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## Review article

## Evolutionary course of the femoral head osteonecrosis: Histopathological - radiologic characteristics and clinical staging systems

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## ABSTRACT

Osteonecrosis of the femoral head (ONFH) is a recalcitrant ischemic disorder, which could be classified into two major categories: traumatic and nontraumatic. Regardless of different risk factors, it has been testified that ONFH results from primitive vascular problems, leading to temporary or permanent loss of blood supply to bone tissue. Histopathological and microarchitectural alterations ensue, which is a gradual evolutionary process involving bone marrow and osteocyte necrosis, progressive destruction of subchondral bone, unsuccessful reparative process, and eventual articular collapse and degenerative arthritis. Based on the imaging features of ONFH, different classification systems have been developed to evaluate the severity and prognosis of the disease, which is pivotal for implementation of treatment strategy, especially the joint-preserving surgery. However, patients classified with the same severity stage, especially in the peri-collapse stage, sometimes responded differently after similar joint-preserving surgery. The unusual phenomenon may be attributed to the limitation of the current imaging classification systems, which might underestimate the disease severity, especially when referring to the early stages. In this review, we briefly summarize the etiology and pathogenesis of ONFH. The imaging features and staging classification systems of ONFH are also described. More importantly, we focus on histopathological and microstructural alterations of the femoral head, and provide an overview of their essential contribution to ONFH progression. Given the observation of discordance between imaging characteristics and histopathological alterations, a substantial amount of research on the relationship between imaging and histopathological features is required to further modify and revise the current wide-accepted classification systems.

## 1. Introduction

Osteonecrosis of the femoral head (ONFH) is a recalcitrant and common disease, which is triggered by disruption of blood supply in the femoral head with various etiologies [1]. ONFH has an extremely high disability rate, affecting the quality of living of patients, which occurs frequently in young and middle-aged population [2]. ONFH brings about necrosis of the peri-articular bone and cartilage degeneration in the femoral head, ultimately leading to joint collapse [3].

Although ONFH has been attracting extensive research interest in last decades, there is no wide-accepted consensus to the exact etiology and pathogenesis [4]. Regardless of different risk factors and underlying

diseases, it has been testified that ONFH results from primitive vascular problems, leading to temporary or permanent loss of blood supply to the bone tissue [5]. Histopathological and microarchitectural alterations ensue, which is a gradual process involving bone marrow and osteocyte necrosis, progressive destruction of the subchondral bone, unsuccessful reparative process around the necrotic zone, and eventual articular collapse and degenerative arthritis of the joint [6,7]. Based on the imaging features of ONFH, different classification systems have been developed to evaluate the stage of severity and prognosis of the disease, which is pivotal for implementation of the treatment strategy, especially the joint-preserving surgery [8,9]. However, patients classified with the same severity stage responded differently after similar joint-preserving

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surgery [10]. The unusual phenomenon may be attributed to the limitation and defect of the current imaging classification systems, and inconsistency between histopathology and radiological stage has been observed [11].

In this review, we briefly summarize the etiology and pathogenesis of ONFH. The imaging features and staging classification systems of ONFH were also described. More importantly, we focus on histopathological and microstructural alterations of the femoral head in ONFH, and provide an overview of their essential contribution to the progression of ONFH.

## 2. The etiology and pathogenesis of ONFH

ONFH can be divided into two major categories: traumatic and non-traumatic. The main etiological factors for traumatic ONFH include femoral head and neck fracture, acetabular fracture, hip dislocation, and severe hip sprain or contusion (no fracture, with intraarticular haematoma) [12–17].

Nontraumatic ONFH is not only closely associated with glucocorticoid (GC) and alcohol use, but is also related with blood dyscrasia, metabolic and coagulation disorders [4,18]. GC administration is the most common cause of secondary osteoporosis, and the main cause of nontraumatic osteonecrosis. In patients receiving long-term therapy, GC-induced fractures were found in 30 %–50 % of these patients and osteonecrosis in 9 %–40 % [19,20]. Non-traumatic ONFH is found to be correlated with low bone mineral density, evidenced by a study showing that fractural stages of ONFH were associated with a 5-fold risk of osteoporosis [21].

There are five theories about the pathogenesis of GC-induced ONFH: 1) The lipid metabolism disorder theory; 2) The decreased osteogenesis potential of bone marrow mesenchymal stem cells theory; 3) Insufficient blood supply theory; 4) The inflammation and cell apoptosis theory; 5) The gene polymorphism and non-coding RNA theory [22]. The study have shown the relevance between ONFH and dose and treatment duration of GC, although it is debatable [23]. The comparative study of Kameda et al. presented that the progression of ONFH relied on the response to a high dose of GC therapy and a decrease in the bone mineral density value in the 1st year [24]. Saito et al. pointed out a noteworthy dose–response relationship between the development of ONFH and the entire dose of GC administered in the first 2 weeks after renal transplantation [25]. Platelet activation is involved in development of GC-induced ONFH and the effect may be secondary to endothelial cell damage induced by GC [26]. Wada et al. discovered that warfarin reduced the occurrence of ONFH in spontaneously hypertensive rats [27]. Motomura et al. demonstrated that the combined use of warfarin and probucol facilitates to prevent GC-induced ONFH in rabbits [28]. Kang et al. also noticed that combination treatment with enoxaparin and lovastatin lowered the incidence of GC-induced ONFH in the rabbit [29]. Therefore, coagulation abnormalities may play a vital role in GC-induced ONFH.

Underlying diseases have been widely considered to play as an important risk factor in the pathogenesis and progression of osteonecrosis [23]. Systemic lupus erythematosus (SLE) is reported to be positively correlated with ONFH as an independent risk factor [30]. Shigemura et al. led a prospective study and revealed a higher rate of GC-induced ONFH in the SLE group than the non-SLE group [31]. Apostolopoulos and Morand provided evidence for the destructive effects of GC in SLE and proposed therapeutic options that would downgrade reliance on GC [32]. Additional study displayed that an elevated triglyceride level was a crucial risk factor for silent ONFH in patients with SLE [33].

There has been a consensus that osteonecrosis results from primitive vascular problems, including vessel infarction, stenosing arteritis, arterio-sclerotic disease, extraosseous arterial involvement or extraosseous venous abnormality, or hypercoagulability and hypo-fibrinolysis. The inherited hypofibrinolysis has been considered to be a risk factor

of idiopathic ONFH [5]. Jones et al. observed intraosseous fibrin thromboses after induction of experimental fat emboli and speculated that fat emboli could initiate intravascular coagulation [34]. Sun et al. investigated the etiology of post-severe acute respiratory syndrome (SARS) ONFH and revealed that Plasminogen activator inhibitor-1 (PAI-1) was a sensitive blood symbol for screening high-risk susceptible populations [35]. After early damage of endothelial cells activated by GCs or additional factors, a hypercoagulable state is formed. This is followed by vascular problems (thrombosis, poor blood flow, and ischemia), and this conversely brings about endothelial cell damage, which may be cyclic [26,36,37]. Endothelial cell apoptosis consequently promotes thrombus formation and osteonecrosis by two major mechanisms. First, apoptotic bodies can indirectly cause coagulopathic changes by endothelial dysfunction. Second, apoptotic endothelial cells can accelerate adhesion of platelets to endothelial cells and activate platelets, ultimately leading to thrombus formation [26]. Interruption or a reduction in blood flow along capillaries could also play an etiological part in endothelial cell apoptosis [38,39]. Diminished resistance of the affected bone is supposed to determine secondary vascular impairment at the capillary level either through compression from comparatively inelastic fat cells or through the rupture of small intra-trabecular vessels [40]. Osteonecrosis involves more frequently the convex articular surfaces, which may be owe to the smaller diameter of the terminal vessels of this region and the lack of collateral vascularization [18].

