Journal of Orthopaedic Translation 51 (2025) 256–277

Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

Review Article

Hip joint-preserving strategies for treating osteonecrosis of the femoral head: From nonoperative to operative procedures

Tanqiu Qi [a], Yan Yan [b,c], William Qi [d], Weiheng Chen [b,c,*], Haisheng Yang [a,**]

[a] Department of Biomedical Engineering, College of Chemistry and Life Science, Beijing University of Technology, Beijing, China
[b] Department of Orthopaedics, The Third Affiliated Hospital of Beijing University of Chinese Medicine, Beijing, China
[c] Engineering Research Center of Chinese Orthopaedic and Sports Rehabilitation Artificial Intelligent, Ministry of Education, Beijing, China
[d] School of Engineering and Applied Sciences, University of Pennsylvania, Philadelphia, United States

ARTICLE INFO

Keywords:
Bone graft
Core decompression
Hip-joint preservation
Osteonecrosis of the femoral head
Tissue engineering
Treatment

ABSTRACT

Osteonecrosis of the femoral head (ONFH) has an exceedingly high prevalence and disability rate, causing a tremendous socioeconomic burden. The prevalence of ONFH is increasing, while the population of the patients with ONFH is becoming younger. Once the femoral head collapses, treatment becomes difficult and often requires a hip joint replacement, which is not favorable for young patients. Therefore, hip joint-preserving treatments at an early stage of ONFH are particularly important. This study provides a comprehensive review on hip-preserving strategies for treating ONFH, including nonoperative treatments (e.g., protective weight bearing, hyperbaric oxygen, pulsed electromagnetic, extracorporeal shockwave, bisphosphonate, anticoagulants, hypolipidemics, vasodilators, and traditional Chinese medicine) and operative treatments (e.g., core decompression, osteotomy, bone grafting, mesenchymal stem cell transplantation, tantalum rods, and tissue engineering). Nonoperative treatments aim to slow down the progression of the disease and delay the need for joint replacement; however, they usually cannot effectively prevent the progression of the disease, except in cases of small necrosis areas (<10 %). Additionally, nonoperative treatments have unclear mechanisms that require further investigation. In contrast, operative treatments may stop the negative outcomes of necrosis and therefore appear to be more promising. Currently, an emerging area in operative treatments is regenerative medicine, which could promote the generation of bone tissues and blood vessels and restore hip joint function to pre-necrotic levels as much as possible. This review seeks to not only provide an important reference for clinicians when choosing appropriate strategies for treating ONFH but also offer certain guidance for future basic research in developing ONFH treatments.

The translational potential of this article: The incidence of ONFH is increasing, and patients are becoming younger on average. Therefore, the development of hip joint-preserving strategies to treat ONFH at earlier stages is urgently needed, particularly for young patients. However, a comprehensive review is lacking regarding the currently-available hip joint-preserving strategies and their effectiveness. This study is motivated to fill this gap and serve as an important reference for clinicians in choosing appropriate strategies to treat ONFH.

1. Introduction

As a highly vascularized tissue, the growth, remodeling and regeneration of bone depend on its vasculature. Destruction of the blood supply system in the femoral head leads to osteonecrosis of the femoral head (ONFH), also known as avascular necrosis [1]. ONFH is a disease that presents considerable challenges in management and is characterized by an exceedingly high rate of clinical disability [2]. Local ischemia due to compromised blood flow is the final common pathway in the pathogenesis of ONFH, except in radiation-induced osteonecrosis [3]. At

* Corresponding author. Department of Orthopaedics, The Third Affiliated Hospital of Beijing University of Chinese Medicine, No.51 Xiaoguan Street, Anwai, Chaoyang District, Beijing, China.
** Corresponding author. Department of Biomedical Engineering, College of Chemistry and Life Science, Beijing University of Technology, 100 Pingleyuan, Chaoyang District, Beijing, China.
E-mail addresses: Qitanqiu@emails.bjut.edu.cn (T. Qi), yanyan_1029@163.com (Y. Yan), willqi@seas.upenn.edu (W. Qi), drchenweiheng@bucm.edu.cn (W. Chen), haisheng.yang@bjut.edu.cn, yhs267@foxmail.com (H. Yang).

https://doi.org/10.1016/j.jot.2025.02.001
Received 18 July 2024; Received in revised form 8 January 2025; Accepted 5 February 2025
Available online 19 March 2025

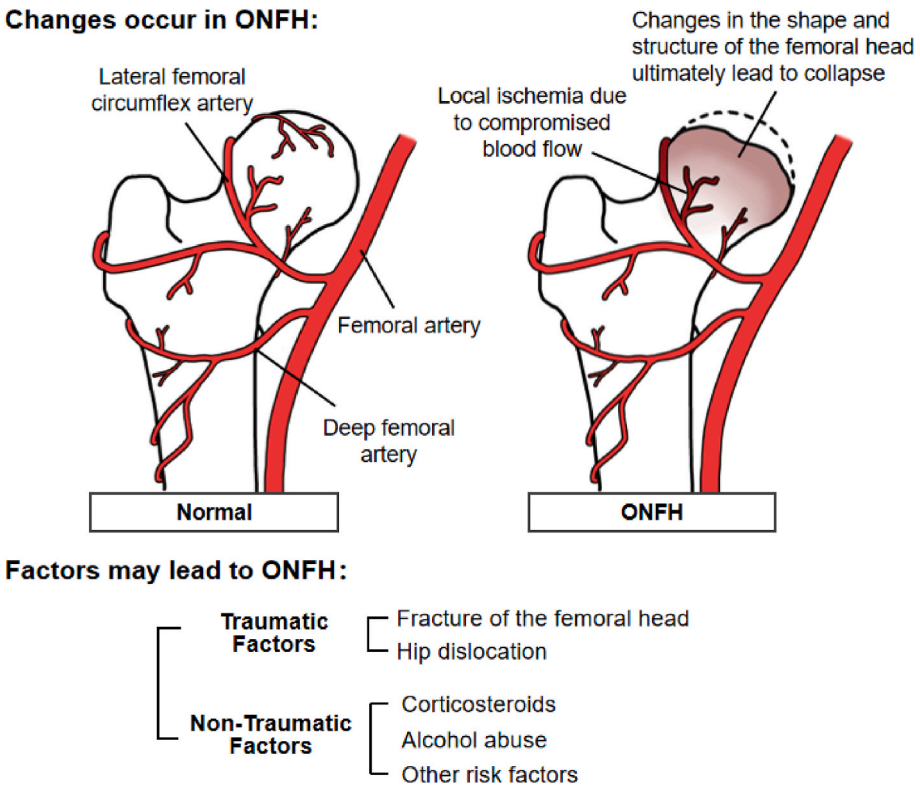

Fig. 1. Pathological changes and risk factors for osteonecrosis of the femoral head (ONFH).

the early stages of ONFH, tissue damage occurs due to ischemia and hypoxia, resulting in the death of bone cells and structural deterioration within the femoral head [4]. As the disease progresses, changes in the shape and structure of the femoral head culminate in its collapse, which may also lead to osteoarthritis [4,5]. When the necrotic region is located in the load-bearing area, the collapse of the femoral head may be accelerated. ONFH has numerous etiologies, which are primarily divided into traumatic and non-traumatic causes. Corticosteroid use and excessive alcohol intake are associated with more than 80 % of the ONFH cases [1]. Risk factors interact, collectively contributing to the development of ONFH (Fig. 1).

The prevalence of ONFH is increasing, although it is unclear whether this represents a true increase or is due to heightened awareness and diagnostic advancements [1]. ONFH is one of the major sequelae of SARS, and similarly, COVID-19 may also result in ONFH [6–8]. Statistics show that the incidence of ONFH in males is about three times higher than in females, with bilateral ONFH occurring in up to 75 % of cases [9]. Asian populations appear to be more susceptible to developing avascular necrosis; in China, the number of new cases per year is estimated at 75,000 to 150,000, with around 8.12 million patients suffering from nontraumatic osteonecrosis [2,10]. Nationwide surveys in Japan and South Korea have reported an annual prevalence of over 10,000 cases [9]. In the United States, new cases of ONFH are estimated to be between 20,000 and 30,000 cases per year, primarily affecting young adults aged 20–40 years [11,12].

ONFH has a high disability rate, and if not treated promptly, it can rapidly progress to femoral head collapse. Total hip arthroplasty (THA) is the most commonly performed surgical procedure to treat ONFH [13]. However, younger patients are often reluctant to undergo THA. For those who do accept THA, the limited lifespan of the prosthetics may necessitate multiple replacements and revision surgeries [14,15]. It is predicted that THA revisions will increase by 137 % from 2005 to 2030. This not only subjects patients to repeated physical trauma and financial burdens but may also result in disability due to delayed diagnosis and intervention, further exacerbating the societal and familial burden. Consequently, there is a growing trend toward developing and utilizing hip joint-preserving procedures for treating ONFH [16]. This underscores the need for a comprehensive overview of current hip joint-preserving strategies.

Although there are similar review articles on the topic of hip joint-preserving treatments for ONFH (see appendix Tab. S1), 1) most of them only focus on individual treatment methods, with no comprehensive review covering all hip joint-preserving approaches, 2) there is little comparison across different hip joint-preserving approaches, making the selection of specific techniques difficult, 3) traditional Chinese medicine (TCM) has largely been ignored, 4) the developmental trends of hip joint-preserving methods remain unclear. In this review, we comprehensively summarize clinical and preclinical hip-preserving strategies for the treatment of ONFH, including nonoperative treatments (e.g., biophysical therapy, pharmacological therapy and traditional Chinese medicine) and operative treatments (e.g., basic surgery and regenerative techniques) (Fig. 2). These procedures are designed with appropriate treatment strategies to target the specific pathogenesis of ONFH (Fig. 3). We also compare the advantages and disadvantages of each therapy. Since the clinical use of traditional Chinese medicine has been gradually increasing in recent years, we provide a detailed introduction to this treatment, including herbal medicine and acupuncture. In addition, we summarize trends in preclinical and clinical studies on the topic of hip joint-preserving procedures. This review aims to serve as an important reference for clinicians in selecting appropriate strategies for treating ONFH and to provide insights for future basic research.

2. Nonoperative treatment

Nonoperative treatment is primarily used for early-stage ONFH, where the lesion is small and the femoral head has not yet collapsed, and there is good potential for repair [1]. Nonoperative treatments are mainly divided into three categories: biophysical therapy, pharmacological therapy and traditional Chinese medicine. These therapies aim to improve blood supply and bone formation within the femoral head [17].

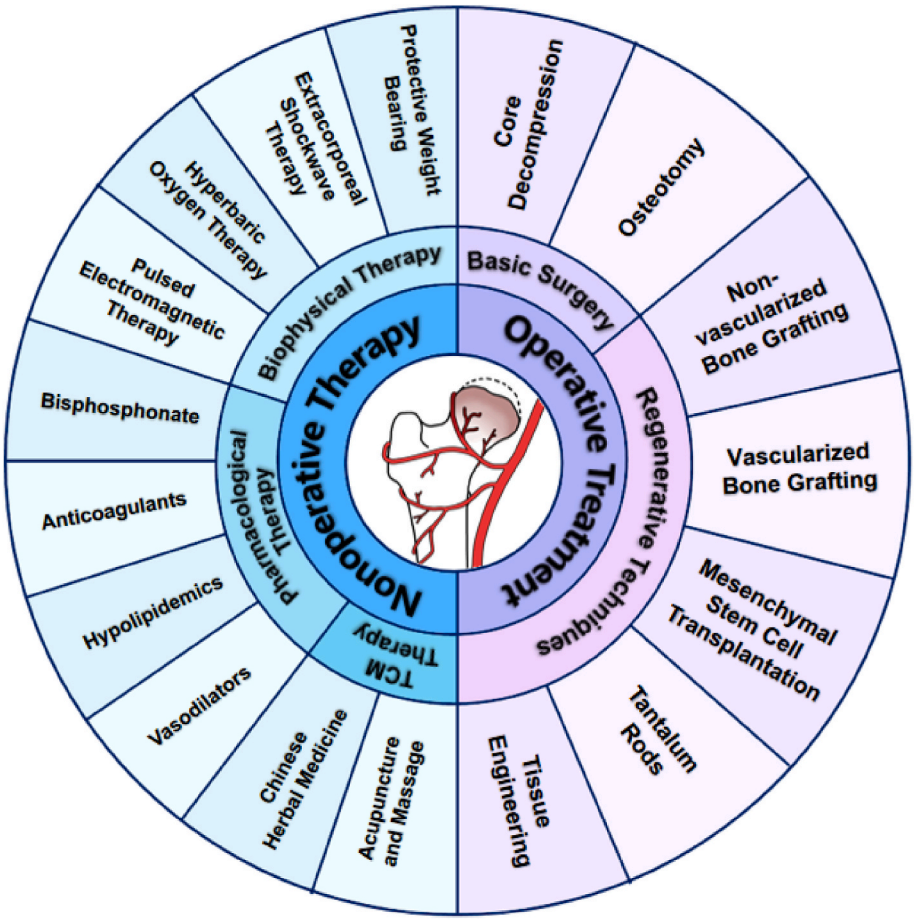

Fig. 2. Hip joint-preserving strategies for treating osteonecrosis of the femoral head.

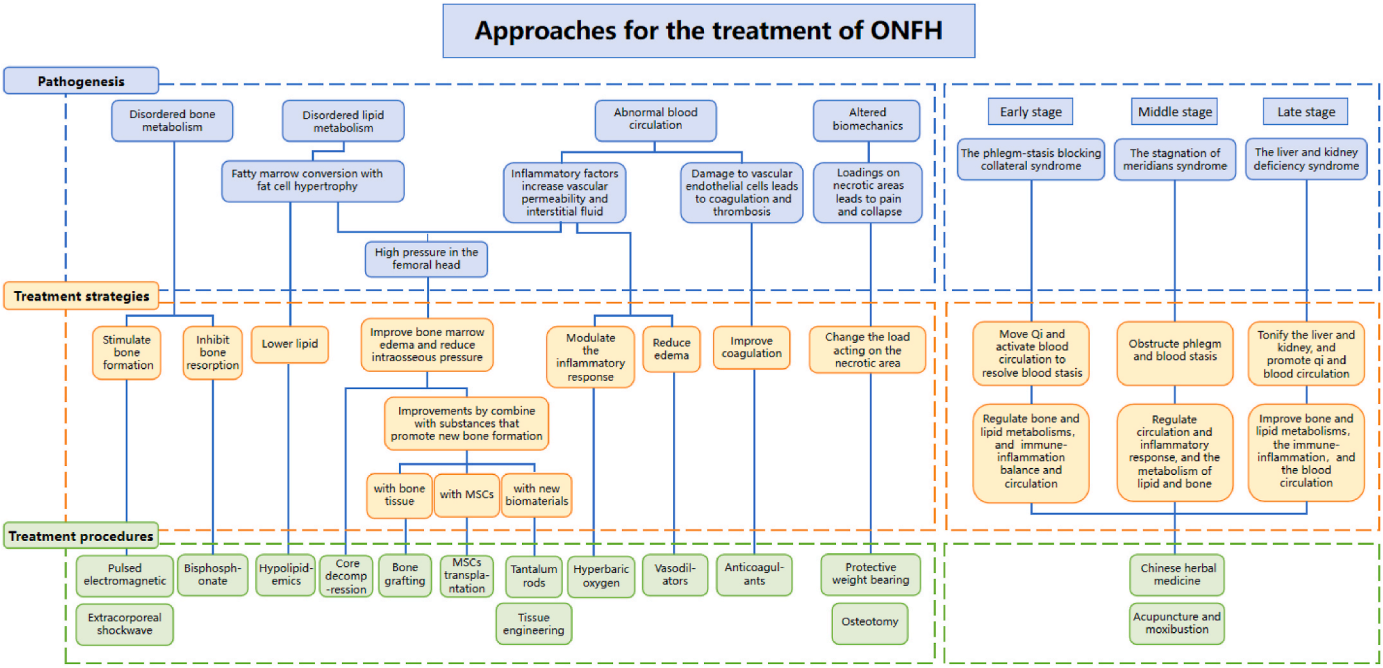

Fig. 3. To treat osteonecrosis of the femoral head (ONFH), various procedures have been developed with different treatment strategies to target specific pathogenesis of the ONFH.

