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Updating Osteonecrosis of the Femoral Head

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Osteonecrosis of the femoral head (ONFH), a condition characterized by the presence of a necrotic bone lesion in the femoral head, is caused by a disruption in the blood supply. Its occurrence is more common in young and middle-aged adults and it is the main reason for performance of total hip arthroplasty in this age group. Its incidence is increasing along with increased use of glucocorticoids for management of adjuvant therapy for treatment of leukemia as well as organ transplantation and other myelogenous diseases. Current information on etiology and pathogenesis, as well as natural history, stage system, and treatments is provided in this review. A description of the Association Research Circulation Osseous (ARCO) criteria for classification of glucocorticoids-and alcohol-associated ONFH, 2019 ARCO staging system, and 2021 ARCO classification using computed tomography for the early stages of ONFH is also provided.

Key Words: Femur head necrosis, Etiology, Pathogenesis, Staging, Classification

INTRODUCTION

Osteonecrosis of the femoral head (ONFH), a condition characterized by the presence of a necrotic bone lesion in the femoral head, is caused by a disruption in the blood supply[1]. The incidence of ONFH is increasing worldwide, particularly among young and middle-aged individuals[2-5]. In the United States alone, the estimated annual occurrence of ONFH is approximately 15,000 to 20,000 new cases[2,6]. Similar trends have been reported in East Asian countries including Japan, and China, where significant numbers of individuals are affected by this condition[4-7]. In South Korea, more than 10,000 new cases of ONFH have been reported annually[7,8].

Trauma, such as a displaced fracture of the femoral neck or hip dislocation, can damage local blood vessels and compromise the supply of blood to the femoral head, leading to development of ONFH[9]. In addition, non-traumatic risk factors associated with ONFH include the use of corticosteroids, excessive consumption of alcohol and tobacco, certain medical conditions such as sickle cell disease and systemic lupus erythematosus (SLE), as well as factors such as organ transplantation, HIV (human immunodeficiency virus) infection, coagulation disorders, genetic factors, Caisson dis-

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ease (divers), myeloproliferative diseases, and radiation necrosis[9-14].

Once ONFH has developed, the size and location of the necrotic portion are critical in determining the risk of femoral head collapse[2,15]. The prognosis may be better for small lesions, which sometimes remain stable without progressing, while progression to collapse is more likely with larger lesions involving the weight-bearing area of the femoral head, leading to development of secondary arthritis of the hip[16-19].

Accurate evaluation and classification of the size and location of the necrotic lesions is important to the process of making appropriate decisions regarding treatment. Lesions that differ in size may require different treatment approaches with the aim of preserving the femoral head and preventing collapse. Accurate assessment of the necrotic portion can be helpful in determining the optimal treatment strategy for each individual case, with the aim of preventing further deterioration and preserving hip joint function[15,20-22].

In this review, we have updated current information on the etiology and pathogenesis of the disease, criteria for classification of alcohol and glucocorticoid associated ONFH, staging system, classification for early-stage ONFH, and treatments.

ETIOLOGY

Caisson disease, dysbaric ONFH in divers, was first reported in 1952[23]. The association of glucocorticoid use and ONFH was reported in 1957[24]. Bone necrosis in patients with sickle cell disease was reported in the 1950s[25]. Excessive alcohol use had been recognized as a risk factor for ONFH by the 1960s[26]. Since 1990, association of hypofibrinolysis, thrombophilia, and impaired angiogenesis due to abnormal enzymes and various polymorphisms with ONFH has been reported[26,27]. Involvement of protein S and protein C deficiencies[27-30], presence of antiphospholipid antibodies[31,32], mutations in the factor V Leiden or the prothrombin 20210A gene[33], polymorphisms of the plasminogen activator inhibitor-1 gene (PAI-1)[34,35], and diminished activity of 5,10-methylenetetrahydrofolate reductase (MTHFR) in hypofibrinolysis/hypercoagulability has been reported[35]. An association of polymorphisms of vascular endothelial growth factor (VEGF) and polymorphism in the endothelial nitric oxide synthase gene with impaired angiogenesis has been reported[21,36-39].