## 3. Histopathological and microstructural alterations of ONFH

ONFH is an evolutionary course involving marrow necrosis and osteocytic death in the femoral head [6,7], reparative process around the necrotic zone, and collapse of the articular surface and following degenerative arthritis of the hip [41]. According to the severity and stage of the disease, the site involved and the factors stimulating its pathogenesis and progression, the morbid anatomy and histopathology of osteonecrosis present a different appearance [18]. Despite different risk factors and postulated associated mechanisms, it is generally used to be thought that pathologic features of ONFH are homologous, regardless of the etiology [42,43]. The histopathologic features of necrosis and repair were reported to be similar in GC-induced and non-GC-induced ONFH, despite a more rapid evolution of pathologic alterations in the GC-induced ONFH [43].

The organizational structure of the femoral head incorporates articular cartilage, subchondral bone, and deep cancellous bone. Owing to its special bone structure characteristics, the femoral head can endure greater compressive stress without collapse within the normal physiological limit [44]. There is evidence that anterior portion of the bone that most often suffers the greater overall collapse, and regional differences exist in the quantity or quality of femoral head bone or in stress distribution in the femoral head [45]. L. Wang et al. also showed that bone resorption triggered further weakening of the subchondral bone and resulted eventually in progressive collapse of the subchondral trabeculae. Consequently, they hypothesized that osteonecrosis is chronologically correlated with these pathological changes in subchondral bone microstructure in rabbits [46].

According to the research by Catto et al. a four-stage system (Stage I, II, III and IV) has been proposed to illustrate the pathological and microarchitectural alterations in ONFH, which has been extensively recognized [47,48]. In the last 60 years, many studies have been conducted to clarify pathological changes in each stage, despite little progress in the prognosis of ONFH. The exact alterations of microarchitecture and pathology of the involved regions in the femoral head require further investigation.

### 3.1. Stage I

In this stage of ONFH, the femoral head typically reveals no gross or macroscopic microarchitectural manifestations and is limited to

microscopic alterations [49]. The early phase of osteonecrosis is cell death, interruption of cell enzymes, and loss of cell metabolic activity [49]. However, the cells that make up bone differ in their ability to resist ischemic injury. Hematopoietic cells are most sensitive and die within 6–12 h [50]. Correspondingly, the earliest signs indicative of bone ischemia have been observed in the marrow spaces, where there is loss of nuclear staining of marrow cells [18]. Bone cells (osteoclasts, osteoblasts, and osteocytes) may survive from 12 to 48 h [50,51]. Nonetheless, chondrocytes are normally adapted to relatively low oxygen tension and do not become devitalized, with the exception of cells in the calcified cartilage, seen as absence of chondrocytes [49].

The gross and histologic changes in the cartilage without radiographic evidence of degeneration were described by several authors. In stage I, standard radiology is of limited value, and only abnormal alterations in soft tissues (such as plasmotaxis and adipocyte alteration) are observable on magnetic resonance imaging (MRI) [52,53]. MRI does not always detect accurate labral injury or chondral damage, and arthroscopy remains the gold standard for detection and staging of chondral lesions [54,55]. Ruch et al. presented poor correlation between radiographic and arthroscopic assessment of femoral head cartilage in patients with early post-collapse osteonecrosis, as arthroscopic evaluation revealed osteochondral lesions that had not been noted on radiograph or MR [56,57]. Mukisi-Mukaza et al. declared that there is no correspondence between histopathology and radiological stage in patients with ONFH [11].

In the early stage of ONFH, marrow edema is detected in subchondral bone and deep cancellous bone, indicative of declined blood supply in this region [58]. Owing to obstructions of the intraosseous venous system, particularly in the transitional zone at the border of the sequester, a significant feature in the pathogenesis of ONFH is obstruction of the venous outflow [26]. Bone marrow mesenchymal stem cells (BMSCs) residing are multipotent cells that have the ability to differentiate into an extensive array of specialized cells such as bone, cartilage, adipose, and muscle [59]. The capacity for multipotent differentiation of BMSCs is dependent upon the local milieu where the cell is placed and the various cytokines and growth factors with which it comes into contact [59]. BMSCs offer a source of osteoblasts to the lesion involved, and these cells may play an important part in osteogenesis and repair the necrotic defect [60–62]. It has been discovered that low-dose allogeneic BMSCs could promote bone regeneration in osteonecrotic lesions of the femoral head [63]. Not only do BMSCs offer the precursor cells for repair, but they also secrete growth factors and pro-angiogenic factors such as BMP-2 and VEGF stimulating the local repair processes in ONFH [64,65].

Skeletal system homeostasis is constantly preserved through the collaborative actions of bone cells, involving bone resorption by osteoclasts and bone formation by osteoblasts, whereas osteocytes act as mechanosensors and orchestrators of bone remodeling process. This process is under the regulation of local and systemic factors [66]. Osteoclasts are multinucleated, giant cells of hematopoietic origin, which are formed by the fusion of mononuclear pre-osteoclasts derived from myeloid cells. Fusion-mediated giant cell formation is crucial for osteoclast maturation, and bone resorption is incompetent without it [67,68]. Osteoclasts have positive and negative regulatory effects on osteoblast functions [67], and the formation, differentiation, and maturation of osteoclasts are also synchronized by various solubility factors released by osteoblasts [69]. There is evidence that modifications of bone remodeling activity and weakening of bone structure with formation of microfractures are implicated in the pathogenesis and development of ONFH [18]. Wang et al. speculated that the altered osteoblast and osteoclast activity bring about a reduction in macroscopic mechanical strength [70]. Interestingly, evaluation of transiliac bone-biopsy specimens from patients with aseptic osteonecrosis and normal kidney function disclosed a marked reduction in osteoblastic appositional rate and in bone-formation rate at the cell and tissue level, signifying that non-apparent metabolic disturbances are present in patients with aseptic necrosis [40].

Non-surgical treatment, including reduced weight-bearing, pharmacotherapy and physiotherapy, could be selected for ONFH patients in Stage I. Alternatively, core decompression is currently the most common operative procedure in the early stages of ONFH, showing significantly higher success rate than that of nonsurgical management [71].

