture injury) or tooth infection. Novartis, at an FDA review in 2005, reported 875 cases of jaw osteonecrosis out of 2.9 million patients treated with intravenous bisphosphonates. Six cases (4056 patients) had previously been identified in all controlled clinical trials and the first post-marketing report was made in December 2002.

Pathophysiology

Various theories have been proposed to describe the pathophysiology of osteonecrosis; the following three mechanisms are the most widely accepted (figure 5).

Intraosseous Hypertension (Compartment Syndrome of Bone)

Raised intraosseous pressures have been consistently found in most cases of osteonecrosis. Blood flow through the intraosseous compartment is inversely proportional to the bone marrow pressure therefore any condition which causes an increase in this pressure will produce a decrease in the blood flow to the bone in that area with subsequent ischaemia and osteonecrosis.

Abnormal Extraosseous Blood Flow

Super selective angiography of the medial circumflex artery has been used for extensive study of the extraosseous femoral head blood flow in patients with osteonecrosis of the femoral head. Consistent loss of transcortical blood flow from the superior retinacular arteries and alterations in revascularization has been demonstrated.

Fat Embolism

Alterations in lipid metabolism cause hyperlipidemia with fat mobilization and embolisation to the subchondral arterioles. Overload of subchondral fat results in vascular stasis, local hypercoagulability, endothelial damage, and subsequent intravascular coagulation. The use of lipid lowering agents has been consistently shown to improve this alteration in blood flow.
Figure 5

Pathology\textsuperscript{9,20}

Macroscopically bone necrosis, fibrous tissue deposition and subchondral collapse occurs. Later, osteonecrosis in humans is characterized by a generally consistent histopathology (figure 6). The earliest observation on light microscopy is necrosis of haematopoietic marrow and adipocytes. This is followed by liquefaction necrosis and interstitial edema, and subsequently by osteocyte necrosis. Osteocyte necrosis occurs after 2-3 hours of anoxia but histological signs of osteocyte death are apparent only after 24-72 hours. Histologically, early changes involve autolysis of osteocytes (14-21 days) and necrotic marrow, followed by inflammation with invasion by buds of primitive mesenchymal tissue and capillaries The necrotic area is surrounded by a zone of reactive hyperaemia and fibrous repair. Capillary neogenesis and revascularization proceed to a limited degree from the reactive zone into the necrotic zone. With the entry of blood vessels into the zone of necrosis, a repair process begins. This consists of bone resorption and formation, which produces the radiographic appearance of sclerosis and lucency. New woven bone is laid down on top of dead trabecular bone. This stage is followed by resorption of dead trabeculae and remodelling via "creeping substitution". The repair process is self-limited and the dead bone is incompletely replaced. In subchondral bone, bone formation occurs at the slower rate than does resorption, resulting in the net removal of bone, loss of structural integrity, and subchondral fracture. It is not the necrosis \textit{per se} but rather the resorptive component of the repair process that leads to the loss of structural integrity, collapse, and joint incongruity.
Summary

The pathogenesis of osteonecrosis is still an enigma, which remains to be solved. Understanding the pathogenesis of osteonecrosis will have a significant impact on the prevention and treatment of this debilitating disease. At the moment, therapeutic efforts are focused on the structural consequences of osteonecrosis. A better understanding of the pathogenesis might allow earlier, more focused, treatment to reverse mechanisms leading to hypoperfusion and ischaemia. More research needs to be undertaken to determine if a genetic predisposition to hypercoagulability increases a patient’s risk of developing osteonecrosis. Most of the evidence points to the existence of a final common pathway (coagulopathy) regardless of the etiological factors involved. Research has shown that treating hypercoagulable states with warfarin and using lipid-lowering agents, which effect the local hyperlipidemia associated with early osteonecrosis, lowers the incidence of osteonecrosis.

References