In addition, smoking, pelvic radiation therapy, non-glucocorticoid chemotherapeutics, HIV infection, rheumatic disease, Gaucher's disease, SLE, and pancreatitis have also been reported as associated conditions or risk factors for ONFH[40].

In 2019, a Delphi survey was conducted by Association Research Circulation Osseous (ARCO) in order to develop criteria for classification of alcohol-associated and glucocorticoid-associated ONFH. The ARCO criteria for classification of alcohol-associated ONFH were as follows: (1) patients must have a history of alcohol consumption >400 mL/week (320 g/week, any alcoholic drink); (2) diagnosis of ONFH must occur within one year after consuming this amount of alcohol; and (3) patients must not have any risk factors other than alcohol abuse[11]. The ARCO criteria for classification of glucocorticoid-associated ONFH were as follows: (1) patients must have taken glucocorticoids that totaled more than 2 g of prednisolone or its equivalent in the previous three months; (2) diagnosis of osteonecrosis must occur within two years of glucocorticoid usage; and (3) other than glucocorticoids, patients should have no other risk factors[10].

PATHOGENESIS

The pathogenesis of ONFH is complex and research is ongoing. However, over the past three decades, knowledge of the pathophysiology of the disease has shown significant advancement, and various consensuses have been reached.

First, ONFH has a multi-factorial etiology involving exposure to risk factors and genetic predispositions. Reciprocal interaction and cooperation occurs among these elements in the pathogenesis[9,12,41]. This genetic predisposition explains why the condition affects some users of glucocorticoids and alcoholics while it may not affect others. Second, the first event of ischemia occurs in the marrow space, not inside the vessel. Third, the process of pathogenesis involves (1) bone marrow necrosis and death of osteocytes, (2) a fibrovascular healing process in the area surrounding the necrotic marrow zone, (3) fracture and collapse of an osteonecrotic lesion, and (4) secondary osteoarthritis of the hip[9,12,41].

A reliable model of the pathophysiology of non-traumatic ONFH was presented by ARCO in 2019[9]. Mesenchymal stem cells differentiating to adipocytes are stimulated by glucocorticoids and alcohol, leading to activation of intracellular synthesis of lipids and induction of adipocyte hypertrophy[42-44]. An increase in the number and volume of marrow fat cells results in intraosseous hypertension in the femoral head, which causes squeezing of the venous sinusoids and intravascular coagulation. This leads to restriction

of arterial blood flow, resulting in ischemic alternations in the femoral head. Marrow adipocytes die within two days of developing ischemia. The ischemia is usually recovered by thrombolysis and angiogenesis, and the presence of lesions does not lead to irreversible necrosis. However, in cases of ischemia that is sustained for two to five days, osteocytes die and vanish completely within 2-4 weeks, leaving a sequestrum. Because gradual replacement of dead bone with new bone does not occur, a foreign body reaction occurs in the area surrounding the sequestrum, resulting in the formation of fibrovascular tissue that encapsulates the lesion. Histologic criteria for ONFH include marrow necrosis, osteocyte death, and encapsulating fibrovascular tissue. Advancement of the ischemic lesion is determined by the restoration of vascular perfusion. Restoration of vascular perfusion is hindered by hypercoagulability/hypo-fibrinolysis genetic predispositions and/or hypoangiogenesis (Fig. 1)[9,12,41].

NATURAL HISTORY ACCORDING TO SIZE AND LOCATION OF OSTEONECROSIS

The fate of ONFH is largely determined by the size and location of osteonecrosis. The risk of femoral head collapse is influenced by the size and location of the necrotic portion. Even without medical or surgical treatment, collapse of small lesions seldom occurs, whereas progression of large lesions is more likely, leading to collapse of the femoral head[16,18,19]. Once ONFH has developed, the size of the necrotic lesion remains stable and does not increase regardless of the progression of the disease[45]. This means that expansion or enlargement of the necrotic portion does not occur over time during the disease course. Thus, measurement of the size of osteonecrosis should be performed prior to planning treatment for ONFH patients, and small osteonecrosis lesions should not be treated. Therefore, cautious assessment based on the size of the necrosis and the predicted course of the condition is necessary for determining the most appropriate treatment approach for each individual.

