Key pathway to prevent the collapse of femoral head in osteonecrosis

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Abstract. – OBJECTIVE: Osteonecrosis of the femoral head (ONFH) is a multifactorial disease, with unclear pathogenesis. The collapse of the femoral head is an important turning point in ONFH, especially for young patients. Many methods have been proposed, but the best treatment lacks consensus among orthopedic surgeons. Thus, understanding the collapse mechanism of the femoral head in ONFH is the key to a successful outcome of joint preservation. This review aims to provide an update of the collapse mechanism of the femoral head in ONFH and to focus on the most appropriate therapeutic strategies to adopt in clinical practice.

MATERIALS AND METHODS: We reviewed the international literature to identify studies focusing on ONFH and therapeutic options. PubMed, Medline and Cochrane Library databases were searched for English language papers. We used the following key words: osteonecrosis of femoral head (ONFH), avascular necrosis (AVN), collapse, mechanism, treatment. The literature search was conducted by two reviewers, independently of one another, and any discrepancy was resolved by consensus with a third author.

RESULTS: An imbalance between bone resorption and bone formation as well as stress distribution on insufficient trabecular bone may be the most important collapse mechanism in ONFH.

CONCLUSIONS: Treatment to avoid femoral head collapse should focus on local effective mechanical support with modification of bone remodeling in the femoral head.

Key Words:
Osteonecrosis of femoral head (ONFH), Avascular necrosis (AVN), Collapse, Mechanism, Treatment.

Introduction

Osteonecrosis of the femoral head (ONFH), also called avascular necrosis (AVN), causes decreased vascular supply to the trabecular bone of the femoral head, thus resulting in osteocyte death and collapse of the articular surface and eventual osteoarthritis (OA). As early as 1738, Munro first described a case of ONFH. More than 200 years later, Mankin² reported on a series of 27 cases and named the disease AVN. Although the exact incidence of the condition is unclear, an estimated 15,000 new cases present each year in the United States² and the incidence has almost certainly increased over the past decade³. In Japan, the number of patients who sought medical care for ONFH during 2004 was estimated to be 11,400⁴. In the United States, approximately 5% to 18% of all hip arthroplasty is performed in patients with a primary diagnosis of ONFH²,⁵. In Taiwan, 46.3% of all hip replacements are for ONFH⁴. ONFH mainly affects adults in their third, fourth or fifth decade of life⁶. Males are affected up to 3 times more than females, and bilateral ONFH is found in up to 75% of cases⁷. The disease frequently progresses to femoral head collapse, thus leading to debilitating OA in the affected hip (Figure 1)⁸. Despite the fact that total hip arthroplasty (THA) is considered effective to treat the disease in the later stage, prevention of femoral head collapse is important in the early stage, especially for young patients. Many methods to preserve the femoral head have been proposed, but the best treatment lacks consensus among orthopedic surgeons. So understanding the collapse mechanism of the femoral head in ONFH is the key to a successful outcome of joint preservation. Therefore, a review of the collapse mechanism of ONFH is worthwhile.

Materials and Methods

We reviewed the international literature to identify studies focusing on ONFH up until October 2013. PubMed, Medline and Cochrane Library databases were searched for English language papers. We used by using the following key words: osteonecrosis of femoral head (ONFH) (ONFH), avascular necrosis (AVN) (AVN), collapse, mechanism, treatment. The literature search was conducted by two reviewers, independently of one another, and any discrepancy was resolved by consensus with a third author.

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Figure 1. An AP radiograph showing secondary OA in the end stage of bilateral ONFH.

Results and Discussion

Etiology and Pathogenesis

The pathophysiologic process of ONFH has not been completely elucidated. Some cases clearly have a direct cause (trauma, radiation, or Caisson disease). Recognized risk factors include chronic steroid use, alcoholism, smoking, hip trauma including femoral neck fracture and hip dislocation, and prior hip surgery. Other potential etiologies include childhood history of slipped capital femoral epiphysis, deep-sea diving or other hyperbaric conditions, systemic lupus erythematosus and other connective tissue disorders, autoimmune diseases causing vasculitis, sickle cell anemia, coagulopathy such as thrombophilia or disseminated intravascular coagulation, HIV infection, hyperlipidemia, fat embolus syndrome, treatment of developmental hip dysplasia, chemotherapy and/or radiation, organ transplantation, chronic liver disease, Gaucher disease, gout, and metabolic bone disease.

