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Review

Histopathological aspects and staging systems in non-traumatic femoral head osteonecrosis: an overview of the literature

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Summary. *Background:* The pathogenesis of non traumatic osteonecrosis of the femoral head (ONFH) has not yet been established. The literature shows a variable nomenclatura for this condition that often leads to confusion. Several risk factors have been identified but histopathological and radiological outcomes are common. *Purpose:* To provide the overview on the current knowledges about the nomenclatura, etiology, disease progression, relationship between histopathological changes and imaging techniques in order to stage the disease accurately. *Etiology and pathogenesis:* Genetic predisposition, metabolic factors, local factors affecting blood supply such as vascular damage, increased intraosseous pressure and mechanical stress are involved in this desease. The final results are bone ischemia and infarction getting bone deathand FH collapse. *Histopathological aspects and staging systems:* Several staging systems have been developed to stage ONFH based on imaging techniques.The subchondral collapse, the size or quantification of the lesion, and the lesion location within the femoral head are identified as the most important prognostic factors in ONFH disease. Histological analysis plays a critical role to evaluate the quality of necrotic area and the differences between microscopic, macroscopic and imaging outcomes were detected. *Conclusions:* an ideal staging system is necessary to stage ONFH desease to detect several aspects, but itìs more difficult to create. At the present time we summarize some aspects that are advisable to focus during ONFH for the correct treatment.(www.actabiomedica.it)

Key words: osteonecrosis, histopathological aspects, staging systems, femoral head

Background

Osteonecrosis (ON) is a disease characterized by an impaired blood flow in the bone. It is the final outcome of severe and prolonged ischaemia (1). The literature shows a variable nomenclatura for this condition that often leads to confusion. The terms "aseptic, avascular, ischemic necrosis" and "bone infarction" share the same etiology and pathogenesis. The first three terms are generally used for epiphyseal or subchondral bone necrosis and "bone infarction" is used for a metaphyseal and diaphyseal necrosis (2). In 1991 the Association Research Circulation Osseous (ARCO) defined " idiopathic osteonecrosis" of the femoral head (ONFH) as a disease that causes an ischemic necrosis without trauma or sepsis and it evolves into secondary osteoarthritis (3,4). Although steroids and alcohol are important etiological factors, some authors include the "steroids and alcohol induced" necrosis in the idiopathic form because the pathogenesis have not yet been established (2). However, the various forms of idiopathic ONFH have a common histopathological and radiological outocmes (5).

The name avascular necrosis may be misleading because there was not evidence that bone cells die by necrosis. Moreover cell swelling and inflammatory re-

sponses do not occur in ONFH as it happens in soft tissue necrosis (6).

Aim

Our intention was to provide the overview on the current knowledges about the nomenclatura, etiology, disease progression, relationship between histopathological changes and imaging techniques in order to stage the disease accurately.

Etiology and pathogenesis

ONFH is an significant socio-economic problem since it affects about 75% of patients between 30 and 60 years of age. It has often constrained patients to change their lifestyles and work activities (8,9). The true prevalence of the disease is unknown. Approximately 20,000 to 30,000 new patients with ONFH are diagnosed each year in the USA and there are 300,000-600,000 people having the disease (9,10).

Genetic predisposition, metabolic factors, local factors affecting blood supply such as vascular damage, increased intraosseous pressure and mechanical stress develop this disorder. The final results are bone ischemia and infarction getting bone deathand FH collapse (11-13).

The pathophysiology of non-traumatic ONFH remains unclear. Most studies agree that ONFH is associated with microvasculature occlusion of terminal vascular network, direct cellular toxicity, or altered mesenchymal stem cell differentiation (14).

The main risk factors of nontraumatic osteonecrosis associated with microvasculature occlusion are: the therapy with high doses of glucocorticoids (GCs), excessive alcohol intake, adipocytes hypertrophy, antiphospholipid antibodies, inherited thrombophilia, and hypofibrinolysis, sickle cell anemia, Gaucher disease, decompression sickness (14-17). The direct cellular damage is due at radiation therapy, chemotherapy and antiretroviral therapies for HIV-AIDS (14,18). Recently, some studies have estimated an incidence of 9% in patients undergoing organ transplantation (19).

The estimated frequency of these risk factors in the USA is alcohol abuse (20-40%), corticosteroid therapies (35-40%) and the rest of osteonecrosis are considered idiopathic (20-40%) (20).

Many studies in the past decade have shown that genetic factors have been implicated in the etiology of ONFH. Among these alpha-2-macroglobulin (A2M) gene, that experesses for a plasma protein implicated in hemostasis as thrombin regulator (21-24), has been shown to be upregulated on glucocorticoid induced ONFH in rat model. Glucocorticoids, infact, are the most common non-traumatic cause of ONFH, because of their modification in endothelial function, by modulation A2M gene expression, and because of their effect on procoagulation mediators (Factor VIII & IX & VWF) and fibrinolysis inhibitor mediator (PAI-1) that promote the thrombus formation and subsequently induces ischemia.

Other major players in this process are 20210A gene mutation, especially on the knee and hip avascular necrosis (25, 26) and Hypoxia-inducible factor-1 α (HIF-1α), a master regulator of cellular response to hypoxia. It has been reported that, after an ischemic event in the cartilage, there is a coordinated upregulation of HIF-1a and Vascular Endothelial Growth Factor (VEGF) expression (27). Also nitric oxide regulates bone turnover through osteoblasts and osteoclasts. Jun et al. in 2014 reported that the expression level of inducible nitric oxide synthase (iNOS) increases in osteonecrotic samples, suggesting that more nitric oxide is being produced in this tissue.