ARCO STAGING

The first ARCO ONFH staging system was developed in 1994. However, it had been reported that progression of a stage 0 lesion: marrow necrosis with viable osteocytes to definite osteonecrosis does not occur[41]. Thus, the ONFH staging system was updated by ARCO in 2019. In the 2019 revised version of the staging system, stage III was divided into two parts: early IIIA and late IIIB based on a head depression depth of 2 mm, sub-classification of size and location was not included, and stage 0 was removed (Fig. 2, Table 1)[46].

ARCO CLASSIFICATION OF SIZE AND LOCATION OF NECROSIS IN EARLY STAGE ONFH

Various systems for classification of ONFH have been introduced in order to characterize the extent and location

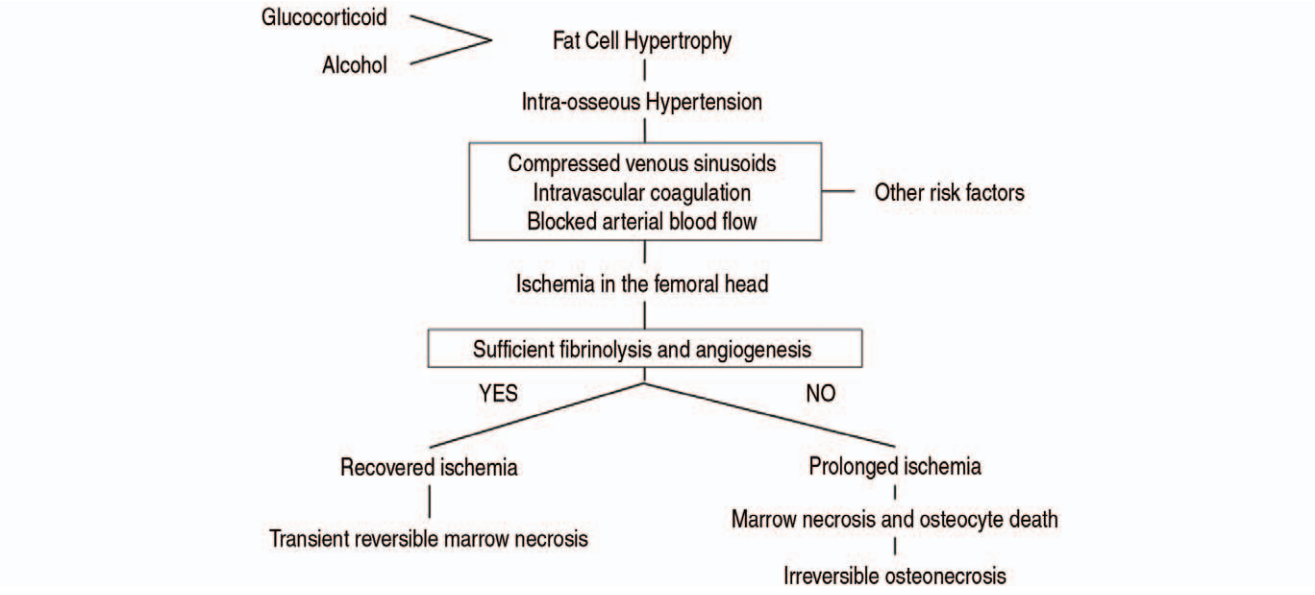

Fig. 1. Summary of the pathophysiology of non-traumatic osteonecrosis of the femoral head.