The most common causes are systemic steroid administration (51%) and habitual alcohol use (31%). Corticosteroid use is ranked top of all possible etiologies. ONFH can develop in approximately 5% to 25% of patients who receive intensive corticosteroid therapy (more than 1 month). In addition, the risk of ONFH increases with both the dose and duration of glucocorticoid treatment. In approximately 15% of cases, no predisposing factors can be identified and are referred to as idiopathic. Many cases previously thought to be idiopathic ONFH were in fact related to genetic traits. Some patients with familial ONFH carry collagen type II A1 mutations.

Although several different etiologic factors can lead to osteonecrosis, the pathogenesis is unclear. Numerous investigators have proposed a multi-hit hypothesis, which suggests that the development of ONFH requires the presence of multiple insults to the bone or surrounding tissues. Disruption of the blood supply to the femoral head is commonly believed to cause bone necrosis and further hip joint destruction. With traumatic osteonecrosis, the pathway seems clear, with physical destruction of tissue playing an obvious role. Angiography studies also confirmed that in early stages of osteonecrosis, the lateral and medial circumflex femoral arteries are frequently not visualized, and their absence may have a major role in the pathogenesis. Once the vascular supply to the femoral head is disrupted, cell death occurs. In time, edema associated with osteocyte death increases the local osseous compartment pressure and further inhibits vascular flow to the femoral head. In animal experiments, steroid-induced enlargement of marrow fat cells within the hard cortex may have caused high intraosseous pressure and ischemia. In addition, increased intraosseous pressure can result in disrupted bone blood flow. This situation may help explain the high incidence of ONFH in workers in hyperbaric environmental conditions (dysbaric osteonecrosis). However, Welch et al. found no correlation between increased intraosseous pressure and the development of osteonecrosis.

The pathophysiologic features of non-traumatic osteonecrosis are more complex than that of traumatic osteonecrosis, and corticosteroid-induced osteonecrosis presents the greatest challenge because of the multiple effects of corticosteroids on multi-system pathways, including osteoblast differentiation, osteoblast and osteoclast apoptosis, lipid metabolism, coagulation pathways, and calcium metabolism. Glucocorticoid receptors have been found in cartilage, osteoblasts, osteoclasts, and osteocytes. The actions of glucocorticoids on the immune system are numerous and extremely complex. Glucocorticoids can affect transcription of genes at various levels, in both inhibitory and excitatory pathways. The extent to which these pathways are affected has a profound influence on both immune and bone homeostasis, because many of the regulatory factors are common to both systems. Osteoclasts and osteoblasts may undergo apoptosis after prolonged treatment with glucocorticoids in vivo. Corticosteroids might direct stromal cells into the adipocytic
pathway as opposed to the osteoblastic pathway\textsuperscript{26}. The overall effect of glucocorticoids on bone is likely multifactorial and includes suppression of osteoblast or osteoclast generation in the bone marrow, increased apoptotic activity of cells, and prolongation of the lifespan of some osteoclasts while decreasing the survival of others\textsuperscript{17}.

After bone death in osteonecrosis, the normal repair mechanisms may be disrupted. Normal repair processes include angiogenesis and penetration of new vessels into the necrotic bone, followed by bone resorption and new bone synthesis. Creeping substitution follows: osteoclasts resorb areas of bony necrosis, and osteoblasts lay new bone down over the acellular trabecular\textsuperscript{27}. Osteogenesis and angiogenesis are intimately associated with the reparative process in bone. In ONFH, even though the progression of bone resorption by osteoclasts may be followed by femoral head collapse, the reparative reaction remains unknown. Although the exact reparative reaction mechanism of the femoral head is unknown, the repair process probably takes place as bone remodeling coupled with osteoclastic resorption and bone formation\textsuperscript{28}. In one study\textsuperscript{29}, TRAP-positive cells were detected around the teres insertion and at the retinaculum in the early radiological stage of femoral head collapse and increased in number throughout the reparative interface zone in the late stage; hypoxia-inducible factor 1a, vascular endothelial growth factor, and fibroblast growth factor 2 were detected in the necrotic zone only in the early stage and did not induce new vessels in the necrotic zone.