They also found that the apoptosis of numerous osteocytes in the avascular necrosis group was mainly associated with the consistently high expression level of iNOS. Moreover nitric oxide production is impaired by T-786C eNOS single nucleotide polymorphism, that leads to vasoconstriction, platelet aggregation, reduced angiogenesis and bone formation, all of which may be associated with avascular necrosis of the hip (28).

Several studies have identified that also hyperlipidemia in the femoral head, induced by GCs and alcohol abuse, is associated with ONFH: Kim et al. in 2008 evaluated the association between sterol regulatory element binding factor (SREBP-2) gene polymorphisms and the susceptibility of ANFH in the

Korean population (29). A year later Lee et al. likewise reported that a polymorphism in intron 7 of the SREBP-1 gene is associated with an increased risk of avascular necrosis (30). This would provide the association between ONFH and altered lipid metabolism.

Noteworthy is COL2A1 mutation, that have been reported to be associated with ONFH affecting both femurs in autosomal dominant inheritance pathway in a Japanese family.

This mutation (p.G1170S) alters type II collagen structure which could be the cause of inherited ONFH (31). Confirming this hypothesis, abnormal large-diameter collagen fibrils was present in the epiphyseal cartilage of ONFH patients (32).

Recent studies have showed that bone's remodeling balance is maintained in the microenvironment of the femoral head, although this process is both local and systemic. The major systemic regulators include growth hormone, parathyroid hormone, glucocorticoids, thyroid hormones, and sex hormones. As far as local regulation of bone remodelling is concerned, many cytokines and growth factors including OPG/RANK/RANKL have been recently identified (33). It was found that the expression of these genes was higher in osteonecrotic samples (34) and, at the same time, different expression levels of bone morphogenetic protein (BMP), that promote bone and cartilage formation, was found in healthy and necrotic sites of femoral heads in patients with avascular necrosis (35).

The balance between bone resorption and osteogenesis can maintain the integrity of the bone microenvironment but when regulators switch the balance into increasing bone resorption and decreasing bone formation in the bone microenvironment of femoral head, thus, femoral head will collapse (36).

The natural history of anuntreated non-traumaic ONFH shows a progressive subchondral fractures and collapse femoral head usually occurs within 2 years,. This happens particularly in patients with bilateral involvement and uncontrolled etiology (37-39, 40-43).

While patients with unilateral non-traumaic ONFH have an high risk to develop contralateral non-traumaic ONFH within the first 2 years after diagnosis, This risk decreases thereafter (43-47).

Several studies have examined disease progression without treatment (45,48,49). Ha et al. using Kerboul classification demonstrated that the hips with a combined necrotic angle of <190° did not develop collapse; instead the hips with a combined necrotic angle of > 240° collapsed. (44)

Fifty percent of the lesions between those values collapsed.

In Mont et al., <10% (seven) of 101 hips with asymptomatic, small (a Kerboul angle of <200°), medially located lesions progressed to collapse compared with 25% for all others (45).

Histopathological aspects and staging systems

The most common affected region is the anterior-lateral area of the femoral head because it is the

most stressed area of the skeleton having to deal with great mechanic stress and support heavy loads (50). The histological aspect of osteonecrosis is empty osteocytic lacunae. Loss of osteocytes is complete after two-four weeks after the onset of ischemia (51-53)

The first microscopic signs of ischemia begin in the marrow spaces after two days, as well as loss of nuclear staining of marrow cells, and large round and ovoid spaces filled with fat (54).

Then the fat and hematopoietic marrow disappear and small vessels show necrosis; after 2 weeks the osteocytic lacunae are empty and the trabecular surface is devoid of cells. Capillaries with fibroblasts and foamy histiocytes, which breakdown of necrotic fatty marrow, appear at the edges/rims of the necrotic area and osteoclasts remove partly of dead bone, replaced by newly formed trabeculae; alternatively bone tissue is stored on the surface of necrotic trabeculae.

The necrotic bone is replaced slowly through a "creeping substitution" defined by Phemister to distinguish it by the massive resorption or sequestration of dead bone that occurs in osteomyelitis (55, 56).

Frost signaled the almost constant presence of trabecular microfractures as failure of the micro damage and subsequent stress fractures (57).

Inoue et al. (1976) (58) have found histological evidence of recurrent necrosis that plays an important role in the pathogenesis of this disease. The incomplete revascularization of the femoral head in idiopathic avascular necrosis may also be due to two or more episodes

of infarction occurring within the head. They observed two types of recurrent necrosis. Type I showed necrosis of young fibrous tissue with high osteogenic activity in presence or not of twisted bone repair tissue. Type II involved the advancing edge of mature granulation tissue without osteogenic activity. In the early stages, Type I changes were usually present extensively, whereas in the later stages either a mixture of Type I and Type II necrosis or Type II only was seen and the distribution of Type II was sometimes patchy. In some advanced cases, a necrotic portion of subchondral bone was completely separated from the remainder of the femoral head. In non-traumatic ONFH, recurrent necrosis of young fibrous tissue (type I) is widely present; while after fracture of the femoral neck recurrent necrosis of mature granulation tissue (type II) is sometimes observed (58).

The macroscopic findings change with the stage of the disease. The early alterations appear in stage III by Ficat staging, the shape and contour of the femoral head is maintained and the necrotic area was neatly defined. In some patients, the viable tissue was separated by a hyperemic area lying between normal tissue and the necrotic area. In stage IV by Ficat the loss of shape and contour of the femoral head is common to all the patients, the structural abnormalities are the flattening and collapsing of the femoral head. There are also alterations in the articular cartilage integrity above the area of necrosis (59).