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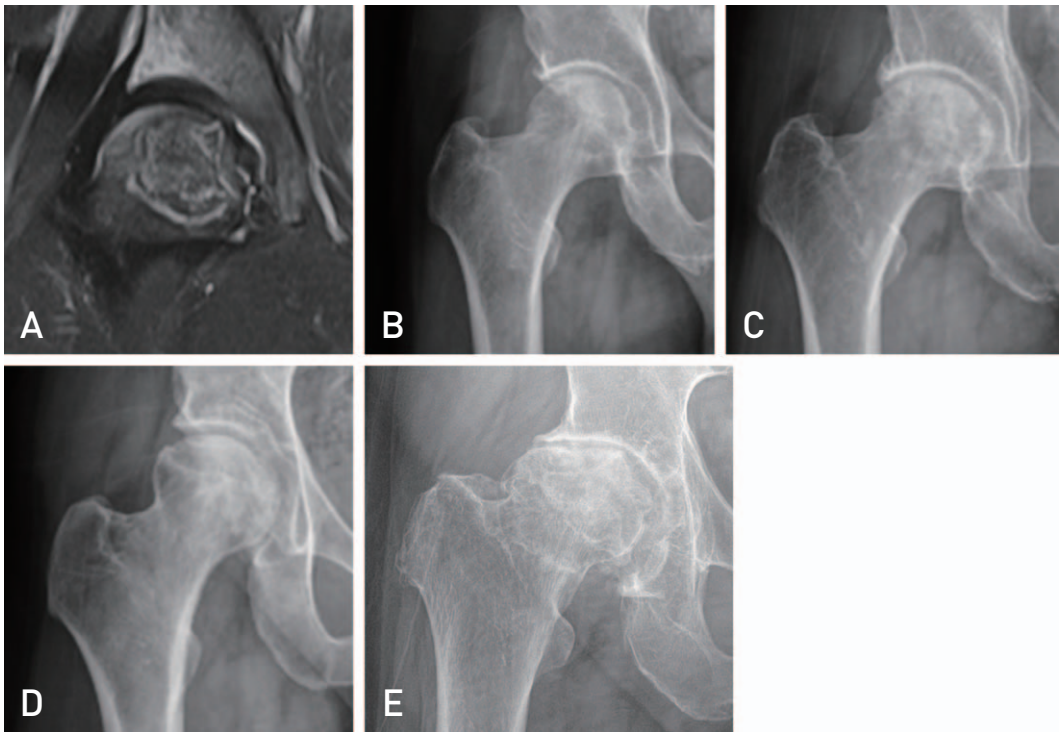

Fig. 2. The 2019 ARCO (Association Research Circulation Osseous) staging system for osteonecrosis of the femoral head. (**A**) Stage I. (**B**) Stage II. (**C**) Stage IIIA. (**D**) Stage IIIB. (**E**) Stage IV.

Table 1. The 2019 Revised ARCO Staging for Osteonecrosis of the Femoral Head

ARCO stage	Image findings
I	X-ray: normal
	MRI: low-signal band on T1-weighted MRI
II	X-ray: abnormal
	MRI: abnormal
III	Subchondral fracture on X-ray or CT
IIIA (early)	Femoral head depression ≤2 mm
IIIB (late)	Femoral head depression >2 mm
IV	X-ray: osteoarthritis

ARCO: Association Research Circulation Osseous, MRI: magnetic resonance imaging, CT: computed tomography.

of osteonecrosis. There are currently three classification systems that are frequently employed, Japanese Investigation Committee (JIC) classification, Steinberg classification, and modified Kerboul classification.

However, there is no consensus regarding which method is universally acknowledged. Development of a unified system for classifying the amount and location of osteonecrosis was required. A novel system for classification of necrotic size and location in the early stage of ONFH (pre-collapse) was developed by ARCO in 2021. Using that classification, necrotic lesions were classified into three types: type 1 is a small lesion, where the lateral necrotic margin is medial to the apex of the femoral head; type 2 is a medium-sized lesion, with the lateral necrotic margin located between the apex of the femoral head and the lateral acetabular edge; and type 3 is a large lesion, which extends outside the lateral acetabular edge (Fig. 3). The 2021 ARCO classification is considered highly reliable and valid and use of this method as a unified system for classification of ONFH in the early stages is recommended by ARCO[47].