Table 1
The indications, contraindications, and side effects of each nonoperative therapies.

	Treatment	Mechanism	Drugs	Indications	Contraindications	Adverse reactions
Biophysical Therapy	**Protective Weight Bearing** [2,19–22]	Reduces weight on the necrotic area	—	Children with LCPD or all ONFH stages; after hip-joint preservation surgery with limited weight-bearing but not wheelchair use.	—	—
	Hyperbaric Oxygen Therapy [23–29]	Enhances reactive oxygen and nitrogen species production, promotes cell growth, and modulates the inflammatory response.	—	Traumatic ischemia, necrotic soft tissue injury, radiation-induced osteonecrosis	a) Absolute contraindications: Untreated pneumothorax, mediastinal emphysema, pulmonary bullae, active internal bleeding and hemorrhagic diseases, formation of tuberculous cavities and hemoptysis b) Relative contraindications: severe upper respiratory tract infection, severe emphysema, bronchiectasis, severe sinusitis, second degree or higher atrioventricular block, high blood pressure (systolic blood pressure ≥160, diastolic blood pressure ≥100 mmHg), bradycardia (<50 beats/minute), untreated malignant tumors, retinal detachment, early pregnancy (within 3 months)	Equalization disorders in the middle ear, barotraumatic lesions, O_2 toxicity, confinement anxiety, and visual effects
	Pulsed Electromagnetic Therapy [30–34]	Induces mechanical strain via the converse piezoelectric effect, stimulating osteogenesis (Wolff's law) and chondrocyte activity.	—	Early avascular necrosis, and ONFH patients with local osteoporosis or decreased bone mass	a) Patients with implantable pacemakers, implantable brain nerve stimulators, or cardiac stents b) Patients who have implanted iron containing metal implants in their bodies c) Patients with tumors, high fever, angina pectoris, severe heart, liver, lung, and kidney failure, acute bleeding or bleeding tendency, or white blood cell count below 4000/cm^3 d) Pregnant women and children	No significant side effects have been reported yet
	Extracorporeal Shockwave Therapy [35–38]	Generates significant velocity and pressure within the femoral head, producing a certain mechanical stimulation that leads to secondary tissue repair	—	Early-stage adult femoral head necrosis without femoral head collapse (ARCO stages I and II). Relative indications: ARCO stage III and some stage IV femoral head necrosis patients who are unwilling or unable to undergo surgery; ONFH patients with traumatic arthritis of the hip joint; patients with hip socket fractures and femoral head fractures who may experience femoral head blood circulation disorders	a) Absolute contraindications: Abnormal coagulation function, presence of blood clots in the treatment area, severe cognitive impairment, and patients with mental illness b) Relative contraindications: Severe arrhythmia, severe hypertension and poor blood pressure control, pacemakers, multiple metastases of malignant tumors, pregnant women, sensory dysfunction, acute gout attacks c) Except for systemic contraindications, there may be acute soft tissue	Transient pain after treatment, dysesthesia, swelling, ecchymosis and/or petechiae, severe headache, bruising and a throbbing sensation

(*continued on next page*)

Table 1 (*continued*)

	Treatment	Mechanism	Drugs	Indications	Contraindications	Adverse reactions
					infection or skin damage in the local treatment area	
Chemotherapy Therapy	**Bisphosphonate** [39–46]	Inhibit bone resorption and increase osteogenesis	Alendronate sodium Zoledronate	ONFH patients with local osteoporosis or decreased bone mass; femoral head collapse prevention	a) Patients with renal dysfunction and osteomalacia are prohibited from using it b) Pregnant women, breastfeeding women, adolescents and children, as well as those with hypocalcemia and allergies to this product, are prohibited from using it	Increased risk of atypical femur fractures, osteonecrosis of the jaw, gastrointestinal side effects, or atrial fibrillation; Oral administration of bisphosphonates may cause adverse reactions such as esophagitis, esophageal ulcers, and esophageal erosion, with rare cases of esophageal stenosis
	Anticoagulants [47–52]	Reduce the formation of microthrombi, lower intraosseous venous pressure, improve blood circulation reverse hypoxia, reduce bone cell death, promote bone healing and bone repair	Heparin: low molecular weight heparin and enoxaparin Vitamin K antagonists: warfarin and coumarin Cyclooxygenase inhibitors: aspirin	Patients with primary ONFH or ONFH induced by corticosteroids	a) Organ damage with a risk of bleeding b) Allergic to heparin, low molecular weight heparin, and their derivatives c) Patients with a history of thrombocytopenia associated with the use of low molecular weight heparin d) Postpartum hemorrhage and severe liver and kidney dysfunction e) Patients with severe hypertension, severe traumatic brain injury, and acute infective endocarditis	Bleeding can occur in any part of the body; an increase in systemic arterial calcification allergic reactions such as chills, fever, urticaria, etc.
	Hypolipidemics [53–56]	Raise adiponectin levels, inhibit osteoclast activity, increase osteoblast activity	Statins: Pravastatin, Simvastatin, Lovastatin	ONFH patients receiving systemic steroid therapy and ONFH patients with concomitant hyperlipidemia	a) Individuals allergic to statins b) Patients with active liver disease c) Patients with severe renal dysfunction; d) Muscle disease patients e) Patients who use cyclosporine simultaneously f) During pregnancy, lactation, and women who may become pregnant but have not used appropriate contraceptive measures	Long-term use of statins may damage the liver; Neuromuscular side effects that represent about two-third of all adverse events, including cramps, myalgia, weakness, immune-mediated necrotizing myopathy and, more rarely, rhabdomyolysis; Headache, nausea, slight increase in blood sugar levels, muscle and joint pain
	Vasodilators [57–61]	Lower intraosseous venous pressure, improve blood circulation reverse hypoxia, reduce bone cell death, promote bone healing and bone repair	Prostaglandin Eloprost Iloprost	Patients with early-stage ONFH, especially those with bone marrow edema	a) Organ damage with a risk of bleeding; b) Allergic to heparin, low molecular weight heparin, and their derivatives c) Patients with a history of thrombocytopenia associated with the use of low molecular weight heparin d) Postpartum hemorrhage and severe liver and kidney dysfunction e) Patients with severe hypertension, severe traumatic brain injury, and acute infective endocarditis	Fever and headache, gastrointestinal reactions such as nausea, vomiting, abdominal pain, and diarrhea; serious adverse events include congestive heart failure, supraventricular tachycardia, and renal failure
Traditional Chinese Medicine	**Chinese Herbal Medicine** [62–65]	Invigorate blood and tonify the kidneys, resolve blood stasis and relieve pain	Chinese herbal medicine for promoting blood circulation, removing blood stasis, tonifying kidney and strengthening bones	Patients with ARCO stages I-II, small necrosis area, and no anterolateral femoral head involvement; can be used as a supplementary therapy throughout	a) Patients with liver and kidney dysfunction b) Pregnant and lactating women, as some Chinese medicines with blood activating effects may cause miscarriage or affect milk secretion.	May irritate the gastrointestinal tract, causing discomfort symptoms such as nausea, vomiting, diarrhea, and abdominal pain; may damage liver and kidney function and

(*continued on next page*)

Table 1 (*continued*)

	Treatment	Mechanism	Drugs	Indications	Contraindications	Adverse reactions
				the course of ONFH treatment		requires regular monitoring of the patient's liver and kidney function.
	Acupuncture and Moxibustion [66–71]	Promote blood circulation, improve hip joint circulation, and alleviate muscle cramps	—	Patients with early-stage ONFH	Patients with infectious diseases, such as colds, skin sores, ulcers, etc. Patients with hemorrhagic diseases Pregnant women and infants	Needle sickness and infection

Table 2
Comparison of joint hip-preservation nonoperative treatments.

	Treatment	Advantage	Disadvantage	Applicable people
Biophysical Therapy	**Protective weight bearing** [21,22,72,73]	Can effectively relieve pain and delay the occurrence time of femoral head collapse (controversy still exists)	Cannot stop the progression of ONFH	Suitable for all stages and is usually used in combination with other procedures
	Hyperbaric Oxygen Therapy [26–28]	① Can enhance the reactive oxygen species and reactive nitrogen species production, promote cell growth, and modulate inflammatory response ② Can improve vascularization and post-ischemic tissue survival	① Most research focuses on Asian populations ② High treatment costs and limited feasible institutions	Early stage ONFH or as an adjuvant therapy for other methods
	Pulsed Electromagnetic Therapy [31,32,77]	Can effectively relieve pain and protect the hip joint	The therapeutic effect is limited and can only treat patients with small necrotic areas	PEMF may play a role in managing early avascular necrosis
	Extracorporeal Shockwave Therapy [35–38]	Can effectively alleviate joint pain caused by ONFH, and improve hip joint function	The therapeutic effect is limited and can only treat patients with small necrotic areas	For patients in the early stage of ONFH
Chemotherapy Therapy	**Bisphosphonate** [39–46]	Can inhibit osteoclast activity and improve bone mineral density in the femoral head	① No significant efficacy has been observed in the treatment of ONFH in clinical studies ② The results of animal experiments do not match clinical results ③ There have been reports of serious adverse reactions	For early to mid-stage patients who are unable to receive other treatment or as an adjunctive medication to other treatment
	Anticoagulants [47–52]	Can relieve the spread of blood clots and promote dissolution, thereby reducing ischemic conditions in the femoral head and relieving high pressure due to vascular obstruction	① Limited clinical data ② Its therapeutic effect is limited	Have a positive effect against primary ONFH (Ficat stage I or II) before collapse, but cannot provide protection against secondary ONFH
	Hypolipidemics [53–56]	① Can inhibit certain inflammatory mediators, regulate cartilage homeostasis, promote bone formation, and increase bone density ② Can prevent ONFH caused by high-dose steroids	① Limited clinical data ② Long-term use of statins may damage the liver	For patients using high-dose steroids or as an adjunctive medication to other treatment
	Vasodilators [57–61]	① Can improve local circulation and reduce blood pressure by promoting vasodilation ② Can reduce edema and improving painful symptoms	Its therapeutic effect is limited and generally cannot be used alone	For patients with bone marrow edema or as an adjunctive medication to other treatment
Traditional Chinese Medicine	**Chinese Herbal Medicine** [62–65]	Can improve local blood circulation and promote bone repair by regulating the overall state of the body	Most of the studies were localized in China and larger studies are needed to confirm its efficacy	As an adjuvant therapy suitable for all stages of ONFH
	Acupuncture and Moxibustion [66–71]	Can activate menstrual channels, regulate qi and blood, and nourish the internal organs, eventually enhance body function	Most of the studies were localized in China and larger studies are needed to confirm its efficacy	For early to mid-stage patients who are unable to receive other treatment or as an adjunctive medication to other treatment

Biophysical therapy includes protective weight bearing, hyperbaric oxygen, pulsed electromagnetic fields and extracorporeal shockwave therapy. Except for protective weight bearing, which remains controversial regarding its outcomes in treating ONFH, the other methods have demonstrated improvements in hip function and pain relief at early stages of ONFH. Pharmacological therapy mainly involves bisphosphonates, anticoagulants, hypolipidemics, and vasodilators. Among these, bisphosphonates are the most widely used in clinical practice. However, their efficacy has been questioned [18]. Traditional Chinese medicine has gained popularity in recent years due to its fewer side effects and its applicability throughout the entire course of ONFH treatment [19].

Nonoperative treatment requires strict adherence to indications during its application (Table 1) and could positively delay femoral head necrosis, collapse, or the need for THA. However, due to its limited efficacy, nonoperative treatment is often used in combination with other treatment modalities. Despite its limitations, nonoperative therapies are still being widely used for patients who are economically disadvantaged, unwilling to undergo surgery, or unable to undergo surgery since they play a positive role in delaying femoral head collapse. Different nonoperative hip joint-preserving treatments have their own advantages and disadvantages (Table 2), which should be taken in to account during clinical application.

2.1. Biophysical therapy

2.1.1. Protective weight bearing

Standing or walking may induce high stresses in the necrotic area, predisposing it to trabecular microfractures and leading to femoral head collapse (Fig. 3 and Table 1) [20,21]. Protective weight bearing can effectively relieve pain and delay the time to femoral head collapse (Table 2) [2]. An early study showed that, following non-weight-bearing therapy, only 22.7 % of patients achieved a satisfactory clinical outcome (Harris Hip Score [HHS] of >80 points), with no significant difference in the success rates between full weight-bearing, partial weight-bearing, and non-weight-bearing groups [72]. Other studies also found that this therapy has no effect on preventing the progression of ONFH [73]. However, a meta-analysis involving 813 patients (1025 hip joints) showed that protective weight bearing could achieve satisfactory results in terms of THA rates, collapse rates, HHS, and Visual Analog Scale (VAS) scores [75]. Currently, protective weight bearing is used in conjunction with other operative treatments and is rarely employed alone in clinical practice. Additionally, this treatment has been used as an adjunctive therapy for children with Legg-Calvé-Perthes disease (LCPD), reducing the probability of femoral head deformity [22,23].

From the perspective of bone mechanobiology and Wolff's law, a decrease in mechanical loading through protective weight bearing can increase bone resorption, potentially accelerating the formation of the crescent sign and increasing the risk of femoral head collapse. Conversely, from a biomechanics viewpoint, non–weight-bearing reduces mechanical forces acting on the femoral head, potentially decreasing the risk of its collapse. Thus, the role of protective weight bearing in ONFH remains paradoxical and requires further mechanistic investigation.

