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TOPIC HIGHLIGHT

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Osteonecrosis of the femoral head: An update in year 2012

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Abstract

Osteonecrosis is a phenomenon involving disruption to the vascular supply to the femoral head, resulting in articular surface collapse and eventual osteoarthritis. Although alcoholism, steroid use, and hip trauma remain the most common causes, several other etiologies for osteonecrosis have been identified. Basic science research utilizing animal models and stem cell applications continue to further elucidate the pathophysiology of osteonecrosis and promise novel treatment options in the future. Clinical studies evaluating modern joint-sparing procedures have demonstrated significant improvements in outcomes, but hip arthroplasty is still the most common procedure performed in these affected younger adults. Further advances in joint-preserving procedures are required and will be widely studied in the coming decade.

Key words: Osteonecrosis; Avascular necrosis; Femoral head; Total hip arthroplasty; Core decompression; Hip

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INTRODUCTION

Osteonecrosis of the femoral head, also referred to as avascular necrosis, is a pathological state with multiple possible etiologies that causes decreased vascular supply to the subchondral bone of the femoral head, resulting in osteocyte death and collapse of the articular surface. The ischemic injury upregulates tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts to resorb dead trabeculae of subchondral bone[1]. These trabeculae eventually fail under the repetitive loads of weight bearing during walking and other activities[2-4].

Total hip arthroplasty (THA) is commonly utilized as a definitive treatment for high-grade osteonecrosis with articular collapse. However, as this disorder is commonly seen in young adults, joint-sparing therapeutic techniques have been studied extensively in the past decade and will be a major focus of orthopaedic research in the coming years. Osteonecrosis is undoubtedly a challenging condition to treat, but ongoing basic science and clinical investigations are progressing toward effective future treatment options.

EPIDEMIOLOGY

Approximately 5%-18% of all hip arthroplasties are completed on patients with a primary diagnosis of osteonecrosis[4-6]. Patients are generally younger adults age

35 years to 45 years, and risk factors for 75%-90% of cases include chronic steroid use, alcoholism, smoking, hip trauma including femoral neck fractures and hip dislocations, and prior hip surgery. Other potential etiologies for osteonecrosis include childhood history of slipped capital femoral epiphysis (SCFE), deep sea diving or other hyperbaric conditions, systemic lupus erythematosus (SLE) and other connective tissue disorders, autoimmune diseases causing vasculitis, sickle cell anemia, coagulopathy such as thrombophilia or disseminated intravascular coagulation, human immunodeficiency virus (HIV) infection, hyperlipidemia, fat embolus syndrome, treatment of developmental hip dysplasia, chemotherapy and/or radiation, organ transplantation, chronic liver disease, Gaucher disease, gout, and metabolic bone disease[3,4,6-10]. Males are affected up to three times more than females, and bilateral femoral head osteonecrosis is found in up to 75% of cases[3,5]. Incidence in the late 1990's was reported to be 10 000 to 20 000 new patients per year, but this incidence has almost certainly increased over the past decade[4].

PATHOPHYSIOLOGY

The blood supply to the femoral head originates primarily from the basicervical extracapsular articular ring and ascending branch of the medial femoral circumflex artery, as well as smaller secondary contributions from inferior and superior gluteal arteries and artery of the ligamentum teres[11]. The interruption of this blood supply can be multifactorial, either extravascular or intravascular. Extravascular disruption is commonly attributed to traumatic causes. Proximal femur fractures resulting in displacement of the neck affect the basicervical arterial ring, whereas hip dislocations can disrupt the ligamentum teres and cause intracapsular hematoma, making the integrity of the extracapsular ring an important factor in the survival of the femoral head. Intravascular embolic matter such as clots, lipids, immune complexes, or sickle cells can also occlude the terminal arterioles in the subchondral bone of the femoral head[2-4,12].

Regardless of the underlying etiology of osteonecrosis, several studies suggest a common pathogenic pathway involving apoptosis of osteoblasts and osteocytes[13-15]. Following infarction, oxygen- and nutrient-deprived osteocytes and marrow cells die unless they can receive blood supply from collateral circulation. As the collateral circulation supplying the epiphyses is limited, capillary arterialization may not restore sufficient blood flow to the tissues[16]. In addition to vascular compromise and programmed cell death, defective bone repair is also a key component of osteonecrosis[17]. Adipogenesis has been shown to be a causal factor in steroid- and alcohol-related osteonecrosis, as it leads to compression of venous sinusoids and congestion. The venous congestion increases intraosseous pressure, preventing adequate arterial blood flow, eventually leading to bone infarction[18,19]. In certain cases, genetic factors, such as mutations in the *COL2A1* gene, have been associated with the pathogenesis of osteonecrosis[20].