TREATMENTS

Determining the treatment approach for ONFH is based on the size and location of the necrotic lesion, as well as the risk of progression to femoral head collapse. It should be noted that progression to collapse does not often occur with small lesions even without medical or surgical intervention, whereas progressive deterioration is more likely to occur with larger lesions[16,18,19]. The extent of the necrotic portion is typically established during the ischemic attack, so that once ONFH has developed, the size of the lesion remains constant regardless of disease progression stage[45]. Consequently, evaluating the size of the necrotic portion prior to initiating treatment is essential, and caution should be exercised in determining the effectiveness of specific

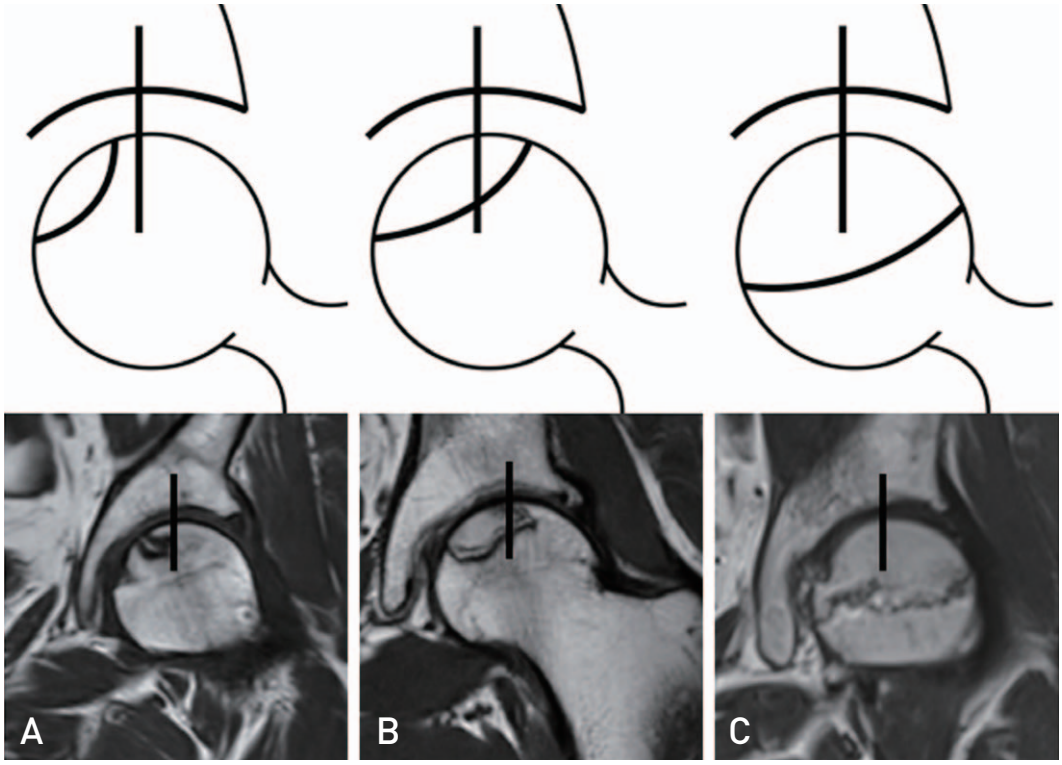

Fig. 3. The 2021 ARCO (Association Research Circulation Osseous) classification for osteonecrosis of the femoral head in the early stages (computed tomography-based): (**A**) Type 1 is a small lesion that is restricted medial to the apex of the femoral head; (**B**) Type 2 is a medium-sized lesion where the lateral margin of the necrotic portion is located between the apex of the femoral head and the lateral edge of the acetabulum; and (**C**) Type 3 is a large lesion that extends laterally to the lateral edge of the acetabulum.

treatment modalities, with consideration for the varying natural courses based on the size and location of the necrotic lesion.