2.1.2. Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is a treatment procedure that involves breathing high oxygen concentrations at pressures that exceed 1 atm ab (101.325 kPa). Its efficacy is obtained by enhancing the production of reactive oxygen species and reactive nitrogen species, promoting cell growth, and modulating the inflammatory response (Fig. 3 and Table 1). As a result, vascularization and post-ischemic tissue survival are significantly improved (Table 2) [24–26]. At present, most clinical studies on HBOT have been conducted in Asian populations [27–29]. A meta-analysis involving 305 control cases and 318 HBOT cases showed that the success rate of the HBOT group was 4.95 times greater than that of the control group, indicating that HBOT has great potential in reducing local inflammation before femoral head collapse [27–29]. Hence, HBOT could be used as an alternative non-invasive treatment option. Although many studies have shown that HBOT can significantly improve patients' symptoms and quality of life, it is costly, has limited service availabilities, and has not been approved globally.

2.1.3. Pulsed Electromagnetic Therapy

Pulsed electromagnetic therapy (PEMF) has been recognized as a way to prevent or delay the progression of osteonecrosis due to its positive effects on promoting bone formation and protecting articular cartilage (Table 2). A possible mechanism of PEMF treatment is the induction of mechanical stress *via* the converse piezoelectric effect, which induces osteogenesis as well as chondrocyte formation (Fig. 3 and Table 1) [76]. Animal experiments have shown that PEMF is an effective physiotherapy in the treatment of steroid-induced ONFH, and it protects the balance between adipogenesis and osteogenesis [77]. Whether used alone or in combination with other treatments, PEMF offers a number of benefits, including improved pain relief and enhanced bone repair. As a standalone treatment procedure, PEMF can also be effective, with hip survival rates ranging from 80.2 % to 88.57 % [32,33]. Early Ficat stages have shown the best responses to PEMF, with improvements observed in both clinical outcomes and radiographic parameters [74]. Thus, PEMF may have a role in the management of early avascular necrosis [74]. However, current clinical studies on PEMF are limited and further research is still needed.

2.1.4. Extracorporeal shockwave therapy

Extracorporeal shock wave therapy (ESWT) represents a nonoperative treatment option for early-stage ONFH (Table 1). ESWT originated from extracorporeal shock wave lithotripsy. Initially, it was believed that the effect of ESWT was due to microfractures in the bone, but later it was confirmed that it stimulates bone formation by increasing the proliferation and differentiation of osteoblasts (Fig. 3) [78,79]. Multiple clinical trials and meta-analyses have shown that ESWT can significantly improve HHS, reduce VAS scores, effectively alleviate joint pain caused by ONFH, improve hip joint function, and relieve symptoms of bone marrow edema in the early stage (Table 2) [37,38,80]. Due to the attenuation effect of shock wave energy, divergent ESWT is less effective for treating lesions, while focused and high-energy ESWT achieves better therapeutic outcomes [81]. Some studies have shown that ESWT is more effective than core decompression (CD) and bone grafting for treating early ONFH [39]. Based on the current evidence, ESWT has shown promising prospects as a treatment method to enhance hip function and alleviate pain in the early stage of ONFH.

2.2. Pharmacological therapy

2.2.1. Bisphosphonate

Bisphosphonates are a popular choice for the pharmacological treatment of ONFH, functioning by inhibiting osteoclast activity and improving bone mineral density in the femoral head [40], which could prevent or delay the collapse of the femoral head (Fig. 3 and Table 2). They have been suggested for clinical use in the treatment of early-stage ONFH. In early clinical experiments, bisphosphonates demonstrated good bone repair ability, delayed femoral head collapse, and were considered the drug of first choice for ONFH, regardless of the stage at which patients presented [41]. However, in later studies, the efficacy of bisphosphonates has been questioned. A meta-analysis showed that bisphosphonates do not provide better clinical outcomes in the treatment of ONFH compared to a placebo, and even serious adverse reactions have been reported (Table 1) [18]. Other controlled experiments and meta-analyses have also found similar results [43–45]. Although bisphosphonates can significantly improve bone remodeling outcomes in animal models, no significant efficacy has been observed during the treatment of ONFH in clinical studies. Further studies are required to resolve the discordant outcomes between animal and clinical studies.

2.2.2. Anticoagulants

Primary ONFH is usually associated with genetic factors, such as hypercoagulability, hypofibrinolysis, or issues related to angiogenesis [82]. Anticoagulation relieves the spread of blood clots and promotes their dissolution, reducing ischemic conditions in the femoral head and relieving the increased pressure within the femoral head due to vascular obstruction (Fig. 3 and Table 2) [48,83]. Enoxaparin has been shown to significantly prevent the progression of hip joint collapse in primary ONFH [84]. Warfarin, on the other hand, has been found to prevent only symptomatic ONFH and not silent ONFH induced by corticosteroids (Table 1) [52]. There has been limited clinical data on anticoagulant therapy in recent years, with most data being obtained from experiments conducted nearly 20 years ago [49–52]. In a meta-analysis involving 218 hips, Guo et al. [48] showed that anticoagulants have a positive effect on primary ONFH (Ficat stage I or II) prior to collapse but they do not provide protection against secondary ONFH caused by hormones, alcohol, or other factors. Therefore, the efficacy of anticoagulants alone in treating secondary ONFH remains to be further investigated.

2.2.3. Hypolipidemics

Glucocorticoids increase the fat content in the bone marrow and the risk of osteonecrosis. Statins are the most effective lipid-lowering drugs

Table 3
Comparison of joint hip-preservation surgery methods.

Treatment	Advantage	Disadvantage	Applicable people
Core decompression [101–107]	① Simple surgical technique ② Minimal surgical trauma, shorter recovery time, and fewer postoperative complications	① Ineffective for large necrotic areas, unable to fully remove necrotic bone or prevent further femoral head necrosis and collapse ②Lack of mechanical support in the femoral head after removing necrotic bone may lead to fractures ③Possible complications include femoral head collapse, postoperative infection, and progression to advanced ONFH	For patients with symptomatic small to medium-sized pre-collapse lesions (less than 30 % necrotic area) or necrotic areas in non-weight-bearing regions. Not indicated if the femoral head has collapsed.
Osteotomy [109–117]	① Simple procedure, repositions necrotic area from weight-bearing to non-weight-bearing region ② Can effectively alleviate pain at the site of femoral head necrosis	① Osteotomy surgery has significant trauma and damages the blood supply of the femoral head, resulting in uncertain prognosis ② Destroys the normal anatomical structure of the large and small rotors ③ Complications of osteotomy may include shortening of the patient's leg, progressive collapse of ONFH, nonunion, and malunion ④ It is difficult to switch to THA if the surgery fails	When the necrotic area is located in the load-bearing area, or for patients with advanced ONFH
Non-vascularized bone grafting [118–135]	① Transplanted bone can provide partial structural support for subchondral bone ② Autologous bone is used for transplantation and there is no rejection reaction	① Donor site injury: A large amount of bone tissue needs to be removed from the ilium or fibula for transplantation, which may cause pain and fractures in the donor site ② Longer healing time: Due to the lack of blood supply in bone transplantation without blood supply, the bone healing process is relatively slow and requires a longer time ③ Complications may include postoperative functional limitations, non-survival of transplanted bone, incomplete bone reconstruction, resorption of transplanted bone, and bone nonunion	For ONFH patients with ARCOII-III stage, JIC type C1, and lateral femoral head involvement
Vascularized bone grafting [138–147, 149,150]	① Transplanted bone can provide partial structural support for subchondral bone ② Autologous bone is used for transplantation and there is no rejection reaction ③ Can provide bone tissue with blood vessels, thereby increasing local blood supply and promoting the bone healing process	① Donor site injury: A large amount of bone tissue needs to be removed from the ilium or fibula for transplantation, which may cause pain and fractures in the donor site ② Surgical complexity: The surgery is complex and requires high technical skills from doctors, requiring precise surgical techniques to ensure the integrity of blood vessels and the blood supply of transplanted bone ③ The patient's recovery time may be extended, requiring 3–6 months under protective weight-bearing ④ Complications may include infection, graft necrosis, and increased risk of proximal femoral fracture	For patients with JIC type C2, complete involvement of the lateral femoral head, and arterial ischemia in the early to mid-stage of ONFH
Mesenchymal stem cell transplantation [151–162,171]	① MSCs have the ability to differentiate into multiple cell types, including bone cells, which contribute to the regeneration and repairment of damaged tissues ② Can promote angiogenesis, thereby improving blood circulation and promoting tissue repair	① Implanted mesenchymal stem cells may die due to the lack of nutrient rich blood vessels in the early to mid-stages, which may hinder their therapeutic effect ② There is a lack of mechanical support in the femoral head ③ The process of extracting autologous mesenchymal stem cells from patients is painful. The function of MSCs in elderly patients or patients with systemic diseases may be impaired, making it impossible to complete autologous extraction.	Early or mid-stage ONFH patients
Tantalum rods [173–180]	① Good biocompatibility, can promote bone growth, reduces stress shielding ② Provides mechanical support for subchondral bone to prevent premature collapse	① Limited long-term efficacy (52.9 % hip survival rate) ② Bone integration with rods complicates conversion to THA if surgery fails ③ Complications may include recurrent hip pain, tantalum rod displacement, bone resorption and local reactions, and femoral neck fractures	Early to mid-stage ONFH patients; currently not widely used in clinical practice
Tissue engineering [181,216–218]	① Good biocompatibility, can provide sufficient subchondral support ② It can promote the regeneration of necrotic bone tissue and the repairment of the vascular system while providing biomechanical stability to the necrotic area	① High cost due to technological complexity and specialized materials ② Limited clinical trial data: more samples are needed to verify the efficacy	Early to mid-stage ONFH patients or those with good recovery ability

[85]. Statins prevent ONFH by inhibiting certain inflammatory mediators, regulating cartilage homeostasis, promoting bone formation, and increasing bone density (Fig. 3 and Table 2) [86–88]. ONFH caused by familial hyperlipidemia can be treated with hypolipidemics [89]. Among 284 patients who received high-dose steroids and statins simultaneously, only 3 cases (1 %) experienced osteonecrosis (with an average follow-up period of 7.5 years and a minimum of 5 years); this incidence is much lower than the typical 3–20 % reported for patients receiving high-dose steroids [54]. Animal experiments suggest that simvastatin is beneficial in preventing steroid-induced ONFH [86]. In addition, pravastatin is believed to increase the capillary density of the femoral head and is an effective drug for preventing ONFH [55]. However, long-term use of statins may damage the liver (Table 1) [90]. There is only one clinical study (51 hips) on the use of statins in the treatment of ONFH [56]; the rest are animal experiments. Therefore, the role of statins in the treatment of ONFH remains to be further investigated.

2.2.4. Vasodilators

Vasodilators reduce blood pressure and improve local circulation by promoting vasodilation (Fig. 3 and Table 2). Iloprost is a commercially available prostaglandin I2 (PGI2) analogue, exhibits antithrombotic, vasodilative, and antiproliferative effects [91]. Iloprost has been shown to be effective in eliminating bone marrow edema and alleviating painful symptoms [58–61], making it a viable option for treating early-stage osteonecrosis. In a meta-analysis of 190 cases, intravenous injection of iloprost improved 90.7 % of cases with bone marrow edema syndrome (Table 1) [62]. Currently, clinical studies involving vasodilators include patients with bone marrow edema and femoral head necrosis, but there is no clear distinction between these two types of patients [58–62]. Normally, patients with bone marrow edema can recover on their own after 3 to 8 months of protective weight bearing. If these two types of patients are not distinguished, it could lead to an overestimation of the treatment rate for ONFH.

2.3. Traditional Chinese medicine

From the perspective of traditional Chinese medicine, femoral head necrosis is regarded as a type of stasis syndrome. In the early stage, necrosis is caused by intertwined phlegm and blood stasis (non-traumatic) or blood stasis due to qi stagnation (traumatic). In the middle stage, it is mainly caused by meridian blockage. In the late stage, it is caused by liver and kidney deficiency. In China, the most commonly-used regimens for treating ONFH are surgical procedures, Chinese herbal medicine, and a combination of pharmacological medicine and Chinese herbal medicine [92]. The advantage of TCM treatment is its multiple therapeutic methods and good efficacy for early- and middle-stage ONFH. Over the past decade, TCM is consistently recommended as one of the main nonoperative treatments for ONFH [93]. TCM therapy mainly includes Chinese herbal medicine, acupuncture and moxibustion, acupotomy (needle knife), and ointment massage.

2.3.1. Chinese herbal medicine

Chinese herbal medicine (CHM) primarily originates from natural medicines and their processed products, with the majority being herbs. CHM is often used as a complementary treatment alongside surgery or pharmacological medicine [92]. Unlike surgical methods or pharmacological therapies, herbal treatments utilize herbs with specific functions, such as combinations of herbs that invigorate blood and tonify the kidneys, or combinations of herbs that resolve blood stasis and relieve pain. It's been shown that CHM can prevent femoral head collapse and delay the time for THA [63,64]. CHM combined with other therapies may improve the treatment effectiveness of ONFH (Tables 1 and 2) [19,65]. In addition to examining the effects of different combinations of herbs on treating ONFH, many studies have now started to focus on the specific components and treatment mechanisms of the Chinese herbs [93–100].

Chinese herbal treatments have a long history in China, with most relevant articles published in Chinese, forming a concentrated body of research. The main remedies used in TCM for treating ONFH are categorized as follows. For the Qi stagnation and blood stasis syndrome, it is necessary to move Qi and activate blood circulation, and to resolve blood stasis to relieve pain. Taohong Siwu decoction can be used for TCM treatment. For phlegm and blood stasis obstruction, it is necessary to improve the hypercoagulable state of blood, unblock blood vessels, and improve lipid metabolism disorders. For TCM treatment, Linggui Zhugan Decoction and Taohong Siwu Decoction can be used. For meridian paralysis, treatment aims to improve bone and lipid metabolism, immune-inflammation, and blood circulation to promote joint recovery. Chinese medicine treatment can be used to replenish Yang Hui Wu Tang with decoction. For cases of deficiency of kidney qi, treatment involves tonifying the liver and kidney, promoting Qi and blood circulation. Zuogui Pill is adopted for this condition pill (Fig. 3).

2.3.2. Acupuncture and moxibustion

Acupuncture and moxibustion (AM) is a unique treatment procedure originating from China. The distinguishing feature of acupuncture and moxibustion therapy is that it does not rely on taking medicine to treat the disease but instead uses acupuncture at a certain part of the patient's body to prick the nerves and cause local reactions, or uses the warmth of fire to stimulate local cauterization. The former is called acupuncture, and the latter is called moxibustion. Studies have shown that AM has the effects of activating menstrual channels, regulating qi and blood, and nourishing the internal organs (Tables 1 and 2) [66–70].

Acupuncture and moxibustion can target points such as Huantiao, Chengfu, Chengshan, Xuehai, and Taichong, which can be divided into two groups for alternative acupuncture and moxibustion treatments. A meta-analysis involving 630 subjects indicated that AM for early-to middle-stage ONFH is an effective and relatively safe intervention, improving the effective rate, excellent and good rates, and HHS while reducing the incidence of adverse reactions [71]. In clinical practice, AM interventions can be combined with conventional treatments to improve the efficacy of treating early- and middle-stage ONFH. Similar to Chinese herbal medicine, AM is also one of the traditional treatment methods in China. Therefore, most of the relevant literature has been published in Chinese. Further studies from other institutions are needed to confirm its efficacy.

