

TITLE:

Pericollapse Stage of Osteonecrosis of the Femoral Head: A Last Chance for Joint Preservation

ABSTRACT:

**OBJECTIVE:** To propose a new definition of the pericollapse stage of osteonecrosis of the femoral head (ONFH) and review its significance in disease diagnosis and treatment selection. **DATA SOURCES:** A search for eligible studies was conducted in three electronic databases including PubMed, Cochrane Library, and Embase up to August 10, 2018, using the following keywords: “osteonecrosis”, “prognosis”, and “treatment”. **STUDY SELECTION:** Investigations appraising the clinical signs, symptoms, and imaging manifestations in different stages of ONFH were included. Articles evaluating the prognosis of various joint-preserving procedures were also reviewed. **RESULTS:** The pericollapse stage refers to a continuous period in the development of ONFH from the occurrence of subchondral fracture to early collapse (<2 mm), possessing specific imaging features that mainly consist of bone marrow edema and joint effusion on magnetic resonance imaging (MRI), crescent signs on X-ray films, and clinical manifestations such as the sudden worsening of hip pain. Accumulating evidence has indicated that these findings may be secondary to the changes after subchondral fractures. Of note, computed tomography provides more information for identifying possible subchondral fractures than does MRI and serves as the most sensitive tool for grading the pericollapse lesion stage. The pericollapse stage may indicate a high possibility of progressive disease but also demonstrates satisfactory long- and medium-term outcomes for joint-preserving techniques. In fact, if the articular surface subsides more than 2 mm, total hip arthroplasty is preferable. **CONCLUSIONS:** The pericollapse stage with distinct clinical and imaging characteristics provides a last good opportunity for the use of joint-preserving techniques. It is necessary to separate the pericollapse stage as an independent state in evaluating the natural progression of ONFH and selecting an appropriate treatment regimen.

INTRODUCTION:

Osteonecrosis is a refractory and debilitating disease and is associated with high mortality. Once the femoral head collapses and acetabular degeneration or secondary arthritis is present, a total hip arthroplasty (THA) is often the last and most reliable option.[123] Although studies of THA have normally demonstrated excellent results in greater than a 10-year follow-up period compared with that in patients with traumatic osteonecrosis of the femoral head (ONFH), those with nontraumatic ONFH tend to be younger and physically more active, and as a result, replaced hip joint may need to be revised.[1345678]

To salvage the patients' own natural hip joints and delay or avoid joint arthroplasty is one of research focuses in the treatment of ONFH. A successful joint-preserving procedure depends on accurate and early diagnosis (especially those at Association Research Circulation Osseous [ARCO] Stage I/II) and skillful techniques.[123] However, ARCO Stages I and II are also known as subclinical states because lesions at these stages are often insidious, and the symptoms and signs are minimal and nonspecific, which leads to the fact that those patients rarely make a first visit to an orthopedist. Meanwhile, surgical intervention of asymptomatic ONFH is controversial due to the observation of spontaneous repair of necrotic lesions, great variability of progression (with only 7% of small lesions and 80% of large lesions collapsing by the 8th year after diagnosis) at the early stage, and limited evidence for treatment.[3910] On the other hand, the “wait-and-watch” policy may miss the critical window of opportunity to prevent head depression. For children receiving chemotherapeutic treatment for malignancies, up to 72% of patients have already been at Stage IV by the time they are diagnosed.[11] Defining specific biomarkers in the development of ONFH is of great importance to guarantee both diagnostic accuracy and joint-preserving success rate.

The three most commonly used grading systems for the evaluation of ONFH include the Ficat system, ARCO system, and Steinberg system.[12] The Ficat classification system mainly considers collapse observed on standard radiographs, making it impossible to quantify the lesion size and assess disease progression.[13] The classification system proposed by the ARCO consists of four stages with comprehensive reference to X-ray, magnetic resonance imaging (MRI), computed tomography (CT), bone scintigraphy, and histologic findings.[14] In the ARCO system, Stage III indicates evidence of subchondral fracture, and the modified Nijmegen ARCO system further subdivides this stage into an early and late phase according to the existence of femoral head collapse.[15] Mont et al.[16] defined the stages of ONFH as precollapse, early