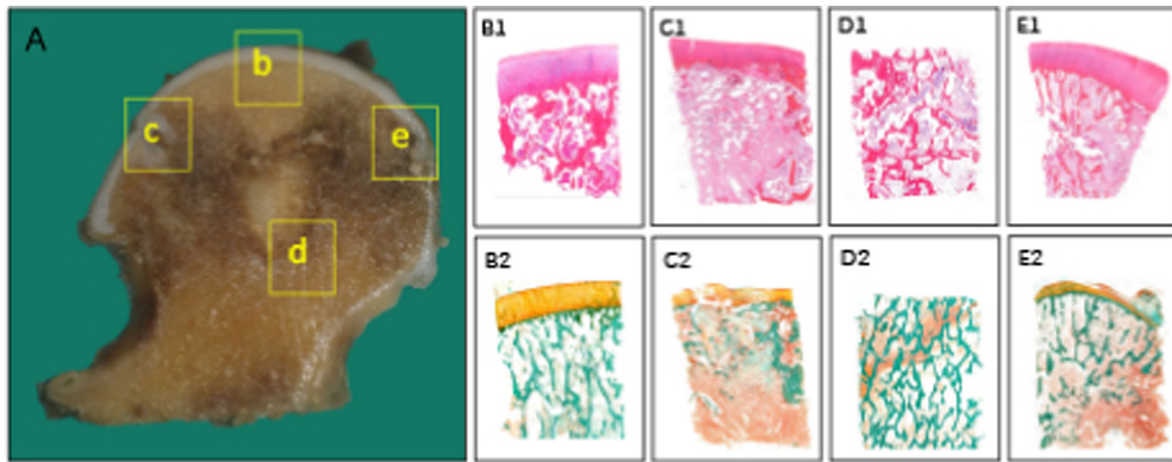
### 3.2. Stage II

The gross appearance of the femoral head does not change considerably in stage II (Fig. 1A) [72]. Due to the progression of reparative processes, the infarcted subarticular necrotic area appears better demarcated on section (Fig. 1), and a peripheral rim of sclerosis is visible radiologically [18].

The articular surface is unaltered as in stage I. In a baboon animal model, interruption of contact between articular cartilage and vascularized subchondral bone brought about cartilage degeneration, which takes three years [73]. The interface between the subchondral bone and calcified cartilage contains numerous vascular canals [74]. Imhof et al. illustrated the dense subchondral vasculature in close proximity to the cartilage and the micro-channels that penetrate the subchondral bone and permit communication between the bone and cartilage [75]. Experiments in joints obtained immediately after death demonstrated that, the tidemark and calcified cartilage are permeable to low-molecular-weight solutes [76]. There are likely to be both vascular and other means, including via the osteocyte lacuna-canalicular network of bone, for signaling molecules to traverse between the bone and cartilage [77]. The zone of calcified cartilage forms an important interface between cartilage and bone for transmitting force, attaching cartilage to bone, and limiting diffusion from bone to the deeper layers of cartilage [78]. The stiffness and hardness of calcified cartilage was typically lower than subchondral bone for the same mineral content [79]. No collagen fibers are successive between the calcified cartilage and the cortical endplate. Consequently, the osteochondral junction is considered as an area of weakness [80]. In contrast, the tidemark which separates the calcified cartilage from the articular cartilage, is traversed by collagen fibrils, leading to a quite strong connection between these two regions. It has been hypothesized that alterations of the calcified cartilage may compromise its mechanical function as a connective and cushioning tissue, leading to degeneration of the overlying articular cartilage [74,78,79].

The tissue adjacent to the necrotic area reveals increased vascularity and marrow reaction with increased inflammatory fibrovascular infiltration (Fig. 1) [81]. The proliferating capillaries and fibroblasts extend into the necrotic area, and dead bone trabeculae are removed by osteoclasts and substituted by viable new ones, laid down by osteoblasts, resulting in the sclerotic rim [18,82]. Utsunomiya et al. speculated that the concentration of stress may increase in association with the increased osteoblastic activity at the lateral boundary of the femoral head in early-stage osteonecrosis [83]. The study by Karasuyama et al. demonstrated that both shear stress and shear strain tend to be concentrated on thickened bone trabeculae at the boundary along with the progression of sclerotic changes, whereas increased osteoclastic activity is not observed unless collapse has occurred [84]. New blood vessels frequently can only propagate into the peripheral region of the necrotic lesion, and new bone tissue emerges surrounding the necrotic region and develops a sclerotic band over time, which further inhibits blood vessels from growing into the center of the necrotic area [85]. Consequently, this area cannot be successfully repaired in most cases and eventually subchondral fracture occurs, which leads to the collapse of the femoral head in late stage. The peak stress from sclerosis rim may be a main factor inducing the formation of cystic lesion in ONFH via an osteoarthritis-like mechanism [86]. Additionally, sclerotic changes are reported to elicit subchondral fractures at the lateral boundary [83].

Combination treatment regimens are commonly employed in the treatment of ONFH patients in Stage II, including non-surgical management and joint salvaging procedures. The most commonly used



**Figure 1.** Histopathological alterations of osteonecrotic femoral heads in Stage II (A) Coronally sectioned gross specimen. The articular surface is not altered considerably as in stage I (b, B1, B2) Necrotic area: There is an accumulation of bone marrow cell debris and bone trabeculae demonstrating empty lacunae, occasionally containing some pycnotic nuclei of osteocytes (c, C1, C2) Lateral transitional zone: Increased vascularity and marrow reaction with inflammatory fibrovascular infiltration is observed, leading to the eventual formation of subchondral cyst (d, D1, D2) Inferior transitional zone: The proliferating capillaries and fibroblasts extend into the necrotic area, and viable new bone tissue is regenerated by osteoblasts, resulting in the sclerotic rim (e, E1, E2) Medial transitional zone: New blood vessels propagate into the peripheral region of the necrotic lesion, and dead bone trabeculae are removed by osteoclasts. Stain: Haematoxylin and Eosin (B1-E1), Goldner's Trichrome (B2-E2), Magnification:  $\times 10.0$ .

procedures are core decompression and vascularized bone-grafting [87]. Nonetheless, a more comprehensive consideration of risk factors, pathologic and imaging stages, and symptoms should be conducted in the decision of therapeutic interventions for early-stage ONFH.

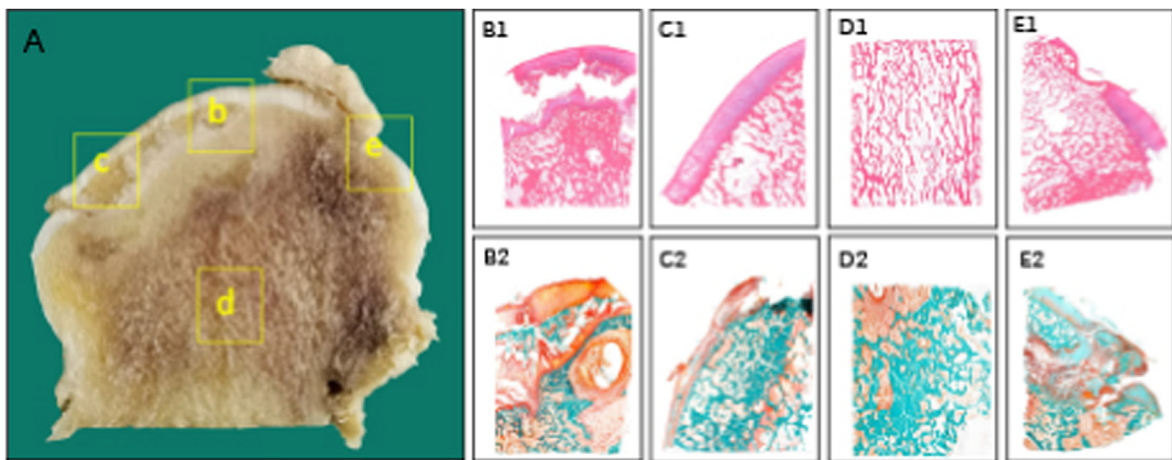
### 3.3. Stage III

There is an obvious alteration of the appearance of the femoral head, due to the subchondral fractures and subsequent collapse of the necrotic bone at this stage (Fig. 2) [18]. As ONFH develops, subchondral fractures appear, and most fractures are initially found between necrotic and sclerotic areas which are caused by abnormal pressure distribution and osteoclast absorption [83,88,89]. Motomura et al. found that the size of the necrotic lesion seemed to contribute to the distribution of subchondral fractures [90]. The most important factor in the prognosis of osteonecrosis is the estimated percentage of compromised load surface

[91]. Ma J et al. hypothesized that discordance between bone structure and function of the femoral head may be involved in the progression of ONFH and more attention should be paid to the prevention and treatment of such discordance [92].