3. Operative treatment

The aim of hip joint-preserving surgery is to eradicate the necrotic area to delay or even stop the progression of necrosis. Although hip joint-preserving surgery and THA are both surgical interventions, there is a clear distinction between the two. Hip joint-preserving surgery aims to preserve the patient's own hip joint, while THA aims to replace the damaged hip joint by implanting an artificial joint. In recent years, regenerative medicine has become a popular concept, leading to the development of various operative approaches. Compared to nonoperative treatments, surgical interventions can provide more immediate results (e.g., removal of necrotic bone tissues), and therefore are more effective in improving hip function and providing better long-term outcomes. However, surgical treatments come with certain risks due to their invasive nature, including risks associated with anesthesia, infection, and postoperative complications, especially for elderly patients. A comprehensive comparison of the advantages and disadvantages between different operative hip joint-preserving treatments was made in this article (Table 3).

3.1. Basic surgery

Basic surgery refers to surgical methods based on anatomy, resection, suturing, and fixation. In the treatment of ONFH, there are two main types of surgeries: CD and osteotomy. These two surgical methods have

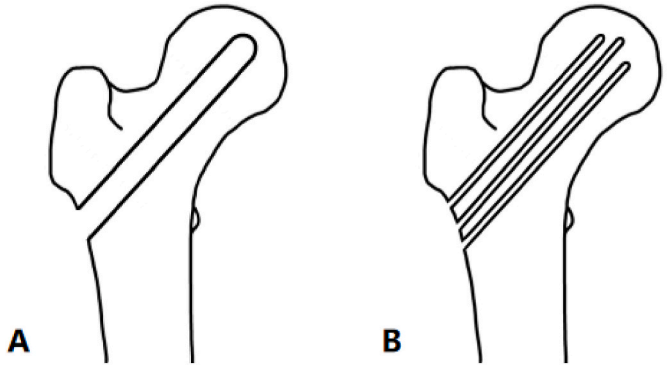

Fig. 4. Two surgical approaches for core decompression (CD). **A**) CD with single-drilling. **B**) CD with multiple drilling.

simple principles and are widely used in clinical practice.

3.1.1. Core decompression

Core decompression aims to stop the progression of ONFH by reducing pressure in the femoral head and promoting the regeneration of blood vessels and bone tissues (Fig. 3). This method has been in use since 1962, making it a well-established approach for over 60 years, and it has been shown to be superior to nonoperative treatments for treating early-stage ONFH [1,101]. There are two surgical approaches for CD: one is traditional single drilling with a diameter of 8-12 mm, and the other is multiple drilling with a diameter of 3-4 mm (Fig. 4). From a biomechanical perspective, compared to simple drilling, multiple drilling forms a honeycomb-like tunnel structure, which can retain some supporting structures and prevent local collapse after CD. The success rate of multiple drilling for early-stage ONFH is 68.6–78.6 %, which is similar to that of simple drilling [102–105]. However, studies have shown that the risk of THA increases following multiple drilling [105]. Complications of CD may include femoral head collapse, postoperative infection, and progression to late-stage ONFH [106]. CD is most effective for treating femoral head necrosis with less than 30 % necrotic area [107]. For advanced femoral head necrosis, the use of CD should be approached with caution (Table 3) [172]. CD is often combined with mesenchymal stem cells to treat ONFH, which can significantly improve its treatment rate. A systematic review of 32 studies involving 2441 hips demonstrated success rates of 57 % for isolated CD, 74 % for CD combined with autologous bone, and 81 % for CD combined with mesenchymal stem cells (MSCs) [172].

3.1.2. Osteotomy

The principle of osteotomy involves altering the angle of the femoral neck to redistribute loading across the femoral head, transforming the necrotic lesion from a weight-bearing to a non-weight-bearing state (Fig. 3). Osteotomy techniques include varus or valgus osteotomy, rotational osteotomy through the femoral trochanter, and rotational osteotomy of the femoral neck base through a surgical dislocation approach [2,108,109].

Trans-trochanteric rotational osteotomies are commonly performed in Japan, whereas intertrochanteric flexion-varus or extension-valgus variants are more commonly performed in Europe [1,110,111]. A meta-analysis of 1069 hips found that Asian patients had a higher survival rate for transtrochanteric rotational osteotomy than non-Asian patients (68 % VS 41 %), with an overall survival rate of 58 % [112]. However, these procedures can cause significant damage to the blood supply of the femoral head, leading to uncertain prognostic outcomes (Table 3). Complications of osteotomy may include shortening of the

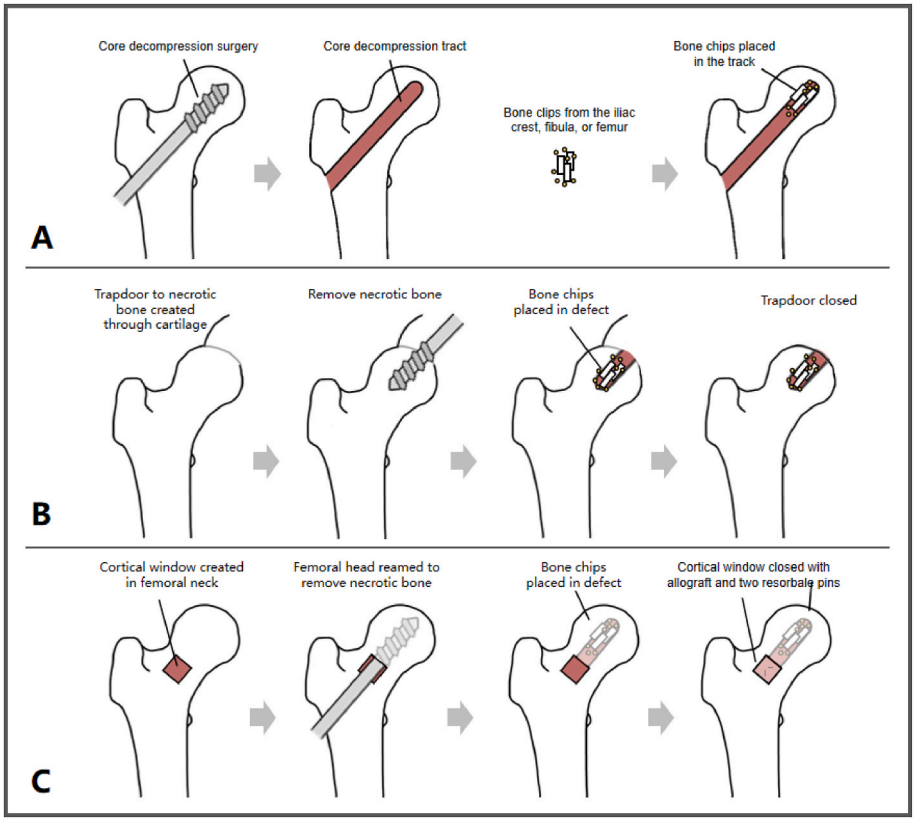

Fig. 5. Techniques for the implantation of bone grafts to treat osteonecrosis of the femoral head. **A**) The Phemister Technique making use of core decompression tract to place the grafted bone. **B**) The Trapdoor Technique grafting through a window or trapdoor in the articular cartilage. **C**) The Light Bulb Technique grafting through a window made in the femoral neck or femoral head-neck junction.

patient's leg, progressive collapse of ONFH, nonunion, and malunion [113]. In the event of osteotomy failure, performing artificial joint replacement is relatively challenging [114,115].

Notably, osteotomy significantly improves functional activity in 90 % of patients with advanced ONFH [116]. Although some complications may arise after surgery, they generally do not impact the efficacy of the procedure or the patients' quality of life. Overall, osteotomy offers a good hip preservation approach for patients with advanced femoral head necrosis.

3.2. Regenerative techniques

Regenerative therapy here refers to implantation of materials with osteogenic capacity, including bone tissue, mesenchymal stem cells, and biomaterials, to restore normal functions of the necrotic femoral head.

3.2.1. Non-vascularized bone-grafting

Non-vascularized bone grafting has been demonstrated as an effective method for treating ONFH [117,118]. The basic principle involves the removal of necrotic bone from the femoral head and its replacement with graft materials. This process blocks the pathological progression of bone necrosis, effectively reduces pressure within the femoral head, and provides mechanical support while promoting new bone formation. Graft materials may be harvested from autologous iliac bone [119,120], fibula [121,122], or some artificial materials [123,124] (Fig. 3). Techniques for implanting these grafts include the Phemister technique, light bulb technique, and trapdoor technique (Fig. 5). These three surgical techniques can also be used for vascularized bone-grafting.

The Phemister technique uses a CD tract to place the grafted bone in the affected region (Fig. 5A). This technique was shown to be clinically successful in early reports [125], but its long-term results are average, as indicated by later studies [126]. Its efficacy in ARCO IIC and IIIA ONFH is also poor [127]. This method does not require opening the joint capsule. The Phemister technique is minimally invasive and simple to operate. However, it is very difficult to completely remove the necrotic bone, and it cannot effectively reconstruct the collapsed femoral head.

The Trapdoor Grafting Technique, which was first introduced in 1965, is executed from either an anterior or posterolateral approach with an open arthrotomy and safe dislocation of the femoral head (Fig. 5B). Under direct visualization, a cartilage window in the femoral head over the necrotic area is created for debridement of the osteonecrotic lesion and implantation of a bone graft. Its advantage lies in the thorough removal of lesions under direct visualization, while handling fractured or free cartilage caps as well. However, the surgery may cause iatrogenic cartilage damage to the non-collapsed femoral head. This technique is superior in patients with post-collapsed osteonecrosis and a large lesion [128–130].

The Light Bulb technique, also known as "subchondral windowing", involves the creation of a cortical window at the junction of the femoral neck and the articular cartilage, followed by the removal of necrotic bone [131] (Fig. 5C). This technique enables surgeons to directly visualize the necrotic areas within the femoral head and to perform precise surgical interventions [132–134]. Compared with the Phemister technique, the larger incision associated with this procedure renders it more invasive and technically demanding. Compared to Trapdoor technology, this technique does not damage the exposed femoral neck under the support of arterial blood supply. This method does not require opening the joint capsule and has minimal surgical trauma but it has the disadvantage of being difficult to completely remove dead bones, and it is unable to effectively reconstruct collapsed femoral heads. The Light Bulb technique compensates for the disadvantages of the Trapdoor technique in terms of cartilage damage while ensuring adequate removal of necrotic areas.

Studies have shown that the conversion rate to THA after non-vascularized bone grafting was 21 %, with the Phemister, trapdoor, and lightbulb techniques occurring at rates of 24 %, 19 %, and 15 %, respectively [173]. Non-vascularized bone transplantation is more effective for adolescents, and the failure rate increases when patients are over 37 years old [122]. Complications may include postoperative functional limitations, non-survival of transplanted bone, incomplete bone reconstruction, resorption of transplanted bone, and bone nonunion. This treatment is relatively easy to operate and has acceptable clinical efficacy, but the graft materials lack nutrient vessels in the early and middle stages of ONFH, which may lead to necrosis and resorption of implanted bone blocks again (Table 3) [174].

3.2.2. Vascularized bone-grafting

Restoration of blood supply to the necrotic lesion is important for the successful treatment of ONFH. Vascularized bone grafting, which has an intact blood supply and osteogenic potential (e.g., vascularized iliac crest graft, vascularized fibula graft), can improve bone healing of the necrotic area and provide viable structural support to prevent articular cartilage collapse (Fig. 3). Vascularized bone-grafting has generally been recommended for Ficat stage I to III ONFH [135–140]. Compared to CD or non-vascularized bone-grafting, vascularized bone-grafting shows slower imaging progression, a lower collapse rate, and a lower THA conversion rate [136,141]. This method is more effective in adolescents under 30 years old and can be used to treat severe bone necrosis [142, 143]. The two most commonly used types of pedicled autogenous bone flap are from the fibula and iliac. As one type of cancellous bone, the iliac bone has a greater histological resemblance to the femoral head compared to the fibular bone, which contains more cortical bone [146]. Also, some complications can be avoided with the use of iliac bone. However, patients receiving iliac bone grafts tend to experience more pain after surgery and have more surgical bleeding compared to those receiving fibular bone grafts.

Vascularized bone-grafting requires more complex surgeries, longer operation time, and higher requirements for surgical personnel. The patient's recovery time may be extended, requiring 3 to 6 months under protective weight-bearing. Complications may include infection, graft necrosis, and increased risk of proximal femoral fracture [175]. In addition, potential harvest-site morbidity including flexor hallucis longus contracture, peroneal nerve injury, ankle instability, and gait alterations, can approach a prevalence of 13 %–20 % (Table 3) [144–146].

3.2.3. Mesenchymal stem cell transplantation

With the development of biotechnology, an increasing number of studies focus on the use of mesenchymal stem cells for the treatment of ONFH. MSC therapy helps slow down or stop the necrotic process and prevent femoral head collapse by promoting bone regeneration and repair and improving blood supply. Since the first report of autologous concentrated bone marrow transplantation in 2002 [147], numerous studies have explored various types of cell-based therapies. Some studies claim that similar results were essentially achieved with stem cell implantation as with the conventional method of CD [148–150]. However, an increasing number of studies, including both clinical and basic research, have confirmed the effectiveness of stem cell therapy in ONFH [151–154]. This therapy is usually combined with CD and can reduce the progression of the disease and the THA conversion rate after CD [155–157]. It has proven to be more effective than other therapies, particularly in pre-collapse (stage I to II) ONFH patients [158].

Growth factors play important roles in various physiological processes, which are crucial for maintaining normal biological function and tissue homeostasis [176]. The expression level and functional status of growth factors directly affect the blood supply of the femoral head and the repair ability of bone tissue. Currently, genetic engineering has been introduced as an attractive strategy to enhance the regenerative ability of MSCs in early ONFH treatment [177–182]. MSCs can reduce the number of senescent cells and downregulate the aforementioned senescence-related genes, thereby inhibiting femoral head collapse [183].

However, many unsolved problems and challenges in the practical

Table 4
Studies on bioceramics in the treatment of ONFH in the past decade.