1. Medical Treatments

Several pharmacological agents including enoxaparin, statins, bisphosphonates, iloprost, and acetylsalicylic acid have been evaluated for their potential to slow down or reverse the progression of ONFH[48-54]. However, it is important to note that the effectiveness of these agents has not been conclusively proven based on high-level evidence[20]. In addition, many of these pharmacological interventions have shown an association with adverse reactions or side effects.

Consequently, there is currently no recommended pharmacological approach for the prevention or treatment of ONFH. Conduct of additional research and clinical trials will be required in order to verify the efficacy and safety of potential pharmacological interventions for treatment of this condition.

2. Core Decompression and Bone Marrow Aspirate Concentration

Core decompression (CD), a surgical technique, is commonly used in the early stages of ONFH, with the aim of preventing collapse of the femoral head and potentially reversing the disease progression. However, results regarding the efficacy of CD have been inconsistent, leading to questions about its effectiveness[55]. In recent years, use of the combination of CD with bone marrow aspirate concentration (BMAC) therapy as a potential improvement has been evaluated. Earlier studies suggested that enhanced treatment outcomes could be achieved with the addition of cell therapy through BMAC[56-61]. However, more recent studies have reported no significant differences in outcomes between CD with BMAC and CD alone. In addition, high rates of progression have been observed in large lesions with use of both CD and BMAC therapies[62-64]. The effectiveness of BMAC remains controversial and further research will be required in order to clarify its role in the treatment of ONFH.

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3. Osteotomies

Several procedures for osteotomy of the proximal femur have been introduced in the effort to preserve osteonecrotic hips. These procedures involve relocating the necrotic portion from the weight-bearing dome to a non-weight-bearing region. Certain factors, including the patient's age (under 40 years), body mass index (below 24 kg/m^2), stage of the disease (ARCO stage 3A or 3B)[16,18,46,65], and size of the necrotic portion (medium-sized lesion), should be considered when selecting candidates for osteotomy. These criteria can be helpful in identifying suitable candidates for osteotomy procedures.

Among these types of osteotomy, transtrochanteric curved varus osteotomy (TCVO) and transtrochanteric rotational osteotomy (TRO) have been predominantly performed in Japan and South Korea[66]. A study conducted by Lee et al.[67] in 2017 compared the outcomes of 91 TROs and 65 TCVOs. According to the results, various aspects of TCVO were found to be superior to those of TRO. Shorter operation times, less blood loss, lower rates of postoperative collapse, decreased osteoarthritic changes (20% vs. 37.4%), and a lower rate of conversion to total hip arthroplasty (THA) (10.8% vs. 16.5%) were obtained with use of TCVO. Based on these findings, TCVO was recommended as the preferred option over TRO.

4. Vascularized Bone Grafts

The technique of vascularized fibular grafting was initially introduced by Judet et al.[68] in 1980 and later gained popularity through the work of Urbaniak et al.[69] and Yoo et al.[70]. Another approach, vascularized iliac bone grafting with a pedicle of the iliac circumflex artery, has also been favored due to its proximity to the femoral head and the absence of microsurgical anastomosis[71]. However, despite their potential benefits, vascularized bone graft procedures have been criticized for their technical complexities and associated donor site morbidities. As a result, use of these procedures is currently limited to a select few specialized centers worldwide where they are performed by experienced surgeons.

5. Resurfacing Arthroplasty

Hip resurfacing arthroplasty (HRA) is regarded as an alternative to THA, particularly in younger patients who wish to maintain high levels of activity after surgery[72,73]. HRA involves the removal of the damaged surface of the femoral head and the placement of a metal cap, while preserving the femoral neck. Use of this technique enables the preservation of more bone stock compared to THA, which involves the complete removal and replacement of the femoral head.

The potential for improved range of motion and function is a main advantage of HRA compared to THA. The preservation of the femoral neck with use of HRA allows for a more natural anatomy and can potentially reduce the risk of dislocation. In addition, use of HRA with the larger femoral head size can result in enhanced stability and contribute to better hip kinematics.