Therefore it is important to correlate histological analysis with imaging outcomes to stage accurately the disease in order to choice the appropriate treatment.

Since several staging systems have been developed to stage ONFH and provide information on prognosis, treatment decision, and outcome comparison, it is difficult to compare and analyze the data from different centers.

Mont et al. (60) identified 16 major classification systems used to classify and describe ON, but only four classifications are widely used: the Ficat Classification (1) (63%), the University of Pennsylvania system (20%) (61,62), the Association Research Circulation Osseous (ARCO) system (12%) (3), and the Japanese Orthopaedic Association system (5%) (2, 63)

Although there is no universal agreement in classification systems, the prognostic factors of most classifications are well established: the extent of the osteonecrotic lesion (44, 64-67), the presence of subchondral fracture (68, 69), and the lesion location (45, 70).

Arlet and Ficat classification was the first staging system for ONFH described in 1960, which had initially only three stages (71). It has been revised with six stages afterwards (1). Initially, this system included clinical symptoms and functional evaluation of bone including: bone marrow pressure, intramedullary venography, and core biopsy. Currently this system is based upon radiographic findings only. The first suggestive radiographic images of the disease may appear after up period of 5 years (5). This system not assess the lesion size or its extention. However, it is still widely utilized because of its simplicity and easy handling.

The introduction of nuclear magnetic resonance (RMN) allowed measurement of lesion size and extention in joint involvement, widely classified in the University of Pennsylvania classification developed by Steinberg in 1995 (61, 62, 72).

RMN allows early diagnosis of osteonecrosis, even in infra-radiological stages.

The ARCO classification system (3) developed in 1991 to establish an easy and uniform staging internationally accepted with uniform definition and terminology. (73).

It is based on radiographic findings, RMN imaging and computed tomography (CT) scanning. The classification system includes the necrotic size, the extent of femoral head involvement and lesion location (medial third, central third, and lateral third of femoral head) within its subclassifications as well (3). The lesion location was included in 1992 when the Japanese Investigation Committee introduced this parameter.

In the original version of ARCO classification, the distinction between a "crescent sign" without femoral head flattening and a hip with flattening was eliminated. This distinction was later restored, now it indicates an Early stage III and a Late stage III, instead of the original stages 3 and 4 (73).

MRI is the gold standard to detect precollapse lesions without subchondral fracture (61,62).

Once collapse or acetabular involvement is present on plain radiographs, no further imaging is needed for treatment decision-making. If subchondral fracture is suspected and is not clearly delineated on radiography, computed tomography is the best choice (74).

Both MRI and CT scanning are helpful to better differentiate between stage 2 and 3 ("crescent") sign, to establish extent of necrosis and to allow a more pragmatic and clinically relevant approach. Stage 0 has become obsolete as not clinically relevant. (75)

CT is a very useful assessment tool in later stages, for determining the lesions extent such as sclerosis and other events occurring in the state of repair. CT provides a detailed analysis of the morphological aspects. In the early stages CT can detect certain alterations in bone density even when radiographic images are normal (5).

In 1987, the Japanese Investigation Committee for Avascular Necrosis introduced the Japanese Orthopaedic Association system (2, 63) rarely used outside Japan. It has been modified in 2001 emphasizing the location of lesion as an important factor to predict impending collapse (76). Subchondral lesions are worrying because of the high risk of joint collapse, while metaphyseal lesions are less baleful (77).

This system indicates that lesions progress from medial to lateral as they become larger and cannot allow the possibility of a small central lesion, which is often present. Nevertheless, large lesions are often located laterally, while small lesions are often located centrally or, rarely, medially (60)

Most lesions are in the anterosuperior side of the head, indicating lesion size and also location.

Below, we have researched the differences between the disease stages according to the most staging systems used in the literature.

Stage 0: it is contained in the Ficat, Steinberg and ARCO classifications (1,3,61,62,71,72). It is a theoretical stage, there are no clinical signs of disease and the X-ray and MRI findings are negative for ONFH; However, there are risk factors and/or contralateral hip osteonecrosis.

Stage 1: it is contained in the Ficat, Steinberg and ARCO classifications (1,3,61,62,71,72). The patient has no symptoms, radiographs are negative, while MRI is positive for ONFH Steinberg has shared the stage I in ABC sub-stages according to the percentage of femoral head affected. In this stage histological aspects show a trabecular bone and bone marrow necrosis(necrotic area), and an "alive area" interposed with a reparative zone (2).

Stage 2: it is contained in Ficat IIA, Steinberg and ARCO classifications (1,3,61,62,71,72). There are no symptoms, radiographically cystic lesions and femoral head sclerosis are reported. Steinberg also divided this stage in ABC sub-stages according to the percentage of femoral head affected. Histologically we can find blood vessels in necrotic area and reparative processes of resorption and bone formation radiographically featured by sclerosis and cystic lesions.

Stage 3: it is contained in Ficat IIB, Steinberg, and ARCO IIIA classifications (1,3,4,61,62,71,72). Here the patient is symptomatic. Radiographically we can see the subchondrale collapse defined as "crescent sign", the femoral head is not flattened.

The progressive bone resorption causes the subchondral fracture and collapse. Steinberg divides it into ABC sub-stages according to the extent of the affected joint surface. Macroscopic alterations include sclerotic changes, cysts, signs of osteoporosis and subchondral fractures.(5)

Stage 4: it is contained in Ficat III, Steinberg and ARCO IIIB classifications (1,3,4,61,62,71,72). In these stages there is a flattening of the femoral head or interruption of its profile. The symptoms are severe, the pain increases and crackles appear. Steinberg divides also this stage in A,B,C sub-stages considering both the possible occurrence and the extent of FH flattening. Histologically the resorption processes are higher.