collapse (head depression  $\leq 2$  mm), late collapse (head depression  $> 2$  mm), and acetabular changes.[1] However, to evaluate the status of ONFH, these classification systems are apparently not sufficient. The pericollapse stage is a conception that is first recommended in an attempt to assess a continuous period before and after head collapse as a whole.[17] At first, this term refers to ARCO Stage II ONFH with necrotic lesions located at the anterolateral part of the femoral head as well as ARCO Stage III ONFH with head depression  $< 4$  mm observed on an anteroposterior film, a faint sclerotic band, and a pain history of  $< 6$  months. It reflects a gray area lasting from the extensive trabecular fracture to early collapse of ONFH.[17] However, this definition has several flaws in its application of clinical diagnosis and treatment guidance. First, ARCO Stage II ONFH is normally asymptomatic and has a variable development process according to this classification system.[3910] Second, by searching related electronic databases, we found that currently, there were no clinical reports regarding the treatment of pericollapse ONFH according to this definition. Therefore, authors of review articles tend to use Ficat Stages II–III or ARCO Stages II–III ONFH to approximately evaluate the pericollapse period, which may impose a big selection bias.[17] Last but not least, the complexity of this definition prevents it from broadly popularizing. To better guide the diagnosis of nontraumatic ONFH, the clinical and imaging manifestations of the pericollapse stage ought to be characteristic and specific; meanwhile, the pericollapse stage should be able to discriminate between reversible and progressive ONFH lesions, providing the opportunity for joint-preserving procedures. By reviewing former studies and summarizing the clinical experiences of the Centre for Osteonecrosis and Joint-Preserving and Reconstruction of China-Japan Friendship Hospital (CJFH), we proposed a new definition of the pericollapse stage of ONFH, which begins with the occurrence of subchondral fracture and ends after the head collapse exceeds 2 mm. Thus, the pericollapse stage is equivalent to approximately Stage III of the Steinberg classification system or Stage IIIa of the ARCO classification system.

#### CHARACTERISTICS OF THE PERICOLLAPSE STAGE OF OSTEONECROSIS OF THE FEMORAL HEAD:

A subchondral fracture exhibits a high T2-weighted signal on MRI but is often obscured by bone marrow edema (BME) and joint effusion. BME is an ill-defined, diffuse abnormality in the femoral head and neck presenting as decreased signal intensity on T1-weighted images. Accordingly, increased signal intensity is observed on T2-weighted images, manifesting elevated free-water content or bleeding in the bone marrow. In contrast to the recognition that BME is the early change in ONFH, BME accompanies disease progression and the onset of collapse, even before subchondral fracture becomes apparent on imaging studies.[18192021222324252627] More cases of subchondral fractures could be detected on additional CT and axial reconstruction is clearer than coronal reconstruction is.[2021] Meier et al. analyzed 37 symptomatic hips in 27 consecutive adult patients with both ONFH and associated BME. Although only 19 cases showed fracture lines on MRI, subchondral fractures were observed in all patients on CT, which recategorized the remaining 18 cases to ARCO Stage III/IV diseases.[20] Studies in pediatric and adolescent patients also demonstrated that the presence of BME on MRI in symptomatic ONFH patients correlated with the occurrence of early subchondral fractures.[18] Delineation of the necrotic area using the linear low-density band on T1-weighted images and the double-line sign on T2-weighted images on MRI with no collapse identified on anteroposterior and frog-leg lateral radiographs are widely used criteria that constitute the diagnosis of ARCO Stage I/II ONFH, which may result in the underdiagnosis of subchondral fractures.[32829] A crescent sign or interruption of the outline of the femoral head appearing on the X-ray film also denotes intra-articular fracture and subchondral collapse, indicating Stage III of the Steinberg classification system.[30] Nevertheless, crescent signs may not be present or only appear in specific planes; under normal conditions, by the time, X-ray radiographs reveal macroscopic epiphyseal fractures, joint motion impairment has become apparent, and core decompression (CD) is less successful.[15] Clinical manifestations after occurrence of subchondral fractures include sudden pain in the groin or hips, painful limping, and aggravated pain with strong internal rotation; most patients are first referred to orthopedists due to these symptoms and signs.[2126] It should be noticed that although aggravated pain, the presence of BME on short-tau inversion recovery (STIR), and accompanied joint effusion on MRI may indicate a high possibility of the appearance of a subchondral fracture, the gold standard technique for diagnosing the pericollapse stage remains CT. These imaging and clinical findings testify extensive trabecular fractures, accompanied structural instability, and further collapse [Figure 1].[1031]

#### PERICOLLAPSE STAGE MAY FORECAST STRUCTURAL INSTABILITY OF THE FEMORAL HEAD:

Close relationships exist among subchondral fractures, ONFH-associated BME of the proximal femur, worsening of clinical symptoms and signs, hip joint effusion, and the ultimate collapse of the femoral head [Figure 2].[1819202122232425262732333435] In fact, the latter four phenomena may occur secondary to subchondral fractures, which forecast the progression of structural instability of the femoral head.