#### 1) Subchondral Fracture

Structural modification of the overlying cartilage seemed morphologically sound, even if subchondral fractures had been observed in some patients [56]. Subchondral fracture consists of the fracture of the subchondral bone plate and that of the subchondral trabeculae underneath. As for the fracture in the subchondral trabeculae, it is characterized by a linear or slightly serpiginous thin trace of low signal intensity on all sequences paralleling the articular surface in MRI [93]. The nano-indentation modulus of the subchondral trabeculae is enhanced in the early stage of ischemic osteonecrosis of the immature femoral head and



**Figure 2.** Histopathological alterations of osteonecrotic femoral heads in stage III (A) Coronal sectioned gross specimen. Subchondral collapse is observed just beneath the osteochondral junction, which is verified by the histological section (b, B1, B2) Necrotic area: Subchondral trabecular fracture is located just beneath the subchondral bone plate level (c, C1, C2) Lateral transitional zone: The initial fracture of the subchondral plate, which is mostly located in the region between necrotic and sclerotic bone tissue, is considered as a starting point to further trigger the collapse of the femoral head (d, D1, D2) Inferior transitional zone: The reactive interface undergoes progressive remodeling at the junction with regenerated bone tissue observed, and vascular-rich granulation tissue is detected in the marrow space (e, E1, E2) Medial transitional zone: When the medial boundary of the necrotic lesion is located lateral to the fovea of the femoral head, revascularization and active bone remodeling occurs in the region. Stain: Haematoxylin and Eosin (B1-E1), Goldner's Trichrome (B2-E2), Magnification:  $\times 10.0$ .

makes it more susceptible to microcrack formation [94]. The specific trabecular fracture is usually located just below the subchondral bone plate level, or less frequently within the deeper necrotic cancellous area or at its periphery on the frontal section [18]. The initial fracture of the subchondral plate, which is mostly located in the region between necrotic and sclerotic bone tissue, is considered as a starting point to further trigger the collapse of the femoral head [89].

A previous report showed that the depth of the low-intensity band on the T1-weighted image is a valuable implement for the differentiation of subchondral insufficiency fracture of the femoral head from ONFH in accordance with the histopathological diagnoses [95]. However, it is reported that the crescent sign is not satisfactory to distinguish subchondral insufficiency fracture from ONFH in cases with collapsed femoral heads, as alterations in bone matrix are triggered only during the regeneration period [96].

In the late stage of collapse, fractures of the necrotic bone at the sclerotic boundary were detected and a low-density tissue that appeared to be fibrous granulation was situated along the necrotic bone side of the sclerotic boundary [97]. Persistent hip pain in ONFH patients is usually considered to be due to subchondral fracture and subsequent femoral head collapse in post-collapse stage, which was not detected in the early stages of ONFH [98,99]. Meier et al. detected a strong correlation between subchondral fracture and bone marrow edema in the post-collapse stage of ONFH [100]. Bone marrow edema of the femoral head represents a secondary sign of subchondral fracture, indicating ARCO Stage III in patients with ONFH [100]. It is rational to assume that bone marrow edema in ONFH might be an inflammatory change to mechanical stress of subchondral fractures or to tissue ischemia around the necrotic area [101–103]. Any lesions vulnerable to collapse ought to be handled to recuperate fundamental strength of the femoral head and halt or even slow the progression of this disease [9].

## 2) Collapse of the femoral head and related mechanism

In the early-collapse stage of ONFH, initial fracture cracks proceeded between separated bone resorption regions at the anterosuperior portion of the femoral head [97]. Recurrent slight damage could bring about subchondral microfractures, which allows the synovial fluid from the joint cavity to infiltrate into the subchondral bone underneath, lifting the intraosseous pressure. The increased intraosseous pressure affects the local microcirculation and triggers a vicious circle which ultimately results in subchondral cyst formation and articular collapse. Cystic lesion in ONFH plays a significant part in exacerbating the development of femoral head collapse [86]. The osteonecrosis complicated by cystic lesions is more likely to cause microfracture, collapse, and crescent sign which specify structural instability of the femoral head [86]. The absence of immobilization, as well as constant weight bearing could eventually result in further subchondral collapse and cartilage damage [80].

Zhang et al. proposed a new definition of the peri-collapse stage of ONFH, which refers to a continuous period in the development of ONFH from the occurrence of subchondral fracture to early collapse (<2 mm) [9]. The peri-collapse stage is a conception that is first recommended in an attempt to assess a continuous period before and after head collapse as a whole [104]. Theruvath et al. described 14 patients with subchondral fracture, and 12 patients experienced collapse with a mean follow-up of 2.6 years [101]. The peri-collapse stage with distinct clinical and imaging characteristics provides a last good opportunity for the application of joint-preserving techniques [105]. It is necessary to separate the peri-collapse stage as an independent state in evaluating the natural progression of ONFH and selecting an appropriate treatment algorithm.

The collapse of femoral head strongly influences the staging and prognosis of ONFH [106]. In regard to its pathogenesis, Bullough and DiCarlo proposed the following three potential causes: 1) the cumulative effect of microfractures induced by fatigue within the necrotic zone; 2) weakness of the trabeculae in the reparative front as a result of osteoclastic activity; 3) focal concentration of stress at the junction between

the thickened sclerotic trabeculae of the reparative zone and the necrotic trabeculae [90].

Bergmann et al. reported that the greatest force is applied to the anterior-superior aspect of the femoral head [107]. It was reported that the anterior hemisphere might be subject to less total load but experiences higher peak load, as it continually osculates between being covered and uncovered by the acetabulum [108–110]. Christian J et al. suggested these osculation-induced peak loads account for the lower bone quality in the anterior hemisphere and the increased susceptibility for it to collapse in ONFH [45]. As such, reinforcement of the femoral head in ONFH should focus on the anterior hemisphere.