Macroscopic alterations include FH flattening, changes in the bone density and aspects of osteoporotic appearance.(5)

Microscopic aspects in stages III and IV(or IIIB) include osteocondensation of the perilesional area and numerous blood vessels that penetrate the overlying cartilage. The outer layer of the cartilage tissue is full of new vessels with disorganized architecture. In subchondral fractures numerous osteoblasts with reduced cytoplasm are detected at the endosteum level.

Several macrophages with intense lysosomal activity have been highlighted in both the necrotic area

and endosteum adjacent areas, indicating an intense activity of these cells(5).

Stage 5: it is contained in Ficat IV, Steiberg and ARCO IV classifications (1,3,4,61,62,71,72). The articular space is restricted, the femoral head has collapsed and the acetabulum may be involved. Histologically there are cartilage detachment and destruction, as in the previous stage.

Macroscopic alterations include changes in the shape and contour of the femoral head, changes in the internal architecture and overlying cartilage, subchondral fractures, and large areas of liquefied necrosis penetrating the cartilage (5).

Stage 6: expected in the Steinberg and ARCO classifications (61,62,71,72). Degenerative lesions are advanced and patient has pain even at rest.

Macroscopic alterations include massive destruction of the femoral head, which completely compromised functionality of the affected hip-femoral joint(5).

Particularly in stages V and VI, the lesion extends to the near cartilage, highlighting multiple neoformation vessels at this level. The chondrocytes in the deep cartilage, maintain the integrity of their morphology, but near the outer layer, there are changes in their shape and structure. Osteocytes near necrotic area are absent or have pyknotic nuclei, cells becomes elongated, nearly spherical, increasing their sizes. Cellularity of bone tissue decreases as the disease is in a more advanced stage.

On some samples from patients in the last two stages staining of the bone tissue, in the area bordering the lesion, decreases. Bone tissue near the necrotic area appears disorganized; it is intertwined or even replaced by fibrous tissue. Bone tissue observed on slides from patients in the last two stages is thin, bone lamellae can easily be seen, having a diminished staining. Osteocytes at this level have a modified shape, a marginal condensation zone and appear without nuclei. In bone and cartilage tissue there are large areas of fibrous and necrotic tissue.

In the last two evolutionary stages macrophages are small in number and have an erratic disposition (5).

Discussion

In literature, ONFH has a variable nomenclature that often causes confusion. The terms "avascular, aseptic, ischemic" are referred to an idiopathic and non-traumatic ischemic necrosis with the same etiology and pathogenesis. Currently "steroids and alcohol induced" necrosis are terms included in the idiopathic form as the pathogenesis have not yet been established (2).

Most authors think that bone necrosis results from primitive vascular problems, including vessel occlusion, stenosing arteritis, arterio-sclerotic disease, extraosseous arterial involvement or extraosseous venous abnormality, or hypercoagulability and hypofibrinolysis, metabolic factors, increased intraosseous pressure and mechanical stress . In the past decade some genetic factors have been investigated (11-14,36).

The present study provides a comprehensive overview of the available staging systems, histopathological changes and imaging techniques order to better define this condition and to provide more framework elements for the following treatment.

Staging systems are used to group together patients that have a similar prognosis so that they may guide treatment decisions. Ideally, the staging is accurate, and simple to use with a minimum of testing data, and compatible with prior staging systems (78).

Over the years, the planing of an ideal staging system has proved difficult for the evolution of our knowledge and the development of better imaging and measurement techniques.

The most important prognostic factors in ONFH are identified in subchondral collapse, size or quantification of the lesion, and lesion location within the femoral head. The subchondral fracture is evaluated through CT with sagittal and coronal reconstructions, while the radiographs are less sensitive to detecting non-displaced fractures (79).

The size lesion can be assessed by MRI and categorized as <15, 15-30, or >30% of the femoral head (62, 72). The location lesion is assessed on radiographs or MRI (2, 63).

The diagnosis should be started with careful history and confirmed with imaging studies including MRI, CT, and radiographies detecting prognostic fac-

tors to make a correct diagnosis and stage accurately (79).

Clinical signs appear when femoral head begins to collapse. This is an important evolution phase because post-collapse the lesion is irreversible and FH saving therapies are not indicated.

However there have been cases where the CT and MRI images have not really shown the full extent of the damage tissue (5).

In stages III and IV the flattening of the femoral head or the decrease in bone density are detected by imaging scans, but Traistaru et al. (5) shown that the precise extension of the necrotic and perilesional areas was much wider on the histopathological examination. Infact histological analysis plays a critical role to evaluate the quality of necrotic area.

Traistaru et al. (5) showed that there are differences in the lesion appearance and extent on the histological images compared to macroscopic images and even to those obtained using imaging tools, particularly in patients presenting evolutionary stage III. Aspects such as the extension of the area of fibrosis, remodeling of the bone tissue, neo-formation vascular network density and degree of cartilage impairment are determined more accurately using histology and immunohistochemistry techniques.

Before classifying patients in a certain stage, after having correlated clinical and imaging data, histopathological aspects should be considered, particularly in patients in stages III and IV, in which total hip arthroplasty could be delayed.

In the future, validated scores for ONFH analysis are required, in addition with data on macroscopic, microscopic and imaging aspects of the necrotic bone to achieve a comprehensive picture of tissue quality.