With the development of ONFH, mechanical strength decreases in the necrotic and cystic zone due to accumulated fatigue fractures of necrotic trabeculae after sustained loads and increased trabecular fragility; meanwhile, shear stress concentrates at the junctional zone between the normal bone and sclerotic zone and the necrotic area, which causes a loss of structural stability of the femoral head.[1819202122232425262732] In these processes, the subchondral fracture impairs the immobilization function of subchondral bone to articular cartilage and initiates head collapse.[1524263236] 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 BME and hip pain.[18192021222324252627] Primary BME of the hip in most cases runs a self-limiting and transient course; however, ONFH accompanied by BME tends to have a larger necrotic volume compared with ONFH without BME, and it was suggested that BME was the most significant risk factor for aggravated pain of osteonecrotic hips.[2126] In Theruvath et al.'s[18] report about pediatric and adolescent leukemia patients with glucocorticoid-induced ONFH, during follow-up, 70% of patients with BME eventually progressed to head collapse, even though edema might completely resolve later during follow-up; surprisingly, however, of 24 patients without BME, only one collapse was observed. Multiple theories such as disruption of sensory nerves within the bone marrow, venous hypertension, regional acceleratory phenomena (acceleratory rapidity of the ordinary biological regional processes after fracture, arthrodesis, or osteotomy), and trauma have been proposed, but no one mechanism has been authenticated for the development of BME.[3334] Given the former findings, it is also rational to assume that BME in ONFH might be an inflammatory change to mechanical stress of subchondral fractures or to tissue ischemia around the necrotic area.[182634]

Causes and severity of pain in patients with ONFH are varied and multifactorial in different stages. Most ARCO Stage I/II cases are asymptomatic, but with the aggravation of bone mass loss, bone marrow necrosis, and bone infarction, intermedullary pressure rises and dull pain may occur at the hips, groin, thighs, or knees in a few cases.[1537] While at a later stage, due to the degenerative osteoarthritic changes, severe pain persistently exists during either physical activity or resting. In the observation of the natural progression of asymptomatic ONFH, obvious pain and other suddenly aggravated symptoms are normally related to the occurrence of femoral head collapse.[10373839] Min et al.[38] reported that after the pain developed, all 62 hips had progressed to Steinberg III or later stages, and of them, 44 cases continued to deteriorate sufficiently to accept hip arthroplasty in 1 year. Possible conjectures for the aggravation of clinical symptoms in the pericollapse stage include deteriorative structural instability of the femoral head, enhanced secretion of inflammatory mediators, elevated intramedullary pressure, and increase in hyperstatic pressure caused by joint effusion, etc.[181920223335] There are, of course, exceptions. In a systematic review including 16 studies involving 664 asymptomatic hips, 26 cases (4%) were identified as Ficat Stage III disease, but the patients did not have pain. Therefore, multiple examinations should be considered to obtain a definitive diagnosis of the pericollapse stage. Considering these specific manifestations and high possibility for further collapse, the pericollapse stage should begin with the occurrence of the subchondral fracture instead of with the classification of ARCO Stage II. However, from the onset of femoral head necrosis, how long does it take to progress to the pericollapse stage? How long will the pericollapse stage last?

#### SIZE AND LOCATION OF OSTEONECROSIS AND PROGRESSION OF THE PERICOLLAPSE STAGE:

It has been widely acknowledged that a large-sized necrotic lesion is a crucial risk factor for the prevalence of collapse.[3740] Meanwhile, when the lesions extend laterally to the acetabular edge, which is considered as the weight-bearing portion, head depression often becomes unavoidable.[37404142] Several classification systems such as the Steinberg classification, modified Kerboul classification, and Japanese Investigation Committee (JIC) classification attempt to quantify and categorize ONFH lesions and therefore predict collapse and prognosis.[14] The lesion volume is the primary reference index of the Steinberg classification system while Kerboul et al.'s[1443] modified method calculates an angle by considering the necrotic portion in both the