Weight bearing during walking generates loads 2 to 3 times body weight on the anterosuperior femoral head articular cartilage and superior acetabular dome and 5 to 6 times body weight during running or jumping[21]. Ischemic disruption of the weight-bearing surface in an osteonecrotic hip significantly affects a person's ability to complete pain-free activities of daily living. Infarcted subchondral bone has trabeculae that become thinned by osteoclastic activity, and the hypoxic environment does not allow for osteoblastic repair or remodeling. The area of bone necrosis becomes surrounded by a reactive, sclerotic rim, and the weakened cancellous bone eventually fails under the repetitive loads of weight bearing, leading to subchondral fracture (the "crescent sign" on radiographs). Subchondral collapse eventually leads to articular degeneration[2,22].

DIAGNOSIS AND CLASSIFICATION

Medial thigh or groin pain with limitation of hip motion in patients less than 50 years of age should raise the suspicion of osteonecrosis. Patients usually present with slow-onset, insidious groin pain that may be unilateral or bilateral. Symptoms are generally amplified with weight bearing and relieved with rest. The pain may also be in the buttocks, knees, or anterior and lateral thigh. Range of motion becomes limited, particularly hip abduction and internal rotation, and logrolling (passive internal and external rotation) elicits pain. Early stages of the disease can often be asymptomatic, and some patients present after articular surface collapse has already occurred. Hip prognosis can be significantly improved with early diagnosis, before articular collapse[4,22].

Laboratory values such as activated partial thromboplastin time (aPTT) and prothrombin time (PT) are generally normal in hip osteonecrosis, although more extensive workup of the etiology may reveal coagulopathy or inflammatory joint disease such as SLE[23]. Plain radiographs should include anteroposterior and frog-leg lateral views of both hips, as the pathology commonly also presents in the contralateral hip. Radiographs may demonstrate normal findings (Ficat stage Ⅰ) or subchondral cyst formation and sclerosis (Ficat stage Ⅱ), but more advanced disease involves femoral head flattening and subchondral collapse, as seen with the "crescent sign" (Ficat stage Ⅲ). Osteoarthritic joint space narrowing with osteophyte formation are findings of untreated osteonecrosis (Ficat stage Ⅳ)[24] (Table 1). Radiographs are highly specific for more advanced osteonecrosis (Ficat Ⅱ or Ⅲ) but not very sensitive for early changes (Ficat Ⅰ)[3].

The advent of magnetic resonance imaging (MRI) and its widespread use gave rise to the Steinberg or University of Pennsylvania osteonecrosis classification system[22,25], which differentiates subchondral collapse from femoral head articular cartilage collapse (flattening) (Table 1). Stages Ⅰ through Ⅳ are classified by percent of

Table 1 Osteoarthritic joint space narrowing with osteophyte formation findings of untreated osteonecrosis

	System		
	Ficat/Arlet	Steinberg/U Penn	ARCO
Stage Ⅰ	Normal radiographs	Normal radiographs	Normal radiographs
Stage Ⅱ	Subchondral cyst formation and sclerosis	Femoral head lucency/sclerosis	Demarcating sclerosis in femoral head, no collapse
Stage Ⅲ	Femoral head flattening, subchondral collapse, "crescent sign"	Subchondral collapse without femoral head flattening, "crescent sign"	Femoral head collapse, "crescent sign", no joint space narrowing
ⅢA			Collapse < 3 mm
ⅢB			Collapse > 3 mm
Stage Ⅳ	Osteoarthritic joint space narrowing, degenerative changes	Subchondral collapse, femoral head flattening, normal joint space	Osteoarthritic degenerative changes
Stage Ⅴ		Flattening with joint space narrowing, acetabular changes, or both	
Stage Ⅵ		Advanced degenerative changes, secondary osteoarthritis	

ARCO: Association Research Circulation Osseous.

femoral head involvement: A < 15%, B 15%-30%, C > 30%. These size modifiers are considered predictors of femoral head collapse. Small lesion size and more medial location are considered prognostically favorable[25].

Another commonly used classification system that utilizes MRI and other radiographic modalities is the Association Research Circulation Osseous (ARCO) staging system, which was introduced in 1992 and is summarized in Table 1[26].