**Femoral Head Collapse**

In patients with ONFH, pain, limping and subsequent progression of disease is related predominantly to collapse of the femoral head. The rate of femoral head collapse varies from 44\% to 79\%, probably because of differences in study populations; the overall average was approximately 50\% and the time to collapse is usually < 2 years after diagnosis of ONFH\textsuperscript{30-33}. In 100 patients with osteonecrosis of the femoral head who received joint replacement on one side and had contralateral hips with evidence of osteonecrosis in the stage before the collapse, collapse time in the contralateral hip was commonly within 2 years. Patients at a relatively young age (< 50 years old), with increased activity levels and increased serum triglyceride levels were at risk of rapid collapse\textsuperscript{34}. Some researchers do not consider the collapse as an important key in the progression of ONFH. Nishii et al\textsuperscript{31} indicated that the collapse of the femoral head does not necessarily determine poor prognosis, and even after the collapse, subsequent cessation of collapse can be expected in a certain percentage of hips. Cessation of collapse and improvement of symptoms with no surgical intervention is highly possible in hips with < 2-mm collapse and necrotic lesions occupying less than the medial two-thirds of the weight-bearing area. Articular cartilage that appears macroscopically normal may remain with mechanical function even in patients with large osteonecrotic lesions or at a late radiographic stage of the disease\textsuperscript{35}.

Collapse of the femoral head is considered a definitive sign of failure, because it represents destruction of the normal structure of the hip\textsuperscript{31}. The occurrence of collapse or collapse > 2 mm is likely to lead to debilitating pain and secondary acetabular changes or subsequent secondary OA. Much research has indicated that once osteonecrosis appears, approximately 80\% of the femoral head collapses and most of patients will need THA. Although arthroplasty procedures have improved over the past decade, patients between 20 and 50 years old will most likely require multiple revision procedures in their lifetime\textsuperscript{36,37}. Hence, disruption of the femoral head contour by collapse of the necrotic segment is thought to be an important turning point in the history of ONFH\textsuperscript{35}.

**Collapse Mechanism**

The explicit mechanism of femoral head collapse has not been elucidated. For small lesions, creeping substitution may replace the necrotic region with normal bone. However, for large lesions, vascular in-growth develops at the periphery of the lesion, and new bone is deposited with increasing thickness and density at the periphery. There is limited vascular penetration through this dense periphery of the lesion, thus inhibiting repair of the more central portions of the lesion and leaving an area of weakened acellular bone prone to fracture and subsequent collapse\textsuperscript{27}. Collapse typically occurs in the anterior region. The anterior portion of the bone most frequently shows the greater overall collapse, because the greatest forces are applied to the anterior-superior face of the femoral head\textsuperscript{38,39}. Christian et al\textsuperscript{40} investigated the histological result of seven femoral heads resected for primary OA and
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Three removed after femoral neck fracture, bone quantity and quality were reduced in the fracture group as a whole; bone quantity was uniform in each femoral head, but the quality was decreased in the anterior portion. The authors suggested that the anterior susceptibility resulted from bone loading and that reinforcement of the femoral head in ONFH should focus on the anterior hemisphere. Brown et al. postulated the trabecular bone “subjacent” to the subchondral plate in the weight-bearing region initiates the collapse as a result of poor quality.

Brown et al. tested the uniaxial compression loading of small cube-shaped samples from adult patients with ONFH. Samples extracted from major infarct regions showed substantially reduced (52%) yield strength, severely reduced (72%) elastic modulus, and modestly increased (29%) strain-to-failure rate as compared with normal femoral heads. In 1983, Brown et al. used 3-D finite element analysis to investigate the effect of several lesion characteristics with mechanical stress in segmentally necrotic human femoral heads. The results revealed very complex stress redistributions in the femoral head due to osteonecrosis. Although subchondral failure was always limited to the entire base region of the infarction wedge, the zones of deep failure varied considerably with changes in lesion geometry, usually concentrated within the infarct near the underlying necrotic/vascular interface. In 1992, Brown et al. demonstrated that even a fully normal subchondral plate can provide only modest stress protection of a weakened underlying segmental infarction, whereas weakening of the necrotic cancellous bone throughout the infarction markedly increased stress in the overlying subchondral plate.

Trabecular microfracture is a subclinical pathologic response to microtrauma in a trabecular of bone that results from excessive load on normal bone or normal load on insufficient bone. Volokh et al. indicated that the normal cancellous bone serves as a strong supporting foundation for the cortical shell and prevents it from buckling. However, with osteonecrosis, the deteriorating cancellous bone is unable to prevent the cortical shell from buckling and the critical pressure decreases with the decreasing Young modulus of the cancellous bone. Local buckling of the cortical shell seems to be the driving force of the progressive fracturing of the femoral head, thus leading to its entire collapse. Therefore, the authors suggested that the reinforcement should be placed as close to the cortical shell as possible.