mid-coronal image and mid-sagittal image of the MRI. The JIC classification considers the location of the necrotic lesion first, and the lesion size is also involved because it is reported that large lesions are prone to locate laterally.[4445] The CJFH classification system is based on the three-pillar structure theory, in which the medial pillar, central pillar, and lateral pillar represent 30%, 40%, and 30% of the femoral head, respectively. According to the involved site of the necrotic lesion, ONFH can be classified as a medial (M) type (only medial pillar involved), central (C) type (medial and central pillars involved), and lateral (L) type (lateral pillar involved). The L type is further divided into an L1 type (partial lateral pillar preserved [sublateral]), L2 type (the lateral pillar involved only [extralateral]), and L3 type (all three pillars involved) [Figure 3]. Preservation of the lateral pillar is the keystone for forestalling the collapse of the femoral head.[46]

The duration of the pericollapse stage and the average intervals from the onset of ONFH to the pericollapse stage varies across the published literature. In the majority of patients who reach the pericollapse stage, head collapse appears within a short period of time. Min reported that for 31 asymptomatic ONFH hips that finally progressed to symptomatic ones, 26 (83.8%) of them collapsed with a mean time of 8 months (range, 1–36 months).[37] In Iida et al.'s study,[24] approximately a 4-month interval (range, 1–7 months) existed from the onset of pain to head collapse. However, Theruvath et al.[18] described 14 patients with subchondral fracture, and 12 patients experienced collapse with a mean follow-up of 2.6 years. The duration of the pericollapse stage should be further confirmed by long-term follow-up. The time needed from the onset of ONFH to the pericollapse stage is mainly determined by the classification, which is consistent with the occurrence of head collapse.[12312] Concerning the data about the natural progression of severe acute respiratory syndrome patients with ONFH, it was observed that no CJFH type M lesions, 6 of 45 (13.3%) CJFH type C lesions, and 20 of 89 (22.5%) CJFH type L1 lesions progressed to the pericollapse stage within 7 years, while all CJFH type L2 diseases and 86.1% of CJFH type L3 diseases progressed to the pericollapse stage within 3 years [Table 1].[46] Nam et al.[38] reported that lesion size is a predictor of developing pain in asymptomatic ONFH: 1 of 21 (4.8%) hips with a small lesion, 11 of 24 (45.8%) hips with a medium-sized lesion, and 50 of 60 (83.3%) hips with a large lesion became symptomatic by the last follow-up. In Mont et al.'s[47] systematic review, the weighted mean time to the appearance of pain in originally asymptomatic ONFH patients was 30 months (range, 1–134 months).

#### Core decompression ::: THE PERICOLLAPSE STAGE AND JOINT-PRESERVING PROCEDURES OF OSTEONECROSIS OF THE FEMORAL HEAD:

CD as well as the modified multiple percutaneous drilling procedure are the most commonly performed joint-preserving procedures, with the tenet of reducing intraosseous pressure and enhancing blood flow in the necrotic area.[3] Such techniques are mainly indicated in the treatment of small-to-medium-sized (<15% of the femoral head or a Kerboul angle <200%) ARCO Stage I/II lesions while the survivorship of lesions in the postcollapse stage (Ficat III) is only 23–35% in published studies.[5051] For lesions in the pericollapse and postcollapse stages, CD combined with bone grafting is normally applied.[4151]

#### Femoral osteotomy ::: THE PERICOLLAPSE STAGE AND JOINT-PRESERVING PROCEDURES OF OSTEONECROSIS OF THE FEMORAL HEAD:

The rationale of femoral osteotomy is to transpose the healthy portion of the femoral head to the weight-bearing area and therefore restore joint congruity, which is mainly suitable for ONFH patients of a young age (<40 years), low body mass index (<25 kg/m<sup>2</sup>), early-stage lesions, and a large postoperative intact ratio.[15] Even in the promising long-term results of angular intertrochanteric and transtrochanteric rotational osteotomies reported in multiple studies in which ARCO Stage IIIa lesions or late-stage osteonecrosis (ON) is present, the progressive collapse of a relocated necrotic lesion was significantly associated with a larger level of preoperative collapse ( $2.1 \pm 1.0$  mm in the progressive collapse group vs.  $4.4 \pm 1.4$  mm in the nonprogressive collapse group).[525354] Meanwhile, osteotomy is less frequently used in China and Western countries due to the complexity of the operation and the high rate of complications (nonunion, delayed union, fixation failure, and increased difficulty in future THA, etc.).[5556]