MRI has become the imaging modality of choice, as it is highly sensitive and specific for osteonecrosis[3]. T1 images on MRI typically demonstrate a serpiginous "band-like" lesion with low signal intensity in the anterosuperior femoral head, and a "double-line sign" can be seen on T2 sequences, which depicts a high signal intensity reparative interface of vascular reactive bone adjacent to necrotic subchondral bone[3]. Radionuclide bone scans are less sensitive and specific than MRI but can be used to detect inflammatory activity in the femoral head when MRI is contraindicated. CT is also less sensitive than MRI in detecting osteonecrosis and has a significant radiation burden. Angiography and biopsy are invasive methods to confirm osteonecrosis and therefore are only used as research modalities[25,27].

CURRENT TREATMENT OPTIONS

Non-operative treatments for osteonecrosis include measures to offload force on the affected hip by limiting weight bearing with a cane or walker, activity modification, and physical therapy. However, these methods have no role in treatment of late stage osteonecrosis and show limited success in preventing disease progression, even in early stage (Steinberg stage Ⅰ and Ⅱ) disease[9,28]. Patients can be encouraged to abstain from or decrease alcohol consumption and smoking[29]. Other conservative options include lipid-reducing agents, bisphosphonates, and hyperbaric oxygen, but these therapies have minimal utility after subchondral collapse has occurred in the femoral head, as seen in a meta-analysis when compared with core decompression[30].

Core decompression is a commonly used prophylactic surgery used in pre-collapse osteonecrosis (prior to Ficat and ARCO stage Ⅱ, Steinberg stage Ⅲ), in which necrotic cancellous bone in the femoral head is drilled and removed from a lateral femoral cortical entry point (Figure 1). This is often stabilized with structural allograft or with autograft by harvesting cancellous bone from the greater trochanter and proximal femur. This cancellous graft contains osteoprogenitor cells that aid in healing. The results for core decompression alone generally deteriorate with more advanced lesions[27]. However, augmentation of the core decompression can be achieved with the addition of bone morphogenic proteins, electromagnetic stimulation, or demineralized bone matrix[27,31]. Although core decompression for Steinberg stage I disease was successful as a definitive procedure in > 80% of patients, Steinberg stage Ⅱ and Ⅲ osteonecrosis treated with decompression required further surgical reconstructive intervention in 37% and 71% of patients, respectively[28,30]. Multiple drilling of the femoral head osteonecrotic lesion can be an alternative, and comparable results have been reported[32]. Another biologic option that has met with some success is the harvesting and *in vitro* culture of autologous mesenchymal stem cells (MSCs) and reimplantation in the core decompression site[33,34]. Studies of the long-term success of using bone morphogenic proteins and autologous MSCs are still underway[35].

Vascularized fibular graft supplementation during core decompression and other salvage procedures has also been studied extensively and implemented for higher stages of osteonecrosis. These grafts deter progression of pre-collapse (Steinberg stage Ⅰ and Ⅱ) lesions and can also delay the development of end stage osteonecrosis after mild collapse (Steinberg stage Ⅲ through Ⅴ) has occurred. The cortical graft not only offers structural stability, but also biologic incorporation, as the vascularized bone promotes callus formation and remodeling in the femoral head[36-39]. Although certain methods such as the patient-specific Ioannina aiming device increase optimal graft placement in the anterosu-