Furthermore, some recent studies have indicated that the repair capacity of the femoral head probably plays an important role in the disease outcome. The repair process in ONFH starts from the reactive interface. It consists of fibrovascular tissue formed on the margin of the lesion as the response of vital tissue to necrosis. Blood vessels from the marginal zone invade the dead bone, thus removing the necrotic tissue by osteoclastic resorption and introducing osteoblasts for new bone synthesis. Limited revascularization and bone repair may occur and occasionally a marginal demarcation of the affected area with sequester formation may follow. The weight-bearing bone is prone to collapse because of excess osteoclast activity. Osteoclasts were detected around the teres insertion and retinaculum in the early radiological stage of 51 hips in 42 patients with ONFH; they were increased in number around the new trabecular bone throughout the reparative interface zone in the late collapsed stage. Progression of collapse is greatly influenced by the repair response, especially bone resorption induced by osteoclasts in the necrotic bone. In the reparative interface, the excessive activity of osteoclasts decreases the quality and mechanical property of trabecular bone. Then trabecular microfractures occur and lead to segmental collapse of femoral head resulting from normal load on insufficient trabecular bone (Figure 2).

Figure 2. A coronal micro-CT image showing the collapse of femoral head. Trabecular fracture in the necrotic region (red arrow). Sclerosis band at the periphery of the lesion (yellow arrow). Subchondral failure in the weight-bearing region (green arrow).
In conclusion, the imbalance between bone resorption and bone formation and stress distributions on insufficient trabecular bone is the most important mechanism of femoral head collapse with osteonecrosis.

**Predictors of Femoral Head Collapse**

Bone mineral density, calculation of articular surface area and lesion size, scintigraphy, Kerboul and modified Kerboul method with use of MRI have been used to predict femoral head collapse in hips with ONFH. The location and volume of the lesions are strongly associated with risk of femoral head collapse. Lesion volume is strongly associated with risk of collapse, and lesion location is an important prognostic indicator of collapse with small necrotic lesions. The necrotic articular surface area and its ratio to the whole articular surface area of the femoral head can be used to predict risk of collapse. Bone scintigraphy used to evaluate the activities of reactive interface revealed that high tracer uptake at the reactive interface in the early phases of ONFH seems to predict femoral head collapse. According to the collapse mechanism, the modified Kerboul method combined with remodeling activity analysis may be the most efficient method to assess collapse in hips.

**Treatment**

Prevention of femoral head collapse and maintaining hip function represents a substantial achievement in the treatment of ONFH. Even with improvements in THA, it is desirable to delay the requirement for this procedure in patients with ONFH, since many of them will live for many years after the operation. Thus, the importance of a joint-preserving treatment must not be underestimated.

Non-operative treatments for osteonecrosis have some roles in treatment of late-stage osteonecrosis but have limited success in preventing disease progression, even in early-stage ONFH. Bisphosphonates, anticoagulants, and vasodilators and biophysical modalities have recently demonstrated efficacy in reducing pain and delaying disease progression in early-stage osteonecrosis. Although they are still thought insufficient, their routine use is supported in the treatment or prevention of osteonecrosis of the hip. Because excess osteoclast activity over osteoblast activity may decrease mechanical strength of the repair region and lead to femoral head collapse, inhibiting bone resorption activity or delaying it by therapeutic procedures may help in prevention. Optimal regulation of osteoclast-mediated bone resorption is crucial in preventing collapse. However, alendronate has no effect on preventing the necessity for THA, reducing disease progression, or improving life quality.

The past decade has seen an explosion in the identification and characterization of numerous growth factors and other cytokines. At least 3 of these groups are potential candidates as therapeutic modalities in treatment of osteonecrosis: (1) cytokines (including interleukins, tumor necrosis factors, and signaling molecules such as fibroblast growth factors, platelet-derived growth factor, insulin-like growth factors, transforming growth factor b), (2) bone morphogenetic proteins, and (3) angiogenesis factors. The long-term success of using bone morphogenesis proteins and autologous MSCs is still being investigated.