Conclusions

In conclusion we summarize key-points that should be considered in ONFH correct staging.

- the histological analysis is important, but not strictly necessary;
- MRI provides the most sensitive and specific data;
- the clinical signs do not indicate the severity of the disease;
- the pre- and post-collapse phases are important to recognize;
- the size of the lesion is an important prognostic factor;
- the location of the lesion is less important than size in large lesions: usually lateral lesion are large, while the rare medial lesions are small with better prognosis;
- the subchondral fracture is the most prognostic factor of evolution disease;
- the "crescent sign" and the measure of collapsed bone are not quantifiable;
- the acetabular involvement indicates severe disease.

Some authors have shown that small, medially located, asymptomatic lesions may be treated with observation alone, while FH saving procedures, such as core decompression (60,80,81) osteotomy (82-85), and nonvascularized or vascularized bone-grafting (60,86-88), are indicated for symptomatic precollapse stage lesions.

Whereas total hip arthroplasty is appropriate choice in postcollapse stage and acetabular involvement (89-91).

References

1. Ficat RP. Idiopathic bone necrosis of the femoral head. Early diagnosis and treatment. J Bone Joint Surg Br 1985 Jan; 67(1): 3-9.
2. Sugano N, Atsumi T, Ohzono K, Kubo T, Hotokebuchi T, Takaoka K. The 2001 revised criteria for diagnosis, classification, and staging of idiopathic osteonecrosis of the femoral head. J Orthop Sci 2002; 7(5): 601-5.
3. Gardeniers J. A new international classification of osteonecrosis of the ARCO committee on terminology and classification. ARCO Newsl 1992; 4(4): 41-6.
4. Gardeniers J. ARCO Committee on Terminology and Staging. Report on the committee meeting at Santiago de Compostella. ARCO Newsl. 1993; 5(5): 79-82.
5. Trăistaru MR, Kamal D, Kamal KC, Rogoveanu OC, Popescu M, Bondari S, Alexandru DO, Ionovici N, Grecu DC. Imaging and histopathological aspects in aseptic osteonecrosis of the femoral head. Rom J Morphol Embryol 2015; 56(4): 1447-53.
6. Weinstein RS, Nicholas RW, Manolagas SC. Apoptosis of osteocytes in glucocorticoid-induced osteonecrosis of the hip. J Clin Endocrinol Metab 2000; 85(8): 2907-12.