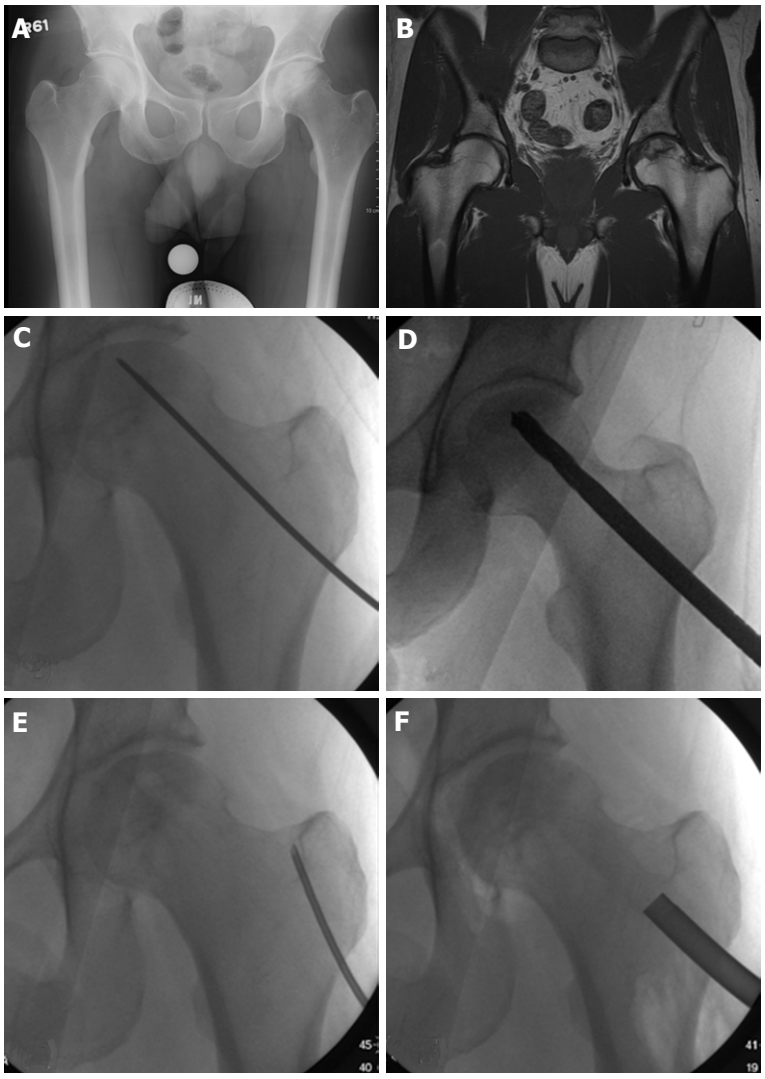

Figure 1 Forty-one year old male with pre-collapse osteonecrosis of left femoral head as evidenced by (A) plain radiograph and (B) magnetic resonance imaging of pelvis. Patient underwent core decompression: (C) Kirschner wire to localize to affected subchondral bone; D: Drilling of lesion; E: Aspiration of bone marrow from cancellous bone in greater trochanter; F: Insertion of bone graft mixed with bone marrow aspirate.

perior aspect of the femoral head, vascularized grafting still remains technically challenging[40]. Non-vascularized fibular grafts have also been studied as an alternative, but vascularized grafts appear to have better clinical results for prevention of femoral head collapse[41].

Several osteotomies have been studied for the treatment of pre-collapse and early post-collapse (Steinberg stage II to IV) osteonecrosis, with the goal of transferring weight-bearing forces away from necrotic subchondral bone toward other areas of the articular surface. These include flexion, extension, varus, valgus, rotation, or combined osteotomies, and subtrochanteric and intertrochanteric osteotomies have also been described[42-45]. These procedures have met with favorable success rates but can have a moderate risk of nonunion, and they can make conversion to total hip arthroplasty more difficult.

The emergence of hip arthroscopy has improved surgeons' ability to visualize and quantify or stage the degree of chondrosis in osteonecrosis[46]. Small-diameter core decompression has been described as an arthroscopic procedure for early stages[47], but arthroscopy is not considered an effective option to treat advanced osteonecrosis.

Advanced osteonecrosis with significant arthrosis is commonly treated with prosthetic replacement, including femoral resurfacing arthroplasty, hemiarthroplasty, and THA. THA has excellent clinical results for pain relief and functional improvement, but these reconstructive arthroplasties in young patients can be problematic, as they are often associated with early failure from loosening and other complications[48-51].

Femoral resurfacing can be used in younger patients with osteonecrosis involving less than one third of the femoral head, and this arthroplasty option has been studied and used more outside of the United States. Technical issues with these implants have been associated in the past with femoral neck fracture, high failure rate, and conversion to THA[48,52]. Newer designs and uncemented implants have yielded more favorable results, but other complications such as ionic metal wear in metal-on-

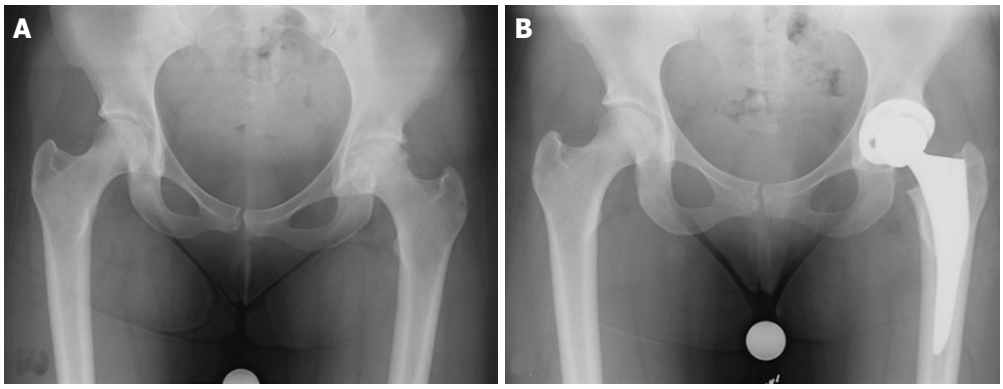

Figure 2 Forty-eight year old female with osteonecrotic left femoral head, with evidence of left hip osteoarthritis (A). Patient underwent left uncemented total hip arthroplasty (B).