However, the risk of complications specific to HRA, such as femoral neck fractures and issues related to metal-on-metal bearing surfaces, including metal ion release and adverse local tissue reactions, may be increased[74-76]. Careful discussion of these factors with the patient is required, and their individual suitability for HRA should be thoroughly evaluated. The use of HRA in the treatment of ONFH has declined significantly as a result of these concerns and complications.

6. THA Using Highly Cross-Linked Polyethylene Liners

The use of more durable bearing materials has gained traction in response to concerns over excessive wear rates and osteolysis associated with conventional polyethylene bearings in young patients[77]. Highly cross-linked polyethylene (HXLPE), with enhanced wear resistance, has rapidly replaced conventional polyethylene in many cases. The crosslinking process involves exposing the polyethylene to ionizing radiation during manufacturing, which increases the number of crosslinks and reduces wear. Current crosslinking techniques utilize gamma-rays instead of electron beam irradiation, followed by annealing or remelting of the polyethylene[78].

HXLPE can be combined with either cobalt chromium or ceramic femoral heads. Promising clinical and radiological results have been reported from short-term and mid-term follow-up studies on the use of HXLPE liners in patients with ONFH[79,80]. In addition, recent long-term follow-up studies have reported a good survival rate for THA with HXLPE liners[81-83]. Conduct of additional research and long-term studies will be necessary in order to evaluate the durability and longevity of HXLPE.

7. THA Using Ceramic-on-Ceramic Bearings

The lowest wear rates have been reported for ceramic-on-ceramic (CoC) bearings compared to other bearing materials[77]. However, the use of CoC bearings is associated with specific complications. The implementation of these bearings has led to concerns regarding fractures of ceramic components as well as audible squeaking noises[84,85].

Despite these potential complications, several studies have reported promising outcomes at mid-term and long-term follow-up with use of CoC THA in patients with ONFH[86-90]. Favorable results in terms of wear reduction and improved longevity have been reported with the use of CoC bearings. A further decrease in the incidence of ceramic fractures as well as enhanced performance of CoC THA is expected with the introduction of newer ceramic materials, such as the delta ceramic[91].

However, it is important to note that there is still no knowledge regarding the long-term outcomes of CoC THA for treatment of ONFH. Continued research and conduct of long-term studies will be necessary for evaluation of the durability, complications, and overall success of CoC bearings in the treatment of ONFH.

SUMMARY

Exposure to risk factors and genetic predispositions can influence the development of ONFH. The size and location of the osteonecrosis is the primary factor influencing the rapidity of disease progression. The size of osteonecrosis is determined during the initial ischemic episode and is not altered. Advancement of small lesions of osteonecrosis does not occur even without intervention, therefore they do not require therapy, whereas most large lesions result in collapse of the femoral head. Medical or surgical treatment may be required for painful ONFH hips with medium-to-large sized lesions. During the last five years, ARCO developed criteria for classification of glucocorticoid-and alcohol-associated osteonecrosis, revised the system for staging ONFH, and developed a system for classification of size/location for early stage ONFH. ARCO has recommended the use of these new systems as unified classification and staging systems. Small lesions in ONFH do not progress and therefore treatment is typically not required. Medical or surgical interventions may be helpful in management of medium-sized to large lesions with accompanying pain. Proven efficacy has not been demonstrated for pharmacological treatments. CD combined with BMAC therapy may not be effective in treatment of large lesions and conduct of additional research will be required. The decision to perform osteotomy should be the result of a selective process. Selective consideration and deliberation are required for HRA. Despite promising outcomes of THA with HXLPE or CoC bearings in the short to medium term, results from long-term follow-up are still anticipated.

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CONFLICT OF INTEREST

Young-Kyun Lee has been an editorial board member since January 2023, but had no role in the decision to publish this article. No other potential conflict of interest relevant to this article was reported.

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