Core decompression with modification is still one of the safest and most commonly used procedures with evidence-based success in the pre-collapse stage of ONFH. Chen et al concluded satisfactory results for core decompression in osteonecrotic femoral heads at the pre-collapse stage and with small necrotic area or good lateral buttress with a follow-up of at least 1 year. A random trial of 37 hips (33 patients) with early-stage ONFH revealed that core decompression may be effective in symptomatic relief but was of no greater value than conservative management in preventing collapse in early ONFH. The additional use of bone morphogenesis protein and bone marrow stem cells may enhance the results of core decompression.

At present, the use of large vascularized iliac grafts, the other surgical procedure with a high success rate, is still not common due to technical difficulties in surgery. Combining vascularized iliac and greater trochanter grafts to reconstruct ONFH with collapse had long-term excellent results in 3 patients and may be valuable in young patients. A retrospective review of 32 patients in whom ONFH with segmental collapse had been treated with vascularized iliac bone grafting demonstrated that the technique is not indicated for treatment of ONFH with segmental collapse.

Titanium implants combined with autogenous bone graft and recombinant human bone morphogenic protein 2 could enhance the repair procedure and prevent collapse of the femoral head. In a prospective study of 21 patients with non-traumatic ONFH (26 hips) receiving 2
or 3 tantalum pegs, more than two-thirds of the surviving hips showed satisfactory clinical outcome, and the mean implant survival was 60 months. However, other studies found that core decompression combined with insertion of a tantalum implant was not superior to core decompression alone.

The use of cement injection to restore the sphericity of the femoral head was proposed in ONFH due to sickle-cell disease and in other cases with different aetiology. The results were good, allowing postponement of THA and providing immediate pain relief. However, cement injection should not be proposed for glucocorticoid-induced ONFH.

For partial osteonecrosis of the femoral head, various types of osteotomies have been developed to save the femoral head and maintain the natural function of the hip joint. Rotational acetabular osteotomy has been efficacious for treating OA of the dysplastic hip. This surgery could relieve the symptoms of young patients with extensive ONFH and prevent femoral head collapse. Intertrochanteric osteotomies, both varus and valgus, were satisfactory for 62% to 87% of cases. Trans trochanteric rotational osteotomy was introduced as a theoretically ideal method for joint preservation. However, its use in treating osteonecrosis has not gained widespread acceptance perhaps because of inconsistent results. Likewise, osteotomies are also not widespread because arthroplasty is becoming more acceptable.

Discussion

ONFH is a pathological state with multiple possible etiologies that causes decreased vascular supply to the subchondral bone of the femoral head, resulting in osteocyte death and collapse of the femoral head. The most common causes are systemic steroid administration and habitual alcohol use.

Collapse of the femoral head is an important key in the progression of this disease. However, the explicit mechanism of femoral head collapse is unclear. Collapse typically occurs in the anterior region because of the greatest forces are applied to the anterior-superior face of the femoral head. We suggested that the repair progress of necrosis trabecula, excessive bone resorption induced by osteoclasts and insufficient bone formation induced by osteoblasts decreases the mechanical properties of trabecula, resulting in trabecular microfracture under normal load condition, consequently, femoral head collapse. The location and volume of the lesions and activity of repair progress, especially the activity of bone resorption, are critical parameters to predict the risk of collapse.

At the time of this writing, a lot of effort is being spent on improving the treatment of ONFH, but most of them were focus on providing effective mechanical support to necrosis zone and ignored regulation the balance between bone resorption and bone formation.

Conclusions

With ONFH, the internal environment of the femoral head changes with disrupted blood supply; cell death occurs and then lacunae appear. In time, edema associated with osteocyte death increases the local osseous compartment pressure. With revascularization, the imbalance between osteoclast bone resorption and osteoblast bone formation decreases the mechanical properties of trabecular bone in the repair interface, then with normal load, insufficient trabecular fracture occurs and results in irreversible collapse of the femoral head. If the goal of treatment is to prevent collapse, then the window of therapy may be limited to an early stage of ONFH before significant collapse of the head. This review suggests that load relief should be considered first, then effective mechanical support with local modification of bone remodeling in the femoral head.

Statement of Interest

This work was funded by a grant from the National Technology Research and Development Program of China (2012AA020502, 2012CB518106) and the National Science Foundation of China (30930092, 30973047, 31240048), and BWS11J025

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References


32) Koo KH, Kim R, Ko GH, Song HR, Jeong ST, Cho SH. Preventing collapse in early osteonecrosis of