Utsunomiya et al. showed that when it was at the early-stage of ONFH, both equivalent stress and shear stress were concentrated at the lateral boundary of the necrotic lesion, where sclerotic changes were observed [83]. As echoing the mechanical findings in the early-stage, collapse has been found to consistently involve subchondral fractures at the lateral boundary in the late-stage of ONFH [56,111]. Radiography may also demonstrate early indications of articular collapse in ONFH, particularly involving the anterolateral and anterior femoral head, in which both frontal and frog-leg lateral projections should be obtained [81]. However, Hengsberge et al. found that the micromechanical properties of bone tissue do not directly affect the overall macro-mechanical properties of bone tissue [112]. Therefore, the collapse of the ONFH is unlikely to be caused by reduced micromechanical properties of bone trabeculae in the weight-bearing region, which could explain that the micromechanical properties of bone trabeculae in collapsed femoral heads with ONFH did not differ significantly between the necrotic zone and the healthy zone in the study by Wang et al. [70]. GC-induced ONFH was characterized by multiple ‘osteolytic bone destruction’, while the alcohol-induced ONFH was manifested by some kinds of ‘coagulative destruction’, exhibiting different features of osteonecrosis [113]. Interestingly, Brown et al. suggested that the degree of structural degradation of the cancellous bone within the main infarct body might be more important than by the degree of structural degradation within the subchondral plate in the onset of collapse [114]. They postulated the trabeculae subjacent to the subchondral plate in the weightbearing region initiates the collapse as a result of its poor quality.

Despite the relative normal structural appearance of the femoral head in the early stage, osteoblast and osteoclast activities had already changed in different regions of the femoral head with osteonecrosis. Specifically, osteoclast activity increased in subchondral bone and the necrotic region while osteoblast activity increased in the sclerotic region [72]. Some authors have conducted experiments using resected femoral heads with late-stage ONFH to investigate the mechanism of collapse. It has been speculated that the altered osteoblast and osteoclast activity leads to a reduction in macroscopic mechanical strength and eventual collapse of the femoral head [70]. Accordingly, it has been proposed that ONFH could be intervened during the early stage, in which osteoblast activity could be promoted and osteoclast activity inhibited as early as possible to prevent collapse of the affected femoral head.

## 3) Reparative procedure and pathological alterations in and about the reactive interface

The reactive interface undergoes progressive remodeling at the junction with the necrotic area [49]. Enchondral ossification is the physiological way of bone formation when fracture ends are well vascularized [96], which could also be observed in the reactive interface. Phemister et al. coined the term “creeping substitution” to indicate the slow replacement of aseptic dead bone [115]. The procedure of osteoblast accumulation of appositional bone, often upon dead trabeculae, and osteoclastic resorption of devitalized bone, occurs in and about the reactive interface [49]. In terms of the bone remodeling related to the necrotic zone, Fan et al. successfully established an emu collapse model of ONFH, in which the extensive trabecular structure was rebuilt and the

original trabeculae was absorbed [116].

Alterations in the remodeling of bone tissue may contribute to the progression of osteonecrosis in several ways, for instance by inducing a healing defect of microfractures and thus facilitating subchondral fractures ultimately leading to femoral head collapse [40]. Subchondral fractures frequently start at the bone resorption area around the reparative interface zone in histological sections of collapsed femoral heads [117]. Focal necrosis of the repair tissue around the area of fracture-collapse may ensue and it should not be interpreted as recurrent osteonecrosis, since it is likely not correlated to a recurrent ischemia but rather to the fracture itself [118]. Histologically, the reparative interface zone is found to be an admixture of fragmented bony trabeculae and cartilage with reparative tissues, including reactive woven bone, metaplastic cartilage, vascularized fibrous and granulation tissue, which is the appearance of unstable fracture elsewhere in the skeleton [18]. Despite the reparative process and reactive woven trabeculae in the area, the subchondral fracture failed to heal. Interference with revascularization occurs repeatedly in the repair process of the necrotic femoral head [119].

Joint-preserving procedures including vascularized bone-grafting and osteotomy, are highly recommended for ONFH patients in the early phase of Stage III, which is usually referred as peri-collapse stage. As for patients in the late phase of Stage III with more severely collapsed femoral head, joint-preserving procedures are still worthy of trying in youngsters, while joint arthroplasty is indicated for older people (>55 years old) [87].

### 3.4. Stage IV

Due to the progressive detachment of osteochondral fragments from the infarcted area, the shape of the femoral head is severely deformed at this stage (Fig. 3) [18]. The degenerated cartilage on the femoral head side caused by depression results in cartilage damage on the acetabular side, and ONFH progresses to secondary osteoarthritis (OA) [120]. Osteochondral debris could be detected in the capsular and synovial tissues [18]. When osteoarthritic changes are fully developed, it may not be possible to recognize the initial cause as that of subarticular avascular necrosis [18]. Chondrocytes close to the necrotic lesion preserve the integrity of their morphology, but when it progresses towards the superficial layer of cartilage, chondrocytes vary in the shape and structure. Cellularity of bone tissue diminishes as the disease is in a more advanced

stage [56].

In the late phase of ONFH, arterial endothelial hyperplasia occurs, the arterial diameter decreases, and the loss of arterial structure is further aggravated, leading to complete arterial occlusion, which indicates OA of the hip joint [121]. This ischemic state is manifested by pathologic and histological changes similar to those that occur in the mid phase of blood supply changes. New vascular penetration occupies the subchondral bone and collapse ensues when weight-bearing zone of the femoral head is replaced by fibrous tissue, and flatness of the head can be easily understood as a secondary episode to collapse [98]. Serious hip function loss or pain often occurs in this stage, and joint replacement should be selected [122].