Author	Year	Study object	Staging of osteonecrosis	Age	Sex	No. of cases	Animal model/Types of osteonecrosis	Therapeutic strategy	Follow-up	Harris Hip Score	Success Rate	THA Rate	Effect
Wang et al. [186]	2019	New Zealand white rabbits	—	Mature	Female 20 Male 0	20	Liquid nitrogen freezing method	Control group: Injected 0.2 ml of saline into the area of the bone defect Experimental group: Injected with 0.2 ml hybrid hydrogel	1 and 2 months after the surgery	—			Accelerate bone regeneration
Wang et al. [187]	2019	New Zealand rabbits	—	2 months old	Female 15 Male 15	30	Injected with methylprednisolone (MPSL)	Control group: Pure CD Experimental group 1: A nano-hydroxyapatite/ collagen I/poly-L-lactic acid (nHAC/PLA) scaffold was designed and was implanted into the bone tunnel of CD Experimental group 2: BMSCs + nHAC/PLA scaffold	4 weeks after the surgery	—	—	—	Stimulate bone formation and facilitating vascularization
Wang et al. [188]	2019	New Zealand rabbits	—	—	Female 0 Male 24	24	Injected with lipopolysaccharide and methylprednisolone (MPS)	Control group: pure CD Experimental group 1: CD + implantation of unmodified β-TCP scaffolds Experimental group 2: CD + implantation of DPI peptide-modified β-TCP scaffolds	12 weeks after the surgery	—	—	—	Stimulate bone formation
Lu et al. [189]	2019	New Zealand rabbits	—	7–8 months old	—	18	—	A: Normal femoral head and neck group; B: Pure CD; C: CD with β - TCP porous bioceramic rods	12 weeks after the surgery	—	—	—	Facilitating vascularization
Aoyama et al. [190]	2014	Human	SDIC 3A or 3B	31.7 (20–48) years	Female 0 Male 10	10	Previous history of steroid treatment: 4 (40 %)	Autologous bone marrow-derived MSCs mixed with β-TCP in combination with vascularized bone grafts for the treatment	2 years	(Japan Orthopaedic Association) 65.6 - 25.5 vs 87.9–19.0	22 %	—	Procedure performed safely, but efficacy still to be determined
Yang et al. [191]	2014	Human	Steinberg I - IIIA	36.4 (<55) years	Female 20 Male 44	64 (84 hips)	Alcohol abuse: 10 (15.63 %), Corticosteroid application: 36 (56.25 %), Idiopathic: 18 (28.13 %)	Control group: Autologous cancellous bone graft in combination with CD Treatment group: CD combined with implantation of a n-HA/ PA66 rod and resorbable bioglass bone graft	CG: 23.24 ± 9.32 (9–36) months TG: 21.78 ± 8.46 (5–36) months	HHS improvement (CG vs TG): 15.58 ± 2.93 vs. 27.19 ± 2.79	CG: 47.83 % TG: 76.32 %	CG: 54.29 % TG: 27.59 %	The excellent biomechanical properties can prevent subchondral collapse
Lu et al. [192]	2018	Human	ARCO IIA - IIIC	44.49 years	Female 17 Male 45	62 (72 hips)	Alcohol abuse: 30 (48.39 %), Corticosteroid Application:15 (24.19 %), Post-traumatic: 6 (9.68 %), Idiopathic: 11 (16.13 %)	Mixed porous (3 g) and dense (5 g) granules with bone sludge (containing BMSCs, stromal cells, and blood cells) into the bone defect after CD, then inserted a bioceramics rod.	26.74 months	58.14 vs 82.27	90.27 %	11 %	The treatment was more effective on patients under 44 years old

(*continued on next page*)

Table 4 (*continued*)

Author	Year	Study object	Staging of osteonecrosis	Age	Sex	No. of cases	Animal model/Types of osteonecrosis	Therapeutic strategy	Follow-up	Harris Hip Score	Success Rate	THA Rate	Effect
Lu et al. [189]	2019	Human	AROC II - III	42 (17–76) years	Female 55 Male 145	200 (232 hips)	—	Mixed porous (3 g) and dense (5 g) granules with bone sludge (containing BMSCs, stromal cells, and blood cells) into the bone defect after CD, then inserted a bioceramics rod.	22.7 (6–73) months	57.3 ± 12.0 vs 79.3 ± 17.3	93.1 %	6 %	Facilitated vascularization and restored mechanical properties
Hernandez et al. [193]	2020	Human	ARCO I - II	37.8 ± 9.31 years	Female 3 Male 7	10 (18 hips)	Alcohol abuse: 4 (40 %), Corticosteroid application:6 (60 %)	CD combined with implantation of autologous bone marrow concentrate with tricalcium phosphate	68.9 ± 9.31 months	76.7 ± 9.8 vs 85.2 ± 11.4	11.76 %	60 %	Harris hip scores improved but could not prevent disease progression to collapse
Liang et al. [194]	2021	Human	ARCO II - IIIA	38.3 ± 7.5 (24–50) years	Female 8 Male 39	47 hips	Alcohol abuse: 21 (44.68 %), Hormonal: 13 (27.66 %), Idiopathic: 13 (27.66 %)	Bone graft was selected from autologous iliac bone mixed with β-tricalcium phosphate porous bioceramic bone (ratio 1:1)	44.6 ± 10.0 months	64.45 ± 2.93 vs 76.29 ± 10.38	63.83 %	25.53 %	Effectively treated non-traumatic ONFH in the pre-collapse stage but had poor efficacy for patients with 25(OH)D deficiency or stage IIIA ARCO
Zhang et al. [195]	2021	Human	ARCO II - III	36.97 ± 6.24 (20–47) years	Female 15 Male 21	36 (39 hips)	Alcohol abuse: 9 (25.0 %) Hormone: 12 (33.3 %), Trauma-related: 6 (16.7 %), Idiopathic: 9 (25.0 %)	Control group: Autologous iliac bone graft in combination with CD Treatment group: CD combined with bioceramics bone graft	29.27 ± 3.56 months	CG: 67.81 ± 4.47 vs 82.31 ± 5.38 TG: 68.45 ± 3.93 vs 83.59 ± 4.97	68.75 % vs 70 %	—	Bioceramic graft materials reduced trauma, bleeding, operation time, and enabled quicker postoperative functional recovery
Jameel et al. [196]	2022	Human	Ficat Arlet I - IIB	29.1 ± 6.3 years	Female 5 Male 33	38 (44 hips)	—	Control group: Autologous iliac crest cancellous bone graft in combination with CD Treatment group: CD combined with calcium-sulfate-hydroxyapatite bioceramic paste graft	CG: 21.2 ± 3.2 months TG: 21.6 ± 3.5 months	—	—	—	Calcium sulfate hydroxyapatite as a void filler in CD for ONFH was not superior to autologous bone in preventing collapse or providing mechanical support
Wan et al. [197]	2022	Human	ARCO II	29.87 ± 5.34 years	Female 91 Male 91	182 (192 hips)	Steroid induced: 85 (45 %), Alcohol-induced: 83 (46 %), Idiopathic: 14 (7 %)	FFG group: Free fibular graft group FVFG group: Free vascularized fibular graft group ABG group: Autologous iliac bone group β-TCPG group: β-tricalcium bioceramics phosphate graft	44.62 ± 1.81 (42–48) months	The HHS in each group was improved significantly from pre-operation to the last follow-up (all $P < 0.01$)	—	—	β-TCP bioceramic graft reduced operation time and blood loss

Table 5
Studies on magnesium and magnesium alloys in the treatment of ONFH in the past decade.

Author	Year	Study object	Staging of osteonecrosis	Age	Sex	No. of cases	Animal model/Types of osteonecrosis	Therapeutic strategy	Follow-up	Harris Hip Score	Success Rate	THA Rate	Effect
Katiella et al. [203]	2016	New Zealand white rabbits	—	4 months old	—	42	Liquid nitrogen freezing method	Mg rod/BMSCs group, Mg rod group, BMSCs group, and blank control group	12 weeks after the surgery	—	—	—	Stimulated bone formation
Wang et al. [204]	2020	New Zealand white rabbits	—	—	Female 65 Male 0	65	Liquid nitrogen freezing method	Blank control group: Undergo no treatment MgAlYb-LDH group: Magnesium-based layered double hydroxide nanosheets	8 weeks after the surgery	—	—	—	Stimulated bone formation
Zhao et al. [205]	2016	Human	AROC II-III	31.6 ± 7.5 (30–48) years	Female 19 Male 29	48	Steroid type: 16 (33.3 %); Alcohol abuse: 12 (25 %); Others: 20 (41.7 %)	Control group: Vascularized bone grafting without fixation Mg screw group: Vascularized bone grafting fixed by Mg screws (purity of 99.99 wt %)	12 months after surgery	Control group: 60.39 ± 6.05 vs 82.88 ± 7.03 Mg group: 63.90 ± 7.12 vs 89.93 ± 8.96	95.7 %	—	Provided better stability of the bone flap and stimulated bone formation
Cheng et al. [206]	2022	Human	AROC II-III	32.5 (21–55) years	Female 0 Male 20	20 hips	Alcohol abuse: 2 (10 %), Hormonal: 5 (25 %), Post-traumatic: 7 (35 %), Idiopathic: 6 (30 %)	Control group: Vascularized bone grafting without fixation Mg screw group: Vascularized bone grafting fixed by Mg screws	1 year	Both groups showed an improvement in Harris scores	—	—	Provided better stability of the bone flap and stimulated bone formation
Sun et al. [207]	2023	Human	AROC II-III	31.8 (18–55) years	Female 10 Male 26	36 (37 hips)	Alcohol abuse: 8 (22.2 %), Hormonal: 13 (36.1 %), Traumatic: 2 (5.6 %), Idiopathic: 13 (36.1 %)	Group A: Fixed with biodegradable Mg screws Group B: Fixed with titanium screws Group C: Directly embedded	6 months	Group A: 64.26 ± 8.17 vs 80.03 ± 5.2 Group B: 66.40 ± 9.52 vs 77.34 ± 5.15 Group C: 67.29 ± 5.54 vs 76.03 ± 3.89		—	Provided mechanical support to the necrotic area and restored blood supply

Table 6
Studies on titanium and titanium alloys in the treatment of ONFH in the past decade.

Author	Year	Study object	Staging of osteonecrosis	Age	Sex	No. of cases	Animal model/Types of osteonecrosis	Therapeutic strategy	Follow-up	Harris Hip Score	Success Rate	THA Rate	Effect
Zhu et al. [208]	2017	New Zealand rabbits	—	—	—	10	Liquid nitrogen freezing method	Control group: ONFH Treatment group: Received a platelet-hybrid scaffold	2 months after the surgery	—	—	—	Can attract and promote the proliferation of osteoblasts as well as bone regeneration
Wang et al. [209]	2019	small tailed Han sheep	—	16–24 months	Female 18 Male 0	18	Liquid nitrogen freezing method	Control group: Pure CD Treatment group: Implanted a porous Ti-Rod with diamond crystal lattice	3 and 6 months after the surgery	—	—	—	Can provide mechanical support and stimulate bone formation
Wang et al. [210]	2020	Small-Tailed Han Sheep	—	16–24 months	Female 18 Male 0	18	Liquid nitrogen freezing method	Control group: Pure CD Treatment group: Implanted a biogenic trabecular porous Ti-rod with lamellar configuration	3 and 6 months after the surgery	—	—	—	Stimulates bone formation
Gao et al. [211]	2020	beagle dog	—	—	Female 0 Male 30	30	Liquid nitrogen freezing method	Control group: Healthy ONFH group: ONFH undergo no treatment IBG group: Iliac bone graft IBG+3DP-scaffold: Implanted a 3D-printed porous Ti-scaffold IBG+3DP-scaffold + TCA group: 3D-printed porous Ti-scaffold combined with daily intraperitoneal trans-cinnamaldehyde (TCA)	12 weeks	—	—	—	Provides mechanical support, stimulates bone formation, facilitates vascularization
Li et al. [212]	2021	Small-Tailed Han Sheep	—	16–24 months	Female 15 Male 0	15	Liquid nitrogen freezing method	Control group: Implanted a traditional porous scaffold (without vessels) Treatment group: Implanted a novel scaffold carrying vascular bundle after CD	3 and 6 months after the surgery	—	—	—	Provide mechanical support, stimulate bone formation, facilitate vascularization
Chen et al. [213]	2015	Human	ARCO I-II	36.2 (22–54) years	Female 19 Male 31	50 (62 hips)	Alcohol abuse: 25 (50 %), Hormonal: 19 (38 %), Idiopathic: 6 (12 %)	Implanted with metal trabecular bone reconstruction system	34.05 (24–46) months	53.24 ± 6.20 vs 81.20 ± 10.0	81 %	—	Stimulates bone formation
Zhang et al. [214]	2018	Human	ARCO II	41.72 ± 3.56 (22–54) years	Female 11 Male 19	30	—	Implanted with a new 3D printed titanium metal trabecular bone reconstruction system	24 months	showed an improvement in Harris scores	—	—	stimulate bone formation
Chen et al. [215]	2019	Human	ARCO IIA-IIIB	40.62 ± 9.14 (20–60) years	Female 31 Male 35	66 (78 hips)	Alcohol-induced ONFH: 66 (100 %)	Control group: Simple ONFH model without surgical treatment Ti-rod treatment group: Treated with a metal trabecular bone reconstruction system Bone graft group: Treated with a free vascularized fibular graft	3 years	Ti-rod group: 63.66 ± 5.47 vs 89.97 ± 7.28 Bone graft group: 64.13 ± 6.24 vs 82.63 ± 6.66	—	—	Ti-rod group has better short-term clinical efficacy

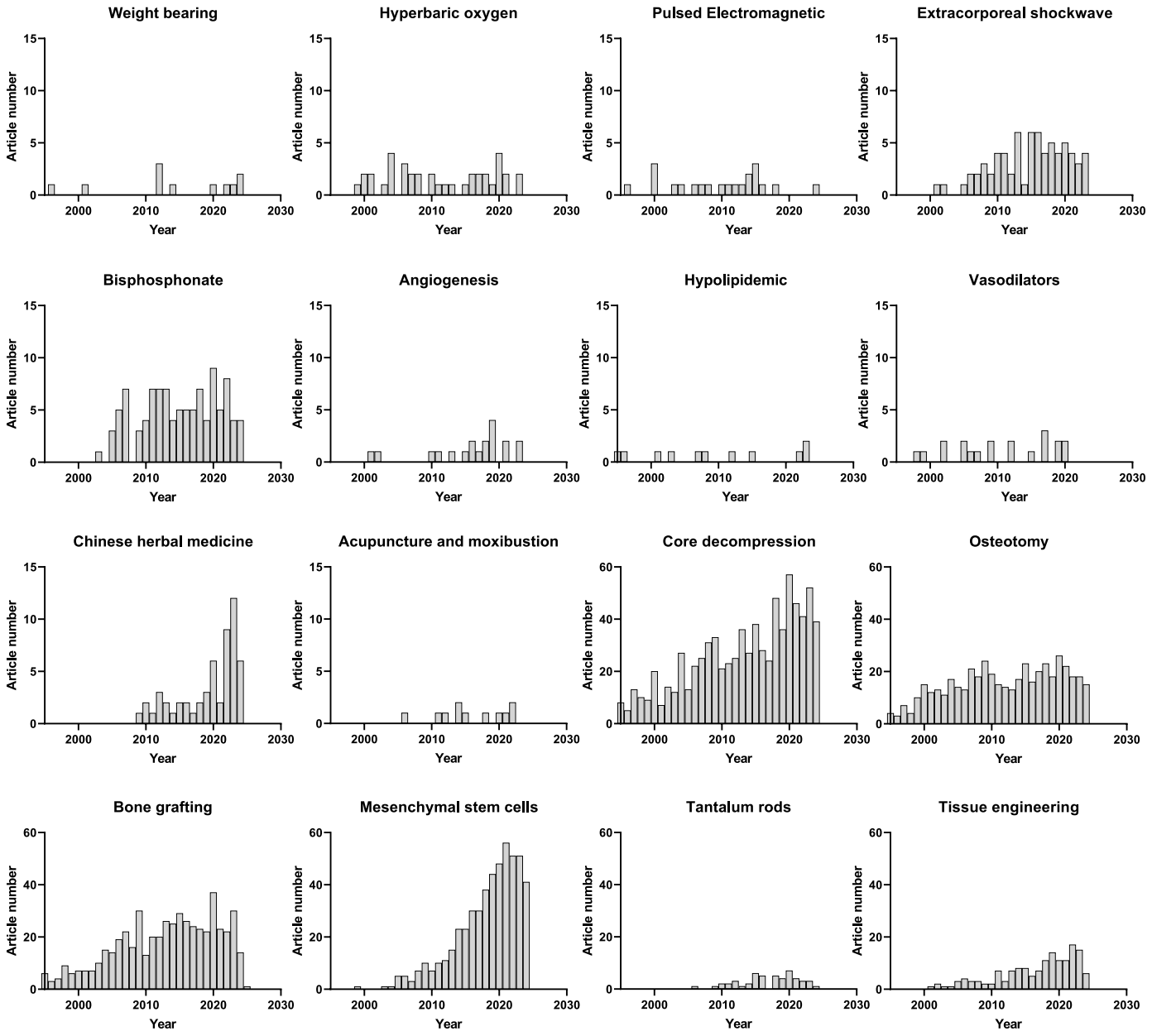

Fig. 6. The number of articles published (according to the Web of Science) during last three decades on each hip joint-preserving procedure for treating the osteonecrosis of the femoral head.

application of stem cell therapy still exist, such as patient selection, standardized procedures, safety assessment, and the fate of transplanted cells in the body [159]. MSCs do have good proliferation and differentiation abilities, but ensuring the stability of differentiation of implanted cells remains a significant question. At present, most of the mesenchymal stem cells used in clinical practice are extracted from the patient's own body, which is a painful procedure. In addition, the function of MSCs in elderly patients or patients with systemic diseases may be impaired, making it impossible to complete autologous extraction (Table 3). Finding alternative solutions to autologous extraction is also an important challenge. Further studies are required to identify ideal cell sources, appropriate transplantation methods, and the optimal number of cells for transplantation.