7. Assouline-Dayan Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. Semin Arthritis Rheum 2002; 32(2): 94-124.
8. Assouline-Dayan Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. Semin Arthritis Rheum 2002; 32(2): 94-124.
9. Lieberman JR, Berry DJ, Mont MA, Aaron RK, Callaghan JJ, Rajadhyaksha AD, Urbaniak JR. Osteonecrosis of the hip: management in the 21st century. Instr Course Lect 2003; 52: 337-55.
10. Aldridge JM, 3rd, Urbaniak JR. Avascular necrosis of the femoral head: etiology, pathophysiology, classification, and current treatment guidelines. Am J Orthop (Belle Mead NJ) 2004; 33(7): 327-32.
11. Mankin HJ. Nontraumatic necrosis of bone (osteonecrosis). N Engl J Med 1992; 326: 1473-1479
12. Hungerford DS. Bone marrow pressure, venography and core decompression in ischemic necrosis of the femoral head. In: Riley LH, editor. The Hip: Proceedings of the Seventh Open Scientific Meeting of The Hip Society. St Louis, MO: CV Mosby; 1979: 218-237
13. Chang CC, Greenspan A, Gershwin ME. Osteonecrosis: current perspectives on pathogenesis and treatment. Semin Arthritis Rheum 1993; 23: 47-69
14. Zalavras CG, Lieberman JR. Osteonecrosis of the femoral head: evaluation and treatment. J Am Acad Orthop Surg 2014; 22: 455-464
15. Jones JP. Fat embolism and osteonecrosis. Orthop Clin North Am 1985; 16: 595-633
16. Goldblatt J, Sacks S, Beighton P. The orthopedic aspects of Gaucher disease. Clin Orthop Relat Res 1978; (137): 208-214
17. Miyanishi K, Kamo Y, Ihara H, Naka T, Hirakawa M, Sugioka Y. Risk factors for dysbaric osteonecrosis. Rheumatology (Oxford) 2006; 45: 855-858
18. Gutièrrez F, Padilla S, Masia M, Flores J, Boix V, Merino E, Galindo J, Ortega E, Lopez-Aldeguer J, Galera C; HIV-related Osteonecrosis Study Group. Osteonecrosis in patients infected with HIV: clinical epidemiology and natural history in a large case series from Spain. J Acquir Immune Defic Syndr 2006 Jul; 42(3): 286-92.
19. Guichelaar MM, Schmoll J, Malinchoc M, Hay JE. Fractures and avascular necrosis before and after orthotopic liver transplantation: long-term follow-up and predictive factors. Hepatology 2007; 46: 1198-1207.
20. Bradway JK, Morrey BF. The natural history of the silent hip in bilateral atraumatic osteonecrosis. J Arthroplasty 1993; 8: 383-387
21. Cvirn G, Gallistl S, Koestenberger M, Kutschera J, Leschnik B, Muntean W. Alpha 2-macroglobulin enhances prothrombin activation and thrombin potential by inhibiting the anticoagulant protein C/protein S system in cord and adult plasma. Thromb Res 2002; 105(5): 433-9.
22. Ma H, Li R, Zhang Z, Tong T. mRNA level of alpha-2-macroglobulin as an aging biomarker of human fibroblasts in culture. Exp Gerontol 2004; 39(3): 415-21.
23. Branson HE, Endo Y, Fagin AR, Schlutz M. Heritable α2-Macroglobulin Deficiency in a Patient With Arterial Thrombosis: α2-Macroglobulin Deficiency Irvine. J Natl Med Assoc 1984; 76(11): 1107.
24. Beheiri A, Langer C, During C, Krumpel A, Thedieck S, Nowak-Gottl U. Role of elevated alpha2-macroglobulin revisited: results of a case-control study in children with symptomatic thromboembolism. J Thromb Haemost 2007; 5(6): 1179-84.
25. Bjorkman A, Svensson PJ, Hillarp A, Burtscher IM, Runow A, Benoni G. Factor V leiden and prothrombin gene mutation: risk factors for osteonecrosis of the femoral head in adults. Clin Orthop Relat Res 2004; 425: 168-72.
26. Bjorkman A, Burtscher IM, Svensson PJ, Hillarp A, Besjakov J, Benoni G. Factor V Leiden and the prothrombin 20210A gene mutation and osteonecrosis of the knee. Arch Orthop Trauma Surg 2005; 25(1): 51-5.
27. Youm YS, Lee SY, Lee SH. Apoptosis in the osteonecrosis of the femoral head. Clin Orthop Surg 2010 Dec; 2(4): 250-5. Epub 2010 Nov 05.
28. Glueck CJ, Freiberg RA, Oghene J, Fontaine RN, Wang P. Association between the T-786C eNOS polymorphism and idiopathic osteonecrosis of the head of the femur. J Bone Joint Surg Am 2007; 89(11): 2460-8.
29. Kim TH, Baek JI, Hong JM, Choi SJ, Lee HJ, Cho HJ, et al. Significant association of SREBP-2 genetic polymorphisms with avascular necrosis in the Korean population. BMC Med Genet 2008; 9: 94.
30. Lee HJ, Choi SJ, Hong JM, Lee WK, Baek JI, Kim SY, et al. Association of a polymorphism in the intron 7 of the SREBF1 gene with osteonecrosis of the femoral head in Koreans. Ann Hum Genet 2009; 73(1): 34-41.
31. Miyamoto Y, Matsuda T, Kitoh H, Haga N, Ohashi H, Nishimura G, et al. A recurrent mutation in type II collagen gene causes Legg-Calve-Perthes disease in a Japanese family. Hum Genet 2007; 121(5): 625-9.
32. Ponseti IV, Maynard JA, Weinstein SL, Ippolito EG, Pous JG. Legg-Calve-Perthes disease. Histochemical and ultrastructural observations of the epiphyseal cartilage and physis. J Bone Joint Surg Am 1983; 65(6): 797-807.
33. Hadjidakis DJ, Androulakis ll. Bone remodeling. Ann N Y Acad Sci. 2006; 1092(1): 385-96. head in Koreans. Ann Hum Genet 2009; 73(1): 34-41.
34. Samara S, Dailiana Z, Chassanidis C, Koromila T, Papatheodorou L, Malizos KN, et al. Expression profile of osteoprotegerin, RANK and RANKL genes in the femoral head of patients with avascular necrosis. Exp Mol Pathol 2014; 96(1): 9-14.
35. Samara S, Dailiana Z, Varitimidis S, Chassanidis C, Koromila T, Malizos KN, et al. Bone morphogenetic proteins (BMPs) expression in the femoral heads of patients with avascular necrosis. Mol Biol Rep 2013; 40(7): 4465-72.
36. Pouya F, Kerachian MA. Avascular Necrosis of the Femoral Head: Are Any Genes Involved?. Arch Bone Jt Surg 2015 Jul; 3(3): 149-55.
37. Koo KH, Kim R, Ko GH et al. Preventing collapse in early