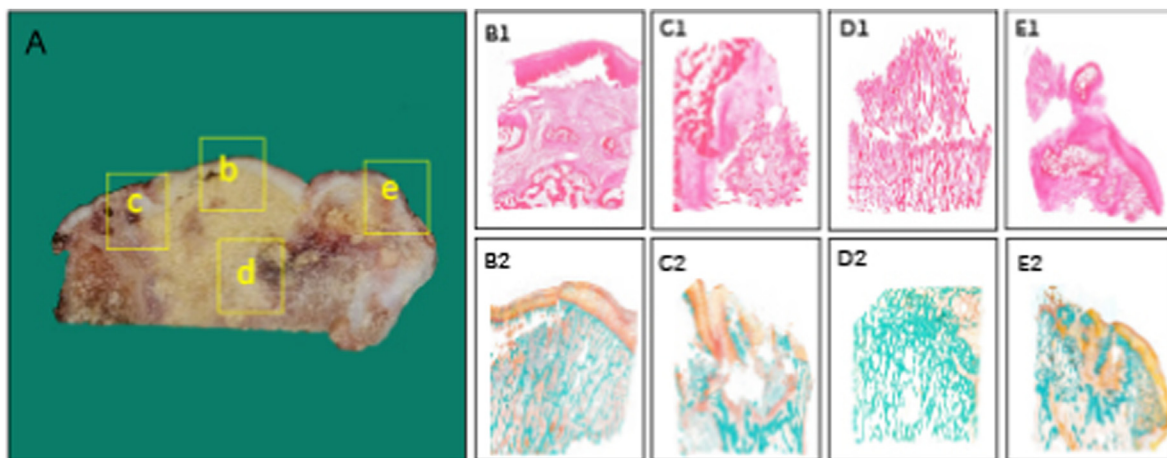
## 4. Imaging features of osteonecrosis

### 4.1. Radiograph

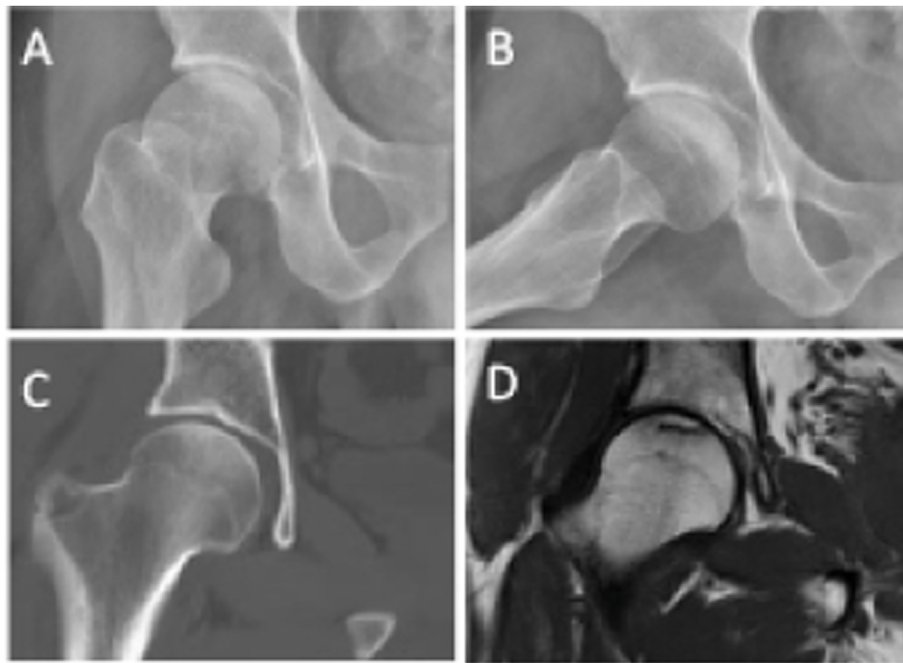
Imaging evaluation of ONFH should begin with radiography (Figs. 4–7), as it is the least expensive and most widely available method of radiologic assessment [81]. Radiography is insensitive for early changes of ONFH, and a normal image obtained by X-ray does not necessarily translate in the absence of the disease [123]. Between the debut of the injury and the first suggestive images of ONFH on radiography, a period of up to five years can pass [123]. However, the imaging features are often characteristic and may obviate the need for additional radiologic evaluation [81]. Radiography manifestations are typically osteosclerosis, cystic change, and a “crescent sign” in earlier stages. Early changes of articular collapse typically occur at the junction of the serpentine sclerotic rim and the articular surface, where stress is maximally exerted [81]. After collapse, there is a loss of sphericity of the femoral head and degenerative arthritis in the late stages. X-ray images obtained using plane radiography can be differentiated from those seen in other disorders: transitory osteoporosis, osteomyelitis, fractures, epiphyseal dysplasia, osteosarcoma, various cancers, bone metastases [123].

### 4.2. Radionuclide imaging

The relative insensitivity of radiography for early changes of ONFH has led to use of additional imaging modalities including nuclear medicine [81]. The addition of single-photon-emission computed tomography (SPECT) may improve the accuracy of radionuclide imaging for diagnosis



**Figure 3.** Histopathological alterations of osteonecrotic femoral heads in stage IV (A) Coronally sectioned gross specimen. The shape of the femoral head is severely deformed at this stage (b, B1, B2) Necrotic area: Chondrocytes close to the necrotic lesion preserve the morphology integrity, but when it progresses towards the superficial layer of cartilage, chondrocytes vary in the shape and structure. Weight-bearing zone of the femoral head is replaced by fibrous tissue, secondary collapse ensues (c, C1, C2) Lateral transitional zone: The osteochondral structure is obviously damaged and shows a chaotic, irregular morphology (d, D1, D2) Inferior transitional zone: Histomorphological characteristics of this region in stage IV is similar to that in stage III (e, E1, E2) Medial transitional zone: Despite the reparative process and reactive woven trabeculae in the area, substitution of necrotic bone with viable new bone tissue fail, exhibiting apparently disarranged structure. Stain: Haematoxylin and Eosin (B1-E1), Goldner's Trichrome (B2-E2), Magnification:  $\times 10.0$ .



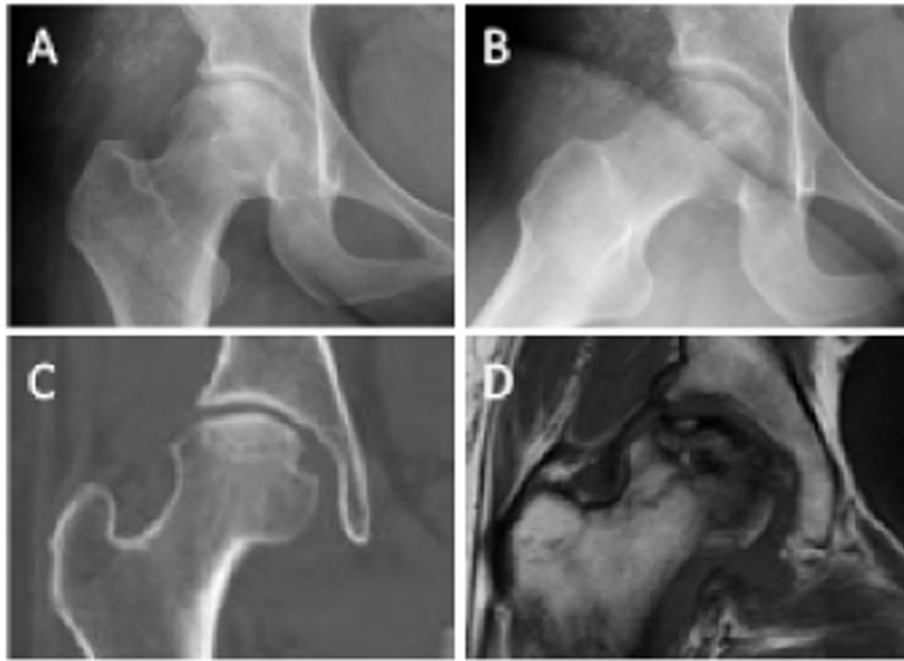
**Figure 4.** ON (ARCO Stage I) of the right femoral head in a 38-year-old male patient (A) Frontal radiograph (B) Frog-leg lateral radiograph (C) Coronal CT image (D) Coronal T1-weighted MR image.