3.2.4. Tantalum rods

Porous tantalum scaffolds have been developed and clinically utilized as superior implantable biomaterials for orthopedic applications due to their exceptional corrosion resistance, biocompatibility, osteointegration, and osteoconductivity [184]. Moreover, the biomimetic porous structure and mechanical properties of these scaffolds match those of human bone tissues. Porous tantalum allows fine bone ingrowth and new bone formation through its inner space because of its high porosity and interconnected pore structure, which are beneficial for the adhesion, proliferation, and mineralization of osteoblasts [160]. At the same time, tantalum rods have sufficient mechanical strength, providing adequate mechanical support for the soon-to-collapse subchondral bone of the femoral head, thereby avoiding premature collapse [161–163]. Despite its numerous advantages, the joint preservation outcomes of this surgical treatment are not satisfactory [162–165]. Some studies reported a survival rate of the hips of only 52.9 % [166]. Complications of tantalum rod implantation include recurrent hip pain, tantalum rod displacement, bone resorption and local reactions, and femoral neck fractures [167]. Since bone grows into its porous structure, separating the rod from the bone becomes difficult, increasing the

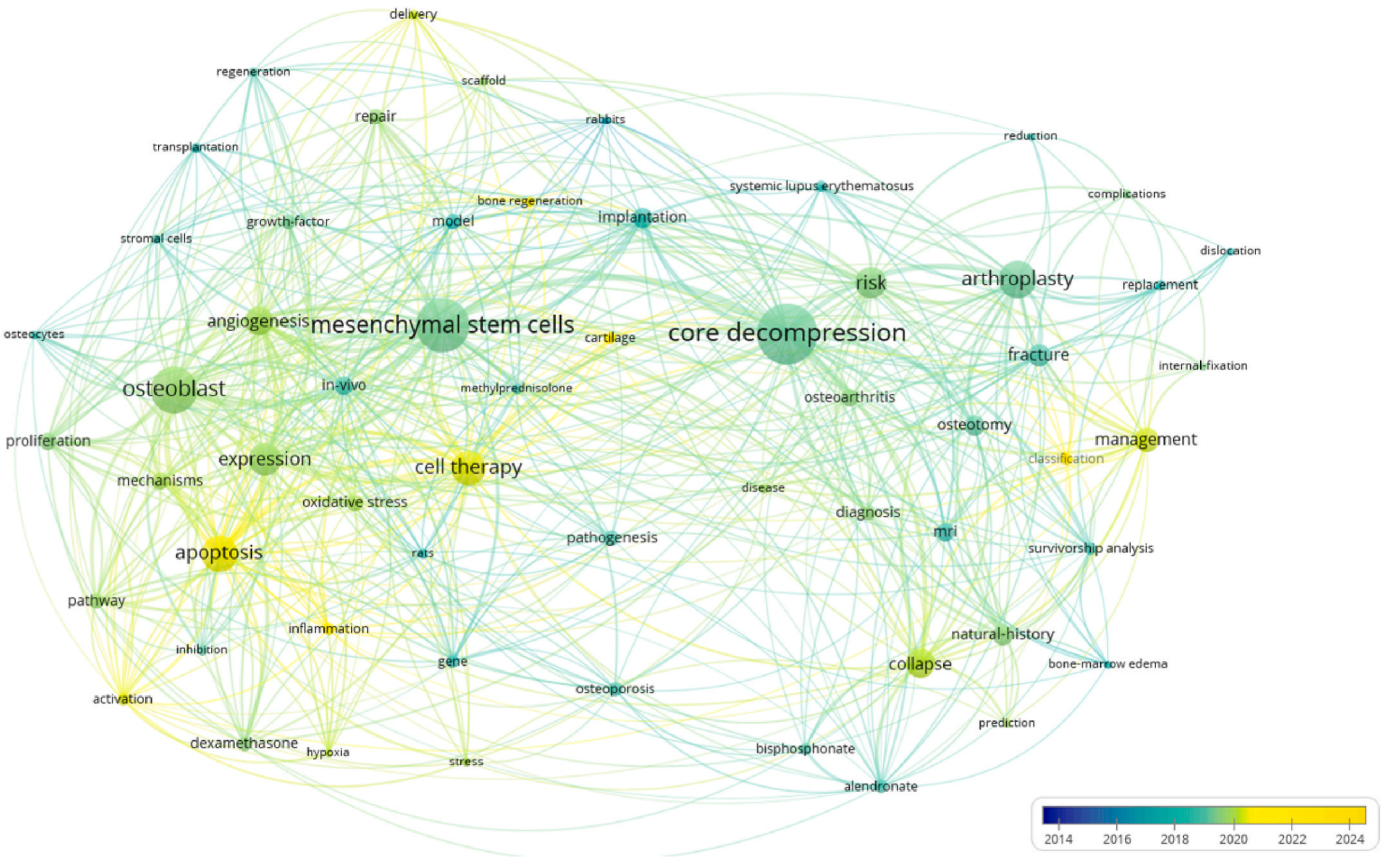

Fig. 7. Keyword co-occurrence map of the literature related to osteonecrosis of the femoral head treatment in the past decade showing amount and trend of development for different research topics.

likelihood of complications during THA. As a result, this treatment modality has fallen out of favor (Table 3) [1].

3.2.5. *Tissue engineering*

Tissue engineering combines advanced technologies from the fields of cell biology, biomaterial science, and bioengineering, aiming to quickly repair damaged tissues. Bone tissue engineering treats ONFH by introducing biomaterials, stem cells, and bioactive factors to areas with bone defects, with biomaterial-based scaffolds playing an essential role not only in mimicking the extracellular matrix but also in acting as a delivery system for bioactive cells and molecules. When selecting and designing biomaterials for the treatment of ONFH, many factors need to be considered, among which the most fundamental are biocompatibility and mechanical properties [168]. The biomaterials must have satisfactory biocompatibility and osteogenic properties, which play an important role in reconstructing the necrotic femoral head (Table 3). Moreover, the biomaterials need to possess good mechanical properties and be space-filling to provide sufficient subchondral support. At present, the most widely used biomaterials in animal experiments and clinical applications include bioceramics, polymers (natural or synthetic), and metals.

Bioceramics have excellent biocompatibility and osteoinductivity. The bioactive ions released from bioceramics, including Ca^{2+}, $PO4^{4-}$, and Mg^{2+}, have the potential to induce bone regeneration [185] (Table 4). Bioceramics have been considered a promising candidate for treating ONFH [186–200].

Natural polymers are a class of polymeric biomaterials derived from living sources. These polymers have excellent biocompatibility and negligible immunoreactivity, making them safe for implantation into the human body. However, due to their poor mechanical properties, they are often used in combination with other hard materials. Among natural polymers, collagen, gelatin hydrogel, and silk fibroin are the most commonly explored biomaterials for repairing ONFH [201–203].

Metals have good biomechanical properties and can provide sufficient subchondral support for the femoral head. Degradable materials are particularly promising as they can avoid the need for secondary surgical removal. Recent advances in additive manufacturing and topology optimization techniques offer unprecedented opportunities to modulate the mechanical properties of metals by adjusting their external and internal structures. To date, magnesium [204–210] (Table 5) and titanium [211–218] (Table 6) are the most widely explored metals for repairing ONFH.

In addition, biological scaffolds can be combined with other methods for treating ONFH, such as MSCs [169], bioactive molecules [170], and arteriovenous loops [171]. Although these biological scaffolds are promising, their therapeutic efficiency and long-term outcomes remain unclear and require further large-scale clinical studies.

4. Summary and conclusion

ONFH has high morbidity and disability rates and imposes a tremendous socioeconomic burden. The prevalence of ONFH is increasing, and the population of patients with ONFH is becoming younger. THA remains the most commonly used surgical procedure to treat ONFH, but it is not the best choice for young patients. With the increasing number of young ONFH patients, the use of hip-preserving surgery is gradually increasing. Patients' goals have shifted from merely delaying THA to preserving their own hip joints. Therefore, the development of joint-preserving procedures to effectively treat ONFH is particularly urgent. A comprehensive review of currently available hip joint-preserving treatments is useful in this context.

There are two types of hip joint-preserving strategies: nonoperative

and operative procedures. Among the nonoperative procedures, bisphosphonates, Chinese herbal medicine, and extracorporeal shockwave are the most commonly-used methods in clinical practice (Fig. 6). Although bisphosphonates have poor efficacy and serious side effects, they are still commonly used in clinical practice [18]. Traditional Chinese medicine, including Chinese herbal medicine, has been increasingly utilized as it can reduce pain and slow down ONFH progression [19,219]. The usage of extracorporeal shockwave therapy in clinical practice is gradually increasing, as it can effectively alleviate joint pain caused by ONFH and improve hip joint function [37,38]. Compared to nonoperative procedures, there is a much larger and growing body of research on operative procedures for ONFH treatment (Figs. 6 and 7). Surgical therapy is more effective than nonoperative treatments, and young people tend to recover faster after surgery. The strategy of using mesenchymal stem cells to treat ONFH has been most studied in the past decade (Fig. 7). They help to slow down or stop the necrotic process and prevent femoral head collapse by promoting bone regeneration and repair, improving blood supply, and utilizing anti-inflammatory and immunomodulatory mechanisms [155]. MSCs are mostly used in combination with core decompression, which has also been extensively studied over the past decade (Fig. 7). With the rapid development of biologics, cell therapy may become the next focus of surgical treatment.

Overall, nonoperative procedures can somewhat slow down the progression of ONFH and delay the need for joint replacement. However, they usually cannot fully cure the disease, except in cases of small necrosis areas (<10 %), likely due to the unclear pathogenesis of ONFH and the unrevealed mechanisms of various treatments [1]. Therefore, more basic research is needed in the future. In contrast, operative treatments aim to reverse the negative outcomes of necrosis by removing necrotic tissues and replacing them with new tissues, and therefore appear to be more promising. Currently, an emerging area in operative procedures is regenerative medicine, which could promote the generation of bone and blood vessels and restore hip joint function to pre-necrotic levels as much as possible. However, more research is necessary to optimize those operative treatments before they can be successfully translated into clinical practice.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

This study was supported by grants from the National Natural Science Foundation of China [grant number 12272017], the National Natural Science Foundation of China [grant number 82030122] and Beijing Natural Science Foundation [grant number L232058].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jot.2025.02.001.