osteonecrosis of the femoral head. A randomised clinical trial of core decompression. J Bone Joint Surg Br 1995; 77: 870-874
38. Mont MA, Hungerford DS. Non-traumatic avascular necrosis of the femoral head. J Bone Joint Surg Am 1995; 77: 459-474.
39. Hungerford DS, Zizic TM. II. The treatment of ischemic necrosis of bone in systemic lupus erythematosus. Med Baltim 1980; 59: 143-148.
40. Castro FP, Barrack RL. Core decompression and conservative treatment for avascular necrosis of the femoral head: a meta-analysis. Am J Orthop 2000; 29: 187-194
41. Stulberg BN, Davis AW, Bauer TW et al. Osteonecrosis of the femoral head. A prospective randomized treatment protocol. Clin Orthop Relat Rel 1991; 268: 140-151
42. Steinberg ME, Hayken GD, Steinberg DR. The "conservative" management of avascular necrosis of the femoral head. In: Arlet J, Ficat RP, Hungerford DS (eds) Bone circulation. Williams and Wilkins, Baltimore, 1984: 334-337
43. Hofmann S, Mazieres B. Osteonekrose: Natu¨rlicher Verlauf und konservative Therapie. Orthopa¨de 2000; 29: 403-410
44. Ha YC, Jung WH, Kim JR et al. Prediction of collapse in femoral head osteonecrosis: a modified Kerboul method with use of magnetic resonance images. J Bone Joint Surg Am 2006; 88: 35-40
45. Mont MA, Zywiel MG, Marker DR et al. The natural history of untreated asymptomatic osteonecrosis of the femoral head. J Bone Joint Surg Am 2010; 92: 2165-2170
46. Lieberman JR, Engstrom SM, Meneghini RM et al. Which factors influence preservation of the osteonecrotic femoral head? Clin Orthop Relat Res 2012; 470: 525-534
47. Tervonen O, Mueller DM, Matteson EL et al. Clinically occult avascular necrosis of the hip: prevalence in an asymptomatic population at risk. Radiology 1992; 182: 845-847
48. Nakamura J, Harada Y, Oinuma K, Iida S, Kishida S, Takahashi K. Spontaneous repair of asymptomatic osteonecrosis associated with corticosteroid therapy in systemic lupus erythematosus: 10-year minimum follow-up with MRI. Lupus 2010 Oct; 19(11): 1307-14. Epub 2010 Jul 06.
49. Kang JS, Moon KH, Kwon DG, Shin BK, Woo MS. The natural history of asymptomatic osteonecrosis of the femoral head. Int Orthop 2013 Mar; 37(3): 379-84. Epub 2013 Jan 23.
50. Aiello MR, Chew FS, Imaging in avascular necrosis of the femoral head, available at http: //emedicine.medscape.com/article/386808; updated: May 25, 2011; accessed: May 30, 2012.
51. Bonfiglio M. Aseptic necrosis of the femoral head in dogs. Effects of drilling and bone grafting. Surg Gynecol Obstet 1954; 98: 591-599.
52. Catto M. A histological study of avascular necrosis of the femoral head after transcervical fracture. J Bone Joint Surg 1965; 47B: 749-776.
53. Young MH. Epiphyseal infarction in a growing long bone. An experimental study in the rabbit. J Bone Joint Surg 1966; 48B: 826- 840.
54. Catto M. Pathology of aseptic bone necrosis. In: Davidson JK, ed. Aseptic necrosis of bone. 1st ed. Amsterdam, Nederlands: Excerpta Medica; 1976: 3-100.
55. Phemister DB. Necrotic bone and subsequent changes which it undergoes. J Am Med Assoc 1915; 64: 211-216.
56. Phemister DB. Repair of bone in the presence of aseptic necrosis resulting from fractures, transplantations and vascular obstruction. J Bone Joint Surg 1930; 12: 769-787.
57. Frost HM. The etiodynamics of aseptic necrosis of the femoral head. Proceedings of the Conference on Aseptic Necrosis of the Femoral Head, National Institutes of Health 1964: 393-414.
58. Inoue A, Ono K. A histological study of idiopathic avascular necrosis of the head of the femur. J Bone Joint Surg 1979; 61-B(2)
59. Kamal D, Alexandru DO, Kamal CK, Streba CT, Grecu D, Mogoantă L. Macroscopic and microscopic findings in avascular necrosis of the femoral head. Rom J Morphol Embryol 2012; 53(3): 557-561
60. Mont MA, Marulanda GA, Jones LC, Saleh KJ, Gordon N, Hungerford DS, et al. Systematic analysis of classification systems for osteonecrosis of the femoral head. J Bone Joint Surg Am 2006; 88 Suppl 3: 16-26.
61. Steinberg DR, Steinberg ME. The University of Pennsylvania classification of osteonecrosis. In: Koo KH, Mont MA, Jones LC, editors. Osteonecrosis. Heidelberg: Springer; 2014: 201-6.
62. Steinberg ME, Hayken GD, Steinberg DR. A quantitative system for staging avascular necrosis. J Bone Joint Surg Br 1995; 77: 34-41.
63. Ono K. Diagnostic criteria, staging system and roentgenographic classification of avascular necrosis of the femoral head (steroid induced, alcohol associated or idiopathic nature) (in Japanese)Annual report of Japanese investigation committee for intractable disease, avascular necrosis of the femoral head. Tokyo: Ministry of health and Welfare; 1987.
64. Kerboul M, Thomine J, Postel M, Merle d'Aubigne R. The conservative surgical treatment of idiopathic aseptic necrosis of the femoral head. J Bone Joint Surg Br 1974; 56(2): 291-6.
65. Koo KH, Kim R. Quantifying the extent of osteonecrosis of the femoral head. A new method using MRI. J Bone Joint Surg Br 1995; 77(6): 875-80.
66. Nam KW, Kim YL, Yoo JJ, Koo KH, Yoon KS, Kim HJ. Fate of untreated asymptomatic osteonecrosis of the femoral head. J Bone Joint Surg Am 2008; 90(3): 477-84.
67. Steinberg ME, Bands RE, Parry S, Hoffman E, Chan T, Hartman KM. Does lesion size affect the outcome in avascular necrosis? Clin Orthop Relat Res 1999; 367: 262-71.
68. Banerjee S, Kapadia BH, Jauregui JJ, Cherian JJ, Mont MA. Natural history of osteonecrosis. In: Koo KH, Mont MA, Jones LC, editors. Osteonecrosis. Heidelberg: Springer; 2014: 161-4.
69. Cheng EY. Osteonecrosis of the femoral head. The North American perspective. In: Bulstrode D, Buckwalter J, Carr A, Marsh L, Fairbank J, Wilson-MacDonald J, editors. Ox-