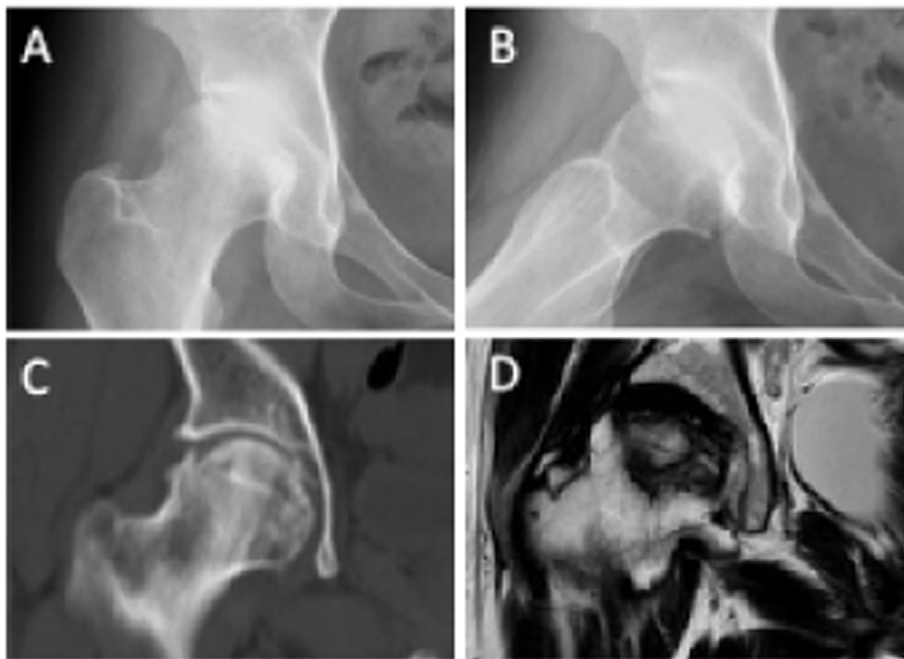
**Figure 5.** ON (ARCO Stage II) of the right femoral head in a 30-year-old male patient (A) Frontal radiograph (B) Frog-leg lateral radiograph (C) Coronal CT image (D) Coronal T1-weighted MR image.

of ONFH and increase the sensitivity [124–126]. SPECT/CT with  $^{99m}\text{Tc}$ -methylene diphosphonate showed that osteoblastic activity gradually increased around the necrotic lesion in early-stage ONFH [127]. Bone scintigraphy with  $^{99m}\text{Tc}$ -methylene diphosphonate, shows high sensitivity for early detection since the radionuclide activity reflects osteoblastic activity and blood flow which are absent in ONFH [128, 129]. For symptomatic disease, the method is able to provide positive findings in 2–3 days after the onset of symptoms (“cold within hot”) and later “hot lesion” reflecting revascularization [130]. However, for the

asymptomatic ONFH, there are not many available data to suggest the diagnostic usefulness of the method [130]. In a study by Ryu and colleagues, SPECT was determined to be more sensitive than MRI (100 % vs 66 %) in detecting early osteonecrosis following renal transplantation [125]. Positron emission tomography may detect signs of ONFH earlier than MRI and SPECT, and can predict progression of ONFH [131]. In addition, nuclear medicine imaging is also applied in post-operative period to detect graft viability or infective complications [132].



**Figure 6.** ON (ARCO Stage III) of the right femoral head in a 24-year-old female patient (A) Frontal radiograph (B) Frog-leg lateral radiograph (C) Coronal CT image (D) Coronal T1-weighted MR image.



**Figure 7.** ON (ARCO Stage IV) of the right femoral head in a 30-year-old male patient (A) Frontal radiograph (B) Frog-leg lateral radiograph (C) Coronal CT image (D) Coronal T1-weighted MR image.

#### 4.3. CT

CT is a very useful assessment tool in later stages of ONFH, for determining the extent of the lesions such as sclerosis and other events occurring in the state of repair [123]. CT provides a detailed analysis of the morphological aspects (Figs. 4–7) [123]. CT usually reveals zones of osteosclerosis surrounding the necrotic bone and repaired bone or shows subchondral bone fracture [133–135]. CT assessment of early ONFH may reveal alteration of the normal “asterisk” that is formed by condensation

of the compressive and tensile trabeculae [81]. However, CT is not advocated for early detection of ONFH and is less sensitive than scintigraphy or MRI [136]. Later stages of ONFH are well depicted with CT, and similar to radiography, show a serpentine or undulating sclerotic margin [81]. CT provides more information for identifying possible subchondral fractures than does MRI and serves as the most sensitive tool for grading the peri-collapse lesion stage [105]. CT is superior to MRI in identifying subchondral fracture and can help diagnose and predict the prognosis of ONFH [137]. CT is not a routinely performed technique, but



is useful to rule out the presence of a subchondral fracture when MRI is doubtful or contraindicated [132]. Lesions which are relevant to indication for hip arthroplasty, tend to be underestimated on conventional MRI compared to high-resolution quantitative computed tomography (HR-QCT), suggesting the importance of CT imaging in ONFH [138]. Nonetheless, multidetector CT, with high resolution, has not been extensively studied in evaluation of ONFH [81]. Multidetector CT is useful for detecting articular collapse location and extent in epiphyseal osteonecrosis and was superior to both radiography and MRI in several studies [139,140]. This information is particularly important in surgical planning for rotational arthroplasty [141].

#### 4.4. MRI

MRI, a non-invasive imaging technique, is generally regarded as the most sensitive and specific image modality for identification of ONFH [130,142–147]. MR could detect the repair process before conventional radiographs and thus would be useful for evaluating the necrotic area and detecting these rare cases of extended osteonecrosis (Figs. 4–7) [148, 149]. Monitoring of high-risk patients with periodic hip MR would help diagnose necrosis in its early stage. It can detect early abnormal lesions in asymptomatic patients, long before they can be viewed on plain radiography, thus facilitating the initiation of treatment, providing a better response to initial therapy and a favorable prognosis [123]. MRI findings of osteonecrosis have been reported to be present as early as 1 week subsequent to induced vascular injury in an animal study by Brody et al. [150]. There are only rare reports of osteonecrosis with a normal MRI examination [151]. A previous case report indicated that osteonecrosis could possibly occur within 3 weeks after initiation of high-dose corticosteroid therapy [152]. A long-term prospective study showed that serial MRI evaluation might be useful in following up the progression of small asymptomatic lesions of ONFH in patients with SARS [153]. Hiruyuki Hatanaka et al. demonstrated that symptomatic pre-collapse ONFH diagnosed based on plain radiographic findings could be distinguished from asymptomatic pre-collapse ONFH by the presence of bone marrow edema on MRI and thus bone marrow edema may be a sign of occult fracture [154].

MRI also helps quantify the area and extent of ONFH in different planes and could also be used to guide treatments as a validated technique in following up patients. The most common MRI pattern seen in osteonecrosis is an area of yellow marrow surrounded by a low-signal-intensity rim with all pulse sequences [81]. The double-line sign may also partially result from chemical-shift misregistration artifact [146, 155]. Two MRI features that increase the risk of development of ONFH are a thick epiphyseal scar and early conversion to yellow marrow [156]. The MRI images correlate closely with the histological changes occurring in the affected hip, and they could describe in details the size of the lesions, enabling accurate staging of the disease, which is used to decide a later therapeutic algorithm [140,157,158]. Mitchell and colleagues described that the MR signal intensity in the area of osteonecrosis may also show intrinsic characteristics other than adipose tissue in a minority of patients, which includes hemorrhage (high signal intensity on T1- and T2-weighted images), cystic areas (low signal intensity on T1-weighted images and high signal intensity on T2-weighted images), and fibrous tissue (low signal intensity with all pulse sequences) [128]. But Murphey et al. suggested that this variability is much more common in epiphyseal areas of osteonecrosis and does not have prognostic significance as originally suggested. But they suggested that this more nonspecific MRI pattern is unusual and is often associated in patients with diffuse marrow disease or red marrow reconversion (sickle cell anemia, Gaucher disease, and chronic renal failure patients treated with erythropoietin) [81]. Additional variations in the MRI appearance of osteonecrosis are also described, including nonspecific diffuse marrow signal abnormality (decreased signal intensity on T1-weighted images and variable signal intensity on T2-weighted images) [146,159,160].