References

[1] Mont MA, Salem HS, Piuzzi NS, Goodman SB, Jones LC. Nontraumatic osteonecrosis of the femoral head: where do we stand today?: a 5-year update. J Bone Joint Surg Am 2020;102(12):1084–99.
[2] Zhao D, Zhang F, Wang B, Liu B, Li L, Kim SY, et al. Guidelines for clinical diagnosis and treatment of osteonecrosis of the femoral head in adults (2019 version). J Orthop Translat 2020;21:100–10.
[3] Hines JT, Jo WL, Cui Q, Mont MA, Koo KH, Cheng EY, et al. Osteonecrosis of the femoral head: an updated review of ARCO on pathogenesis, staging and treatment. J Kor Med Sci 2021;36(24):e177.
[4] Wu T, Jiang Y, Tian H, Shi W, Wang Y, Li T. Systematic analysis of hip-preserving treatment for early osteonecrosis of the femoral head from the perspective of bibliometrics (2010-2023). J Orthop Surg Res 2023;18(1):959.
[5] Sai Krishna MLV, Kar S, Kumar R, Singh H, Mittal R, Digge VK. The role of conservative management in the avascular necrosis of the femoral head: a review of systematic reviews. Indian J Orthop 2023;57(3):410–20.
[6] Li K, Wu Q, Li H, Sun H, Xing Z, Li L, et al. Multiomic characterisation of the long-term sequelae of SARS survivors: a clinical observational study. EClinicalMedicine 2023;58:101884.
[7] Migliorini F, Maffulli N, Shukla T, D'Ambrosi R, Singla M, Vaish A, et al. The pandemic is gone but its consequences are here to stay: avascular necrosis following corticosteroids administration for severe COVID-19. J Orthop Surg Res 2024;19(1):135.
[8] Tang C, Wang Y, Lv H, Guan Z, Gu J. Caution against corticosteroid-based COVID-19 treatment. Lancet 2020;395(10239):1759–60.
[9] Atilla B, Bakircioglu S, Shope AJ, Parvizi J. Joint-preserving procedures for osteonecrosis of the femoral head. EFORT Open Rev 2019;4(12):647–58.
[10] Zhao D-W, Yu M, Hu K, Wang W, Yang L, Wang B-J, et al. Prevalence of nontraumatic osteonecrosis of the femoral head and its associated risk factors in the Chinese population: results from a nationally representative survey. Chin Med J 2015;128(21):2843–50.
[11] Amanatullah DF, Strauss EJ, Di Cesare PE. Current management options for osteonecrosis of the femoral head: part 1, diagnosis and nonoperative management. Am J Orthoped 2011;40(9):E186–92.
[12] George G, Lane JM. Osteonecrosis of the femoral head. J Am Acad Orthop Surg Glob Res Rev 2022;6(5).
[13] Sodhi N, Acuna A, Etcheson J, Mohamed N, Davila I, Ehiorobo JO, et al. Management of osteonecrosis of the femoral head. Bone Joint Lett J 2020;102-b (7_Supple_B):122–8.
[14] Pivec R, Johnson AJ, Mears SC, Mont MA. Hip arthroplasty. Lancet 2012;380 (9855):1768–77.
[15] Sultan AA, Higuera CA. Risk factors in septic revisions following total hip arthroplasty. Lancet Infect Dis 2018;18(9):931–3.
[16] Ng MK, Kobryn A, Golub IJ, Piuzzi NS, Wong CHJ, Jones L, et al. Increasing trend toward joint-preserving procedures for hip osteonecrosis in the United States from 2010 to 2019. Arthroplasty 2023;5(1):23.
[17] Lee YJ, Cui Q, Koo KH. Is there a role of pharmacological treatments in the prevention or treatment of osteonecrosis of the femoral head?: a systematic review. J Bone Metab 2019;26(1):13–8.
[18] Yuan HF, Guo CA, Yan ZQ. The use of bisphosphonate in the treatment of osteonecrosis of the femoral head: a meta-analysis of randomized control trials. Osteoporos Int 2016;27(1):295–9.
[19] Zhang Q, Yang F, Chen Y, Wang H, Chen D, He W, et al. Chinese herbal medicine formulas as adjuvant therapy for osteonecrosis of the femoral head: a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltim) 2018;97(36):e12196.
[20] Wen P, Zhang Y, Hao L, Yue J, Wang J, Wang T, et al. The effect of the necrotic area on the biomechanics of the femoral head - a finite element study. BMC Muscoskelet Disord 2020;21(1):211.
[21] Li TX, Huang ZQ, Li Y, Xue ZP, Sun JG, Gao HH, et al. Prediction of collapse using patient-specific finite element analysis of osteonecrosis of the femoral head. Orthop Surg 2019;11(5):794–800.
[22] Shah H, Singh KA, Joseph B. Does prolonged weight relief increase the chances of a favourable outcome after containment for perthes disease? J Pediatr Orthop 2023;43(2):e144–50.
[23] Peck JB, Greenhill DA, Morris WZ, Do DH, McGuire MF, Kim HKW. Prolonged non-weightbearing treatment decreases femoral head deformity compared to symptomatic treatment in the initial stage of Legg-Calvé-Perthes disease. J Pediatr Orthop B 2022;31(3):209–15.
[24] Giacon TA, Giancola F, Paganini M, Tiengo C, Camporesi EM, Bosco G. Hyperbaric oxygen therapy and A-PRF pre-treated implants in severe periodontitis: a case report. Int J Environ Res Publ Health 2021;18(2).
[25] Paderno E, Zanon V, Vezzani G, Giacon TA, Bernasek TL, Camporesi EM, et al. Evidence-supported HBO therapy in femoral head necrosis: a systematic review and meta-analysis. Int J Environ Res Publ Health 2021;18(6).
[26] Bosco G, Vezzani G, Mrakic Sposta S, Rizzato A, Enten G, Abou-Samra A, et al. Hyperbaric oxygen therapy ameliorates osteonecrosis in patients by modulating inflammation and oxidative stress. J Enzym Inhib Med Chem 2018;33(1):1501–5.
[27] Salameh M, Moghamis IS, Kokash O, Ahmed GO. Hyperbaric oxygen therapy for the treatment of Steinberg I and II avascular necrosis of the femoral head: a report of fifteen cases and literature review. Int Orthop 2021;45(10):2519–23.
[28] Moghamis I, Alhammoud AA, Kokash O, Alhaneedi GA. The outcome of hyperbaric oxygen therapy versus core decompression in the non-traumatic avascular necrosis of the femoral head: retrospective Cohort Study. Ann Med Surg (Lond) 2021;62:450–4.
[29] Li W, Ye Z, Wang W, Wang K, Li L, Zhao D. Clinical effect of hyperbaric oxygen therapy in the treatment of femoral head necrosis : a systematic review and meta-analysis. Orthopä 2017;46(5):440–6.
[30] Memar MY, Yekani M, Alizadeh N, Baghi HB. Hyperbaric oxygen therapy: antimicrobial mechanisms and clinical application for infections. Biomed Pharmacother 2019;109:440–7.
[31] Trock DH. Electromagnetic fields and magnets. Investigational treatment for musculoskeletal disorders. Rheum Dis Clin N Am 2000;26(1):51–62. viii.
[32] Cebrián JL, Milano GL, Francés A, Lopiz Y, Marco F, López-Durán L. Role of electromagnetic stimulation in the treatment of osteonecrosis of the femoral head in early stages. J Biomed Sci Eng 2014;7(5):252–7.
[33] Massari LFM, Cadossi R, Setti S, Traina GC. Biophysical stimulation with pulsed electromagnetic fields in osteonecrosis of the femoral head. J Bone Joint Surg Am 2006;88(Suppl 3):56–60.

[34] Zhang T, Zhao Z, Wang T. Pulsed electromagnetic fields as a promising therapy for glucocorticoid-induced osteoporosis. Front Bioeng Biotechnol 2023;11:1103515.
[35] Vadalà M, Morales-Medina JC, Vallelunga A, Palmieri B, Laurino C, Iannitti T. Mechanisms and therapeutic effectiveness of pulsed electromagnetic field therapy in oncology. Cancer Med 2016;5(11):3128–39.
[36] Roerdink RL, Dietvorst M, van der Zwaard B, van der Worp H, Zwerver J. Complications of extracorporeal shockwave therapy in plantar fasciitis: systematic review. Int J Surg 2017;46:133–45.
[37] Alkhawashki HM, Al-Boukai AA, Al-Harbi MS, Al-Rumaih MH, Al-Khawashki MH. The use of extracorporeal shock wave therapy (ESWT) in treating osteonecrosis of the femoral head (AVNFH): a retrospective study. Int Orthop 2023;47(12):2953–60.
[38] Algarni AD, Al Moallem HM. Clinical and radiological outcomes of extracorporeal shock wave therapy in early-stage femoral head osteonecrosis. Adv Orthop 2018;2018:7410246.
[39] Wang CJ, Huang CC, Wang JW, Wong T, Yang YJ. Long-term results of extracorporeal shockwave therapy and core decompression in osteonecrosis of the femoral head with eight- to nine-year follow-up. Biomed J 2012;35(6):481–5.
[40] Migliorati CA, Siegel MA, Elting LS. Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. Lancet Oncol 2006;7(6):508–14.
[41] Agarwala S, Shah SB. Ten-year follow-up of avascular necrosis of femoral head treated with alendronate for 3 years. J Arthroplast 2011;26(7):1128–34.
[42] Yuan HF, Christina VR, Guo CA, Chu YW, Liu RH, Yan ZQ. Involvement of MicroRNA-210 demethylation in steroid-associated osteonecrosis of the femoral head. Sci Rep 2016;6:20046.
[43] Chen CH, Chang JK, Lai KA, Hou SM, Chang CH, Wang GJ. Alendronate in the prevention of collapse of the femoral head in nontraumatic osteonecrosis: a two-year multicenter, prospective, randomized, double-blind, placebo-controlled study. Arthritis Rheum 2012;64(5):1572–8.
[44] Lee YK, Ha YC, Cho YJ, Suh KT, Kim SY, Won YY, et al. Does zoledronate prevent femoral head collapse from osteonecrosis? A prospective, randomized, open-label, multicenter study. J Bone Joint Surg Am 2015;97(14):1142–8.
[45] Li D, Yang Z, Wei Z, Kang P. Efficacy of bisphosphonates in the treatment of femoral head osteonecrosis: a PRISMA-compliant meta-analysis of animal studies and clinical trials. Sci Rep 2018;8(1):1450.
[46] Reyes C, Hitz M, Prieto-Alhambra D, Abrahamsen B. Risks and benefits of bisphosphonate therapies. J Cell Biochem 2016;117(1):20–8.
[47] Khosla S, Bilezikian JP, Dempster DW, Lewiecki EM, Miller PD, Neer RM, et al. Benefits and risks of bisphosphonate therapy for osteoporosis. J Clin Endocrinol Metab 2012;97(7):2272–82.
[48] Guo P, Gao F, Wang Y, Zhang Z, Sun W, Jiang B, et al. The use of anticoagulants for prevention and treatment of osteonecrosis of the femoral head: a systematic review. Medicine (Baltim) 2017;96(16):e6646.
[49] Glueck CJ, Freiberg RA, Sieve L, Wang P. Enoxaparin prevents progression of stages I and II osteonecrosis of the hip. Clin Orthop Relat Res 2005;435:164–70.
[50] Glueck CJ, Freiberg RA, Wissman R, Wang P. Long term anticoagulation (4-16 years) stops progression of idiopathic hip osteonecrosis associated with familial thrombophilia. Adv Orthop 2015;2015:138382.
[51] Glueck CJ, Freiberg RA, Fontaine RN, Sieve-Smith L, Wang P. Anticoagulant therapy for osteonecrosis associated with heritable hypofibrinolysis and thrombophilia. Expert Opin Investig Drugs 2001;10(7):1309–16.
[52] Nagasawa K, Tada Y, Koarada S, Tsukamoto H, Horiuchi T, Yoshizawa S, et al. Prevention of steroid-induced osteonecrosis of femoral head in systemic lupus erythematosus by anti-coagulant. Lupus 2006;15(6):354–7.
[53] Elango K, Javaid A, Khetarpal BK, Ramalingam S, Kolandaivel KP, Gunasekaran K, et al. The effects of warfarin and direct oral anticoagulants on systemic vascular calcification: a review. Cells 2021;10(4).
[54] Pritchett JW. Statin therapy decreases the risk of osteonecrosis in patients receiving steroids. Clin Orthop Relat Res 2001;386:173–8.
[55] Liao Y, Zhang P, Yuan B, Li L, Bao S. Pravastatin protects against avascular necrosis of femoral head via autophagy. Front Physiol 2018;9:307.
[56] Yin H, Yuan Z, Wang D. Multiple drilling combined with simvastatin versus multiple drilling alone for the treatment of avascular osteonecrosis of the femoral head: 3-year follow-up study. BMC Muscoskelet Disord 2016;17(1):344.
[57] Attardo S, Musumeci O, Velardo D, Toscano A. Statins neuromuscular adverse effects. Int J Mol Sci 2022;23(15).
[58] Jager M, Zilkens C, Bittersohl B, Matheney T, Kozina G, Blondin D, et al. Efficiency of iloprost treatment for osseous malperfusion. Int Orthop 2011;35(5):761–5.
[59] Classen T, Becker A, Landgraeber S, Haversath M, Li X, Zilkens C, et al. Long-term clinical results after iloprost treatment for bone marrow edema and avascular necrosis. Orthop Rev 2016;8(1):6150.
[60] Disch AC, Matziolis G, Perka C. The management of necrosis-associated and idiopathic bone-marrow oedema of the proximal femur by intravenous iloprost. J Bone Joint Surg Br 2005;87(4):560–4.
[61] Zippelius T, Perka C, Preininger B, Matziolis G, Strube P, Röhner E. Long-term effects of intravenous iloprost therapy in patients with bone marrow oedema of the hip. Acta Orthop Belg 2018;84(2):172–8.
[62] Zippelius T, Strube P, Rohe S, Schlattmann P, Dobrindt O, Caffard T, et al. The use of iloprost in the treatment of bone marrow edema syndrome of the proximal femur: a review and meta-analysis. J Pers Med 2022;12(11).
[63] Huang Z, Fu F, Ye H, Gao H, Tan B, Wang R, et al. Chinese herbal Huo-Gu formula for the treatment of steroid-associated osteonecrosis of femoral head: a 14-year follow-up of convalescent SARS patients. J Orthop Translat 2020;23:122–31.
[64] Li ZR, Cheng LM, Wang KZ, Yang NP, Yang SH, He W, et al. Herbal Fufang Xian Ling Gu Bao prevents corticosteroid-induced osteonecrosis of the femoral head-A first multicentre, randomised, double-blind, placebo-controlled clinical trial. J Orthop Translat 2017;12:36–44.
[65] Yeh YA, Chiang JH, Wu MY, Tsai CH, Hsu HC, Hsu HC, et al. Association of traditional Chinese medicine therapy with risk of total hip replacement in patients with nontraumatic osteonecrosis of the femoral head: a population-based cohort study. Evid Based Complement Alternat Med 2019;2019:5870179.
[66] Set T, Maras I, Khan AS, Ozdemir H. Management of Legg-Calve-Perthes disease with acupuncture: a case report. Acupunct Med 2013;31(1):105–7.
[67] Yang SQ. [Eleven cases of avascular necrosis of femoral head treated with moxibustion and acupuncture]. Zhongguo Zhen Jiu 2014;34(2):176.
[68] Wang JL, Hua CL, Nie HL. [Effect of electroacupuncture of quintuple needling combined with adductor relaxation method for osteonecrosis of the femoral head]. Zhen Ci Yan Jiu 2022;47(7):636–9.
[69] Wang Z, Zhou X, Xie L, Liang D, Wang Y, Zhang HA, et al. [Acupotomy and acupuncture in the treatment of avascular necrosis of femoral head at the early and middle stages:a clinical randomized controlled trial]. Zhongguo Zhen Jiu 2016;36(10):1031–5.
[70] Zhang HW, Lin ZX, Cheung F, Cho WC, Tang JL. Moxibustion for alleviating side effects of chemotherapy or radiotherapy in people with cancer. Cochrane Database Syst Rev 2018;11(11):CD010559.
[71] Jin H, Li L, Yu W, Fu Y. The efficacy of acupuncture and moxibustion for early and middle-stage osteonecrosis of the femeral head: a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltim) 2021;100(22):e26210.
[72] Mont MACJ, Fairbank AC. Core decompression versus nonoperative management for osteonecrosis of the hip. Clin Orthop Relat Res 1996;324:169–78.
[73] Huo MH, Stockton KG, Mont MA, Parvizi J. What's new in total hip arthroplasty. J Bone Joint Surg Am 2010;92(18):2959–72.
[74] Al-Jabri T, Tan JYQ, Tong GY, Shenoy R, Kayani B, Parratt T, et al. The role of electrical stimulation in the management of avascular necrosis of the femoral head in adults: a systematic review. BMC Muscoskelet Disord 2017;18(1):319.
[75] Chen WH, Guo WX, Li JX, Wei QS, Li ZQ, He W. Application of protective weight-bearing in osteonecrosis of the femoral head: a systematic review and meta-analysis of randomized controlled trials and observational studies. Front Surg 2022;9:1000073.
[76] Flatscher J, Pavez Loriè E, Mittermayr R, Meznik P, Slezak P, Redl H, et al. Pulsed electromagnetic fields (PEMF)-Physiological response and its potential in trauma treatment. Int J Mol Sci 2023;24(14).
[77] Li JP, Chen S, Peng H, Zhou JL, Fang HS. Pulsed electromagnetic fields protect the balance between adipogenesis and osteogenesis on steroid-induced osteonecrosis of femoral head at the pre-collapse stage in rats. Bioelectromagnetics 2014;35(3):170–80.
[78] Auersperg V, Trieb K. Extracorporeal shock wave therapy: an update. EFORT Open Rev 2020;5(10):584–92.
[79] Wang FS, Wang CJ, Chen YJ, Chang PR, Huang YT, Sun YC, et al. Ras induction of superoxide activates ERK-dependent angiogenic transcription factor HIF-1alpha and VEGF-A expression in shock wave-stimulated osteoblasts. J Biol Chem 2004;279(11):10331–7.
[80] Tan H, Tang P, Chai H, Ma W, Cao Y, Lin B, et al. Extracorporeal shock wave therapy with imaging examination for early osteonecrosis of the femoral head: a systematic review. Int J Surg 2024;;111(1):1144–53.
[81] Moya D, Ramón S, Schaden W, Wang CJ, Guiloff L, Cheng JH. The role of extracorporeal shockwave treatment in musculoskeletal disorders. J Bone Joint Surg Am 2018;100(3):251–63.
[82] Rezus E, Tamba BI, Badescu MC, Popescu D, Bratoiu I, Rezus C. Osteonecrosis of the femoral head in patients with hypercoagulability-from pathophysiology to therapeutic implications. Int J Mol Sci 2021;22(13).
[83] Hou R, Lei J, Xue D, Jing Y, Mi L, Guo Q, et al. The association of an elevated Th/Ts ratio and lupus anticoagulant with symptomatic osteonecrosis in systemic lupus erythematosus patients. Front Immunol 2024;15:1288234.
[84] Chotanaphuti T, Thongprasert S, Laoruengthana A. Low molecular weight heparin prevents the progression of precollapse osteonecrosis of the hip. J Med Assoc Thai 2013;96(10):1326–30.
[85] Riegger J, Maurer S, Pulasani S, Brenner RE. Simvastatin and fluvastatin attenuate trauma-induced cell death and catabolism in human cartilage. Front Bioeng Biotechnol 2022;10:965302.
[86] Yu Y, Lin L, Liu K, Jiang Y, Zhou Z. Effects of simvastatin on cartilage homeostasis in steroid-induced osteonecrosis of femoral head by inhibiting glucocorticoid receptor. Cells 2022;11(24).
[87] Zhang XX, He SH, Liang X, Li W, Li TF, Li DF. Aging, cell senescence, the pathogenesis and targeted therapies of osteoarthritis. Front Pharmacol 2021;12:728100.
[88] Soares EA, Novaes RD, Nakagaki WR, Fernandes GJ, Garcia JA, Camilli JA. Metabolic and structural bone disturbances induced by hyperlipidic diet in mice treated with simvastatin. Int J Exp Pathol 2015;96(4):261–8.
[89] Fusillo TF, Nguyen M. Bilateral avascular necrosis of the femoral heads secondary to familial hyperlipidemia. Cureus 2023;15(9):e44910.
[90] Ajmal M, Matas AJ, Kuskowski M, Cheng EY. Does statin usage reduce the risk of corticosteroid-related osteonecrosis in renal transplant population? Orthop Clin N Am 2009;40(2):235–9.
[91] Pountos I, Giannoudis PV. The role of Iloprost on bone edema and osteonecrosis: safety and clinical results. Expet Opin Drug Saf 2018;17(3):225–33.