ford textbook of orthopaedics and trauma. Oxford: Oxford University Press; 2002: 981-91.
70. Sugano N, Takaoka K, Ohzono K, Matsui M, Masuhara K, Ono K. Prognostication of nontraumatic avascular necrosis of the femoral head. Significance of location and size of the necrotic lesion. Clin Orthop Relat Res 1994; 303: 155-64
71. Arlet J, Ficat RP. Forage-biopsie de la tete femorale dans l'osteonecrose primitive. Observations histopathologiques portant sur huit forances. Rev Rheum 1964; 31(31): 257-64.
72. Steinberg ME, Steinberg DR. Osteonecrosis: Historical perspective. In: Koo KH,MontMA, Jones LC, editors. Osteonecrosis.Heidelberg: Springer; 2014: 3-15. The study describes historical perspective of diagnosis, classification, and treatment of osteonecrosis
73. Gardeniers J.ARCO committee on terminology and staging. A new proposition of terminology and an international classification of osteonecrosis. ARCO Newsl 1991; 3(3): 153-9.
74. Yeh LR, Chen CK, Huang YL, Pan HB, Yang CF. Diagnostic performance of MR imaging in the assessment of subchondral fractures in avascular necrosis of the femoral head. Skeletal Radiol 2009 Jun; 38(6): 559-64. Epub 2009 Feb 21.
75. Roth A, Beckmann J, Bohndorf K, Fischer A, Heiß C, Kenn W, Jäger M, Maus U, Nöth U, Peters KM, Rader C, Reppenhagen S, Smolenski U, Tingart M, Kopp I, Sirotin I, Breusch SJ. S3-Guideline non-traumatic adult femoral head necrosis. Arch Orthop Trauma Surg 2016 Feb; 136(2): 165-74.
76. Sugano N, Ohzono K. Natural Course and the JIC Classification of Osteonecrosis of the Femoral Head. In: Koo KH, Mont MA, Jones LC, editors. Osteonecrosis. Heidelberg: Springer; 2014: 207-10.
77. Banerjee S, Kapadia BH, Cherian JJ, Jauregui JJ, Mont MA. Multifocal osteonecrosis. In: Koo K-H, Mont MA, Jones LC. Osteonecrosis. New York: Springer; 2014: 383-8
78. Ho-Rim Choi & Marvin E. Steinberg & Edward Y. Cheng. Osteonecrosis of the femoral head: diagnosis and classification Systems. Curr Rev Musculoskelet Med 2015; 8: 210-220
79. Stevens K, Tao C, Lee SU, Salem N, Vandevenne J, Cheng C, et al. Subchondral fractures in osteonecrosis of the femoral head: comparison of radiography, CT, and MR imaging. Am J Roentgenol 2003; 180(2): 363-8.
80. Marker DR, Seyler TM, Ulrich SD, Srivastava S, Mont MA. Do modern techniques improve core decompression outcomes for hip osteonecrosis? Clin Orthop Relat Res. 2008 May; 466(5): 1093-103. Epub 2008 Apr 08.
81. Rajagopal M, Balch Samora J, Ellis TJ. Efficacy of core decompression as treatment for osteonecrosis of the hip: a systematic review. Hip Int 2012 Sep-Oct; 22(5): 489-93.
82. HamanishiM, Yasunaga Y, Yamasaki T, Mori R, Shoji T, OchiM. The clinical and radiographic results of intertrochanteric curved varus osteotomy for idiopathic osteonecrosis of the femoral head. Arch Orthop Trauma Surg 2014 Mar; 134(3): 305-10. Epub 2014 Jan 07.
83. Park KS, Tumin M, Peni I, Yoon TR. Conversion total hip arthroplasty after previous transtrochanteric rotational osteotomy for osteonecrosis of the femoral head. J Arthroplasty 2014 Apr; 29(4): 813-6. Epub 2013 Oct 09.
84. Zhao G, Yamamoto T, Motomura G, Iwasaki K, Yamaguchi R, Ikemura S, Iwamoto Y. Radiological outcome
85. analyses of transtrochanteric posterior rotational osteotomy for osteonecrosis of the femoral head at a mean follow-up of 11 years. J Orthop Sci 2013 Mar; 18(2): 277-83. Epub 2013 Jan 24.
86. Yoon TR, Abbas AA, Hur CI, Cho SG, Lee JH. Modified transtrochanteric rotational osteotomy for femoral head osteonecrosis. Clin Orthop Relat Res 2008 May; 466(5): 1110-6. Epub 2008 Mar 19.
87. Hsu JE, Wihbey T, Shah RP, Garino JP, Lee GC. Prophylactic decompression and bone grafting for small asymptomatic osteonecrotic lesions of the femoral head. Hip Int 2011 Nov-Dec; 21(6): 672-7.
88. Seyler TM, Marker DR, Ulrich SD, Fatscher T, Mont MA. Nonvascularized bone grafting defers joint arthroplasty in hip osteonecrosis. Clin Orthop Relat Res. 2008 May; 466(5): 1125-32.
89. Zhang HJ, Liu YW, Du ZQ, Guo H, Fan KJ, Liang GH, Liu XC. Therapeutic effect of minimally invasive decompression combined with impaction bone grafting on osteonecrosis of the femoral head. Eur J Orthop Surg Traumatol 2013 Dec; 23 (8): 913-9. Epub 2012 Nov 27.
90. Sayeed SA, Johnson AJ, Stroh DA, Gross TP, Mont MA. Hip resurfacing in patients who have osteonecrosis and are 25 years or under. Clin Orthop Relat Res 2011 Jun; 469(6): 1582-8.
91. Issa K, Johnson AJ, Naziri Q, Khanuja HS, Delanois RE, Mont MA. Hip osteonecrosis: does prior hip surgery alter outcomes compared to an initial primary total hip arthroplasty? J Arthroplasty. 2014 Jan; 29(1): 162-6. Epub 2013 May 15.
92. Steinberg ME, Lai M, Garino JP, Ong A, Wong KL. A comparison between total hip replacement for osteonecrosis and degenerative joint disease. Orthopedics 2008 Apr; 31(4): 360

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