The use of contrast-enhanced MRI in adult osteonecrosis is typically

not necessary for diagnosis or assessment in the vast majority of cases [81]. However, in animal studies, Nadal and colleagues showed that dynamic contrast enhanced MRI was most sensitive to detect osteonecrosis in early surgically-induced femoral head disease [161]. The typical appearance of osteonecrosis on post-contrast MRI is lack of enhancement of the devitalized tissue [81]. There is often a peripheral rim of enhancement corresponding to the zone of creeping substitution granulation tissue [81]. Dynamic contrast-enhanced studies reveal increased peak enhancement and delayed time to peak enhancement [162,163]. More variable patterns of enhancement, perhaps corresponding to mixtures of ischemia and fibrosis, have been reported by Li and Hauzeur [164,165]. There are results which indicate that contrast-enhanced MRI may be useful for noninvasive evaluation of femoral head perfusion after fracture of the femoral neck [166]. Dynamic MRI is a reliable tool to evaluate vascularity of femoral heads and reduces the uncertainty of outcome of treatment of intracapsular femoral neck fracture (ICFNF), which can be a useful tool to formulate a treatment algorithm in management of ICFNF [47,167]. Foci of osteonecrosis as a result of femoral neck fractures are common and have been reported in up to 75 % of cases at histologic evaluation [47]. MRI with a diffusion sequence, T2 mapping, and apparent diffusion coefficient (ADC) mapping has also been advocated more recently to evaluate epiphyseal osteonecrosis, although these techniques remain investigational [168–170].

#### 5. Clinical staging systems of ONFH

Patients with suspected ONFH would have one or more of the following criteria: (1) throbbing, deep groin pain, and one or more associated risk factors; and (2) a previous ONFH in another joint [171]. ONFH classification systems are excellent tools based on imaging data that are widely used to stratify the severity and prognosis, and guide the treatment strategy [8]. There are various staging systems which have been developed for assessment of adult ONFH. These include the Marcus, Ficat and Arlet, Steinberg, Association Research Circulation Osseous (ARCO) classifications, and the China–Japan Friendship Hospital (CJFH) classification system.

In 1973, Marcus et al. classified ONFH into six stages according to the radiographic findings of the hip [172]. Its main feature is simple, but due to the limitations of imaging techniques at that time, the areas and ranges of necrosis could not be accurately evaluated and staged. Therefore, this classification is no longer used. In 1977, Ficat et al. developed a classification system for ONFH, in which four stages were classified according to clinical symptoms, radiograph, MRI, and isotope bone scan [172,173]. Although this classification system is more detailed and accurate than the Marcus classification system, the areas and ranges of necrosis have not been included either, which are quite important for the selection of assessment of disease progression and treatment chosen [173,174]. In 1995, Steinberg proposed a new classification system [175]. This system is the first to incorporate the size of lesion measurements as part of a complete system [176]. This classification system provides a more detailed staging method, which is much more helpful for the selection of clinical treatment and improvement of the prognosis. However, the assessment methods of this classification system are too tedious, and there is no reproducibility for the determination of stage III, and the distinction between stage V and stage VI is also obscure. The classification system of Association Research Circulation Osseous (ARCO) is more detailed than the Steinberg classification system and takes into account the necrotic areas and extent [172]. The ARCO system originates from the Steinberg classification, and several amendments have been made over the years [87]. This system does not provide a method to evaluate either pre-radiographic lesions or lesions in which the joint line and the acetabulum are involved. The location of osteonecrotic lesion is detected and the relative information is added to each stage in ARCO system as a supplement, but its specific value is uncertain [177,178]. The ARCO classification system is more favorable to the guide of clinical treatment and the assessment of the progress and prognosis of ONFH [179].

However, its disadvantage is that the evaluation criteria of this classification are too detailed and complex to be widely used in clinical practice. The Japanese Orthopaedic Association (JOA) system originated from the Ficat and Arlet system with the location and size of the lesion added to its classification. However, this system only evaluates Ficat Stages II and III and not Stages I and IV [180,181].

In 2013, Professor Li Zirong proposed a new classification system based on the three-pillar structure of the femoral head—China-Japan Friendship Hospital (CJFH) classification, also known as Li's classification [182]. According to the midcoronal section on MRI (stage I and II) and CT (stage II and III), the coronal section of the femoral head was divided into three pillars by two parallel lines to femoral neck axis: lateral (30%), central (40%), and medial (30%) pillars. The pathogenesis of ONFH was identified with its location on these pillars. Preservation of the lateral pillar is the keystone for forestalling the collapse of the femoral head [183].

Our team analyzed the characteristics of the Ficat classification system and proposed improvements based on the pathological and micro-imaging findings. Subchondral bone is composed of the dome-like subchondral plate and subchondral cancellous bone, which is closely related to the occurrence and development of many joint diseases, such as femoral head necrosis and osteoarthritis [184]. Subchondral fracture impairs the immobilization function of subchondral bone to articular cartilage and initiates head collapse [185,186]. Focal resorption of the broken subchondral plate and secondary compaction of necrotic cancellous bone result in the formation of a cavum below the subchondral plate, which appears as a crescent sign or radiolucent line on X-ray radiographs and joint effusion and closely correlates with the occurrence of bone marrow edema and hip pain [159,187,188].

Currently, for the treatment of ONFH, there is a lack of consensus regarding diagnostic methods, evaluation systems, and indications of various treatment options [8]. Therefore, we should incorporate all these together to find a preferable treatment option for ONFH.

## 6. Conclusion

Regardless of etiologies, ONFH results from primitive vascular problems, including obstruction of intraosseous microcirculation, extraosseous arterial involvement or extraosseous venous abnormality. In the aspect of histopathology and micromorphology, ONFH is an evolutionary course involving subchondral bone infarction, progressive destruction of the osteochondral complex, reparative process around the necrotic region, and collapse of the femoral head and following degenerative arthritis. Accordingly, a four-stage system has been proposed to demonstrate the pathological and microarchitectural alterations in ONFH, and every specific stage exhibits distinguished characteristics, despite poor correlation with the existing relative radiological stage.

Many classification systems have been developed to assess the severity of the disease, which is based on the imaging features. These ONFH classification systems have been widely applied in clinic, despite constant suspicion about their efficacy in the guide of joint-preserving strategy. The considerable failure rate brings about the suspicion about the validity and reliability of the imaging-oriented grading systems, which might underestimate the severity of the early stages of ONFH. A substantial amount of research on the relationship between imaging and histopathological features is required to further modify and revise the current wide-accepted classification systems.

## Authors' contributions

All authors listed have read and approved all versions of the manuscript YWC and GYL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy. Critical revision of the article for important intellectual content: YWC, YM, KXL, FX, GYL, CQZ. All authors approved the final version to be submitted for publication.

## Declaration of competing interest

The authors have no conflicts of interest to disclose in relation to this article.

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