#### Nonvascularized bone grafting ::: THE PERICOLLAPSE STAGE AND JOINT-PRESERVING PROCEDURES OF OSTEONECROSIS OF THE FEMORAL HEAD:

Replacing the necrotic bone of the femoral head with cancellous or cortical bone grafting via a window (light bulb technique) at the femoral neck base or decompression tracts (Phemister technique) aims to achieve necrotic area decompression and provide strong structural support for

lesion healing and subchondral bone rebuilding. Compared with CD alone, NVBG is more suitable for ONFH at the pericollapse stage.[49575859] In Steinberg et al.'s[60] study, for lesions in Steinberg Stage III, CD combined with autologous bone grafting could decrease the need for THA from 82% to 23%, while the joint-preserving rate in Steinberg IV is only approximately 50%. Zuo et al.[61] reported that the clinical failure rates of the light bulb technique in patients at ARCO Stage II and IIIa were 25.9% and 16.2%, respectively, and as high as 61.5% at ARCO Stage III (b + c).

#### Vascularized fibular grafting ::: THE PERICOLLAPSE STAGE AND JOINT-PRESERVING PROCEDURES OF OSTEONECROSIS OF THE FEMORAL HEAD:

VBG mainly consists of the following three types: muscle pedicle grafting, vascularized fibular grafting, and vascularized iliac grafting.[62636465] In addition to providing structural support, VBG also attempts to reconstruct the blood supply to the necrotic lesions. In 2006, a study[66] of vascularized iliac bone grafting reported a 66.7% (8/12) success (no progression) rate with a follow-up duration of more than 3 years for the Steinberg Stage III hips but only 37.5% for Steinberg Stage IV hips. A midterm study using free vascularized fibular grafting observed that symptoms in 91.7% (11/12) of Steinberg Stage II cases and 85.7% (24/28) of Steinberg Stage III cases improved after the operation; however, only 45% (9/20) of Steinberg Stage IV cases improved, and because the duration of follow-up (24–40 months) was not long enough, only one case that progressed to THA was observed.[67] Zeng et al.[68] used a vascularized greater trochanter bone graft combined with a free iliac flap and impaction bone grafting to treat ONFH, with a 100% good-to-excellent rate for ARCO IIIa Stage lesions. These results are in accordance with a series of other reports.[64666970717273]

From the abovementioned studies, we noticed a satisfactory prognosis of ONFH in the pericollapse stage after joint-preserving techniques and sharply increased failure rates once evident femoral head collapse occurred [Table 2]. Therefore, the pericollapse stage should end with a head collapse more than 2 mm instead of 4 mm. The pericollapse stage may be the last good opportunity for the use of joint-preserving techniques. Of note, treatment regimens for ONFH should be individualized with consideration of the age and personal needs of patients in addition to staging and classification. For the CJFH L2 and L3 types, the pericollapse stage lesions in patients aged >50 years with severe pain and joint disturbance as well as a high functional requirement, THA may be a good choice.

Limitations of this research concerning pericollapse ONFH merit consideration. First, there are some common flaws existing in now available joint-preserving studies, for example, no powered randomized controlled trials, the inclusion of ONFH with different risk factors (i.e., glucocorticoid, alcohol, trauma, caisson, and sickle cell disease), and a lack of validated patient-oriented evaluation parameters and variability with respect to indications, staging system, surgical procedures, determination of success (progression or conversion to THA), and follow-up duration. [38] Second, there is a paucity of large-scale (even >10 subjects) studies with long-term follow-up (>10 years) investigating the pericollapse stage. Most studies involving joint-preserving techniques were mainly targeted at ARCO or Steinberg Stage I/II ON, and a large number of investigators have adapted the Ficat system, which was incapable of discriminating the pericollapse stage as a distinctive stage.[13] Last but not least, for many studies using Steinberg or ARCO classification systems to assess ONFH, the CT results were missing.[18212224253739] In these studies, many alleged Steinberg or ARCO I/II ONFH cases with obvious hip pain may have been actually at the pericollapse stage. A high index of suspicion is required when younger patients present with worsening hip pain and BME, but no apparent collapse observed on X-ray.

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