metal implants can still occur[53]. Hemiarthroplasty with unipolar or bipolar implants have been utilized but by design do not address pathology at the acetabular surface in late-stage osteonecrosis and are also associated with wear, loosening, groin pain, and conversion to THA[48]; therefore hemiarthroplasty is not recommended.

Ultimately, advanced osteonecrosis and failure of the other aggressive interventions mentioned above may necessitate total hip arthroplasty. THA is the most commonly performed procedure for Ficat and ARCO stage Ⅲ and Ⅳ (Steinberg stage Ⅳ to Ⅵ) osteonecrosis and is highly successful for symptomatic improvement[49,50] (Figure 2). The durability of THA, however, is inferior to the same procedure performed for osteoarthritis, as patients with osteonecrosis are generally younger and have higher functional demands[54]. Associated comorbidities such as alcohol abuse and inflammatory disorders associated with steroid use such as SLE may also contribute to the inferior outcomes. Cemented THA has been documented to have higher complication rates relative to cementless prosthesis with improved modern press-fit designs[55]. THA complications in osteonecrosis include infection (particularly in SLE, sickle cell, and immunocompromised patients), high risk of dislocation (notably in alcohol abusers), compromise in soft tissue healing, and implant loosening. Despite these risk factors and potential complications, however, modern advancements in hip arthroplasty over the past decade have improved outcomes of THA in osteonecrosis, as seen in a recent meta-analysis by Myers *et al*[51].

In summary, there are several pre-collapse treatment options available for symptomatic osteonecrosis; however, the majority of patients progress to advanced stages with articular collapse, requiring total hip arthroplasty. The future of osteonecrosis treatment depends on finding alternative joint-sparing procedures and treatments to delay the need for hip arthroplasty. Basic science and clinical research in this field over the past decade has focused on developing animal models to understand pathophysiologic mechanisms, as well as testing novel growth factor- and cell-based therapeutic options that may prevent or postpone the progression of osteonecrosis.

UPDATE ON BENCH RESEARCH AND CLINICAL APPLICATIONS

As the research and development of new osteonecrosis treatments are continuously being explored, one of the limiting factors that prevents the systemic evaluation of the effectiveness of the treatments is the lack of an animal model that replicates the natural history and progression of osteonecrosis in humans. Nevertheless, several animal models have been developed to evaluate various treatment strategies. Vascular damage is a crucial event in trauma-induced osteonecrosis, and many animal models have attempted to mimic this injury by surgically inducing vascular deprivation. A rat osteonecrosis model in which the femoral head is temporarily dislocated after the ligamentum teres is cut is the most common surgical osteonecrosis model[56-58]. An adult rabbit model of traumatic osteonecrosis has been established by complete surgical removal of the hip joint capsule followed by circumferential cauterization of the periosteum and blood vessels covering the femoral neck to interrupt the blood supply to the femoral head[59]. Cryogenic and thermal insults have been used to induce osteonecrosis in quadrupeds such as canines[60] and bipeds such as emus[61]. Intramuscular injection of methylprednisolone has been used to develop steroid-induced osteonecrosis in mouse[62], rat[63], rabbit[64,65], pig[66], and chicken models[18], where the percent incidence of induced osteonecrosis is dependent on the amount of methylprednisolone injected. These animal models have been used to study the molecular mechanisms of osteonecrosis and assess the usefulness of several therapies over the last few decades.

Some of the more recent efforts in treatment development have focused on the use of cellular therapies for osteonecrosis. In one study, CD34+ cells, known to be both vasculogenic and osteogenic, were intravenously transplanted after G-CSF mobilization in a rat model, resulting in improved outcomes[67]. Since it has been reported that MSC proliferation is affected during

osteonecrosis[68], several studies have attempted to treat osteonecrosis by transplanting MSCs either systemically or locally in various animal models. Li *et al*[69] investigated the efficacy of giving allogeneic MSCs derived from the bone marrow to rabbits with heat-induced femoral head necrosis and showed the directional migration of GFP-labeled MSCs to the defect site. Yan *et al*[70] showed that transplanted MSCs differentiated into osteoblasts and aided in the repair process of traumatic osteonecrosis in a skeletally mature canine model. Another recent study evaluated the effectiveness of biphasic calcium phosphate (BCP) ceramic scaffolds seeded with MSCs on inducing osteointegration and new bone formation in a canine model[71]. These studies indicate the efficacy of exogenous stem cells in osteonecrosis treatment. Early trials outside the United States have also utilized MSCs in humans and preliminarily show good results. For instance, the percutaneous injection of autologous adipose-derived MSCs with hyaluronic acid, platelet-rich plasma, and calcium chloride demonstrate MRI evidence of improvement in osteonecrosis and cartilage regeneration[72]. However, this is an uncontrolled clinical trial, and further study is needed.

Another branch of osteonecrosis research has focused on the effectiveness of bisphosphonates, growth factors, lipid-lowering agents, and combined drug therapies. Lipid-lowering drugs such as statins decrease the incidence of steroid-induced osteonecrosis[73,74]. Other studies have also shown that the simultaneous use of anticoagulants along with lipid-lowering agents can decrease the prevalence of steroid-induced osteonecrosis in rabbits[75,76]. Bisphosphonates, used regularly for the treatment of osteoporosis and other pathologic conditions of bone, have been found to be promising for clinically treating osteonecrosis to postpone surgical interventions[77]. Lai *et al*[78] developed a randomized study that showed that alendronate delays or prevents progression of femoral head collapse in Steinberg stage Ⅱ and Ⅲ disease, and may ultimately reduce the need for joint arthroplasty, although longer term follow-up was needed. Agarwala *et al*[79] showed that a daily dose of alendronate resulted in improved hip function and decreased dependency on nonsteroidal antiinflammatory drugs over a period of 2.5 years. In addition, there was decreased femoral head edema on MRI, suggesting slower progression of osteonecrosis. Along with preservation, it is crucial that the bone undergoes remodeling during osteonecrosis. While bisphosphonates have been known to do the former, Vandermeer *et al*[80] show that combining these drugs with bone morphogenetic protein-2 improved the epiphyseal quotient and trabecular bone remodeling in immature pigs that had surgically-induced ischemic ON. The impact of such combination drug therapies is yet to be fully evaluated in human subjects.

On the surgical forefront, clinical studies have scrutinized older techniques and evaluated novel techniques for treatment of osteonecrosis. Transtrochanteric rotational osteotomy has historically demonstrated variable success for avoidance of femoral head collapse[43,45,81]. Exploration of the risk factors revealed that higher age, higher BMI, and higher stages of osteonecrosis were determinants of likelihood of conversion of osteotomies to THA[82]. These factors can be useful during patient selection for joint-sparing procedures. Advancements in hip resurfacing have made this procedure a viable option in younger patients under the age of 25 years and can help reduce the need for THA, but there are still risks of ionic wear, fracture, and loosening[83]. Total hip arthroplasty itself has undergone technical improvements over the last two decades, and implant survival is significantly higher. Uncemented ceramic-on-ceramic THA has demonstrated some promise for improved outcomes and implant durability in younger patients[84].

Improvements in microsurgical techniques have enhanced outcomes for free vascularized fibula grafting to the osteonecrotic hip. This procedure has been shown to be successful for younger patients in pre-collapse stages and generally delays the need for THA, even in post-collapse osteonecrosis[85]. Other grafting techniques, such as bone graft pedicled with quadratus femoris in a titanium mesh, have also been developed, but long-term effectiveness has not yet been studied[86]. Augmentation of core decompression with porous tantalum rods has also been explored as a treatment method for early stages of osteonecrosis, with some favorable results; however, the release of high-density metal particles as well as progression to femoral head collapse are frequent complications[87]. Other clinical trials involving the use of trabecular metal rods[88] and mesh cages[86] have also been published.

CONCLUSION

Osteonecrosis is a pathology commonly seen in younger adults, in which collapse of the femoral head and early onset of osteoarthritis may eventually necessitate hip arthroplasty when non-operative measures and joint-sparing procedures fail. Basic science research to understand the pathophysiology and to develop therapies that can be translated to clinical application has progressed rapidly, and these advances offer great promise for the future treatment of osteonecrosis. Similarly, technological improvements in surgical treatment methods have also improved outcomes over the past two decades and will continue to help patients recover from this functionally debilitating joint disease.

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