[92] Huang ZQ, Fu FY, Li WL, Tan B, He HJ, Liu WG, et al. Current treatment modalities for osteonecrosis of femoral head in mainland China: a cross-sectional study. Orthop Surg 2020;12(6):1776–83.
[93] Fu F, Huang Z, Ye H, Tan B, Wang R, Chen W. Mechanisms and molecular targets of the tao-hong-Si-Wu-Tang formula for treatment of osteonecrosis of femoral head: a network pharmacology study. Evid Based Complement Alternat Med 2020;2020:7130105.
[94] Zheng H, Yang E, Peng H, Li J, Chen S, Zhou J, et al. Gastrodin prevents steroid-induced osteonecrosis of the femoral head in rats by anti-apoptosis. Chin Med J (Engl) 2014;127(22):3926–31.
[95] Sun K, Xue Y, Zhang X, Li X, Zhao J, Xu X, et al. Tanshinone I alleviates steroid-induced osteonecrosis of femoral heads and promotes angiogenesis: in vivo and in vitro studies. J Orthop Surg Res 2023;18(1):474.
[96] Zhao Y, Li S, Feng M, Zhang M, Liu Z, Yao Y, et al. Effects of puerarin-loaded tetrahedral framework nucleic acids on osteonecrosis of the femoral head. Small 2023;19(41):e2302326.
[97] Wang G, Ma C, Mo L, Chen J, Yuan J, Xu J, et al. Cycloastragenol prevents bone loss via inhibiting osteoclast activity in glucocorticoid-induced osteonecrosis of the femoral head: an in vivo study. J Orthop Translat 2024;45:178–87.
[98] Fang B, Li Y, Chen C, Wei Q, Zheng J, Liu Y, et al. Huo Xue Tong Luo capsule ameliorates osteonecrosis of femoral head through inhibiting lncRNA-Miat. J Ethnopharmacol 2019;238:111862.
[99] Zhang P, Xu H, Wang P, Dong R, Xia C, Shi Z, et al. Yougui pills exert osteoprotective effects on rabbit steroid-related osteonecrosis of the femoral head by activating beta-catenin. Biomed Pharmacother 2019;120:109520.
[100] Yang C, Wang J, Chen L, Xu T, Ming R, Hu Z, et al. Tongluo Shenggu capsule promotes angiogenesis to ameliorate glucocorticoid-induced femoral head necrosis via upregulating VEGF signaling pathway. Phytomedicine 2023;110:154629.
[101] Wang QR, An JJ, Zhang WL, Yang ZY, Zhao X, Kang PD. Core decompression prevents progression of asymptomatic type C osteonecrosis of femoral head according to the Japanese investigation committee classification: a retrospective study. Orthop Surg 2022;14(5):851–9.
[102] Mont MA, Ragland PS, Etienne G. Core decompression of the femoral head for osteonecrosis using percutaneous multiple small-diameter drilling. Clin Orthop Relat Res 2004;429:131–8.
[103] Song WS, Yoo JJ, Kim YM, Kim HJ. Results of multiple drilling compared with those of conventional methods of core decompression. Clin Orthop Relat Res 2007;454:139–46.
[104] Tan Y, He H, Wan Z, Qin J, Wen Y, Pan Z, et al. Study on the outcome of patients with aseptic femoral head necrosis treated with percutaneous multiple small-diameter drilling core decompression: a retrospective cohort study based on magnetic resonance imaging and equivalent sphere model analysis. J Orthop Surg Res 2020;15(1):264.
[105] Liu Z, Yang X, Li Y, Zeng WN, Zhao E, Zhou Z. Multiple drilling is not effective in reducing the rate of conversion to Total hip Arthroplasty in early-stage nontraumatic osteonecrosis of the femoral head: a case-control comparative study with a natural course. BMC Muscoskelet Disord 2021;22(1):535.
[106] Rajagopal M, Balch Samora J, Ellis TJ. Efficacy of core decompression as treatment for osteonecrosis of the hip: a systematic review. Hip Int 2012;22(5):489–93.
[107] Roth A, Beckmann J, Bohndorf K, Fischer A, Heiss C, Kenn W, et al. S3-Guideline non-traumatic adult femoral head necrosis. Arch Orthop Trauma Surg 2016;136(2):165–74.
[108] Nishio A, Sugioka Y. A new technique of the varus osteotomy at the upper end of the femur. J Orthop Traumatol 1971;20:381–6.
[109] Hamanishi M, Yasunaga Y, Yamasaki T, Mori R, Shoji T, Ochi M. The clinical and radiographic results of intertrochanteric curved varus osteotomy for idiopathic osteonecrosis of the femoral head. Arch Orthop Trauma Surg 2014;134(3):305–10.
[110] Sugioka Y, Hotokebuchi T, Tsutsui H. Transtrochanteric anterior rotational osteotomy for idiopathic and steroid-induced necrosis of the femoral head. Indications and long-term results. Clin Orthop Relat Res 1992;277:111–20.
[111] Mont MA, Fairbank AC, Krackow KA, Hungerford DS. Corrective osteotomy for osteonecrosis of the femoral head. The results of a long-term follow-up study. JBJS 1996;78(7):1032–8.
[112] Xu Y, Zeng P. A review and meta-analysis of the survival rate of adult with osteonecrosis of the femoral head treated with transtrochanteric rotational osteotomy. Medicine (Baltim) 2022;101(47):e31777.
[113] Quaranta M, Miranda L, Oliva F, Aletto C, Maffulli N. Osteotomies for avascular necrosis of the femoral head. Br Med Bull 2021;137(1):98–111.
[114] Shigemura T, Yamamoto Y, Murata Y, Sato T, Tsuchiya R, Mizuki N, et al. Total hip arthroplasty after failed transtrochanteric rotational osteotomy for osteonecrosis of the femoral head: a systematic review and meta-analysis. Orthop Traumatol Surg Res 2018;104(8):1163–70.
[115] Osawa Y, Seki T, Morita D, Takegami Y, Okura T, Ishiguro N. Total hip arthroplasty after transtrochanteric rotational osteotomy for osteonecrosis of the femoral head: a mean 10-year follow-up. J Arthroplast 2017;32(10):3088–92.
[116] Atsumi T, Nakanishi R, Yoshikawa Y, Watanabe M, Nishi M, Inagaki K. High-degree posterior rotational osteotomy for extensive collapsed femoral head osteonecrosis in teenagers: remodeling and results with a mean of 10-year follow-up. Arch Orthop Trauma Surg 2023;143(10):6039–48.
[117] Chughtai M, Piuzzi NS, Khlopas A, Jones LC, Goodman SB, Mont MA. An evidence-based guide to the treatment of osteonecrosis of the femoral head. Bone Joint Lett J 2017;99-b(10):1267–79.
[118] Pierce TP, Elmallah RK, Jauregui JJ, Poola S, Mont MA, Delanois RE. A current review of non-vascularized bone grafting in osteonecrosis of the femoral head. Curr Rev Musculoskelet Med 2015;8(3):240–5.
[119] Chen X, Tan X, Gao S, Zhang X, Li J, Liu Y. Sartorius muscle-pedicle bone graft for osteonecrosis of the femoral head. Int Orthop 2016;40(7):1417–25.
[120] Feng W, Chen J, Wu K, Lu L, Deng P, Ye P, et al. A comparative study of cortico-cancellous iliac bone graft with or without the combination of vascularized greater trochanter flap for the management of femoral head osteonecrosis: a minimum 6 years follow-up. BMC Muscoskelet Disord 2019;20(1):298.
[121] Changjun C, Donghai L, Xin Z, Liyile C, Qiuru W, Pengde K. Mid- to long-term results of modified non-vascularized allogeneic fibula grafting combined with core decompression and bone grafting for early femoral head necrosis. J Orthop Surg Res 2020;15(1):116.
[122] Jie K, Feng W, Li F, Wu K, Chen J, Zhou G, et al. Long-term survival and clinical outcomes of non-vascularized autologous and allogeneic fibular grafts are comparable for treating osteonecrosis of the femoral head. J Orthop Surg Res 2021;16(1):109.
[123] Yang S, Wu X, Xu W, Ye S, Liu X, Liu X. Structural augmentation with biomaterial-loaded allograft threaded cage for the treatment of femoral head osteonecrosis. J Arthroplast 2010;25(8):1223–30.
[124] Zhao P, Hao J. Analysis of the long-term efficacy of core decompression with synthetic calcium-sulfate bone grafting on non-traumatic osteonecrosis of the femoral head. Med Sci (Paris) 34 Focus issue 2018;F1:43–6.
[125] Buckley PD, Gearen PF, Petty RW. Structural bone-grafting for early atraumatic avascular necrosis of the femoral head. J Bone Joint Surg Am 1991;73(9):1357–64.
[126] Wu CT, Yen SH, Lin PC, Wang JW. Long-term outcomes of Phemister bone grafting for patients with non-traumatic osteonecrosis of the femoral head. Int Orthop 2019;43(3):579–87.
[127] Yu PA, Peng KT, Huang TW, Hsu RW, Hsu WH, Lee MS. Injectable synthetic bone graft substitute combined with core decompression in the treatment of advanced osteonecrosis of the femoral head: a 5-year follow-up. Biomed J 2015;38(3):257–61.
[128] Cheng Q, Zhao FC, Xu SZ, Zheng L, Zheng X. Modified trapdoor procedures using autogenous tricortical iliac graft without preserving the broken cartilage for treatment of osteonecrosis of the femoral head: a prospective cohort study with historical controls. J Orthop Surg Res 2020;15(1):183.
[129] Akman B, Guven M, Kadioglu B, Ozkan NK, Yonga O, Ozturan B. A new modification of the Trapdoor Procedure without surgical hip dislocation in the management of patients with osteonecrosis of the femoral head: a retrospective case series. Acta Orthop Traumatol Turcica 2021;55(4):299–305.
[130] Mont MA, Einhorn TA, Sponseller PD, Hungerford DS. The trapdoor procedure using autogenous cortical and cancellous bone grafts for osteonecrosis of the femoral head. J Bone Joint Surg Br 1998;80(1):56–62.
[131] Wu CT, Kuo FC, Yen SH, Lin PC, Wang JW, Lee MS. Impaction bone grafting augmented with a wire coil by the lightbulb technique for osteonecrosis of the femoral head. J Arthroplast 2022;37(10):2063–70.
[132] Wang BL, Sun W, Shi ZC, Zhang NF, Yue DB, Guo WS, et al. Treatment of nontraumatic osteonecrosis of the femoral head using bone impaction grafting through a femoral neck window. Int Orthop 2010;34(5):635–9.
[133] Yildiz C, Erdem Y, Koca K. Lightbulb technique for the treatment of osteonecrosis of the femoral head. Hip Int 2018;28(3):272–7.
[134] Wang Q, Li D, Yang Z, Kang P. Femoral head and neck fenestration through a direct anterior approach combined with compacted autograft for the treatment of early stage nontraumatic osteonecrosis of the femoral head: a retrospective study. J Arthroplast 2020;35(3):652–60.
[135] Banerjee S, Issa K, Pivec R, Kapadia BH, Khanuja HS, Mont MA. Osteonecrosis of the hip: treatment options and outcomes. Orthop Clin N Am 2013;44(4):463–76.
[136] Kim SY, Kim YG, Kim PT, Ihn JC, Cho BC, Koo KH. Vascularized compared with nonvascularized fibular grafts for large osteonecrotic lesions of the femoral head. J Bone Joint Surg Am 2005;87(9):2012–8.
[137] Chen CC, Lin CL, Chen WC, Shih HN, Ueng SW, Lee MS. Vascularized iliac bone-grafting for osteonecrosis with segmental collapse of the femoral head. J Bone Joint Surg Am 2009;91(10):2390–4.
[138] Zeng YR, He S, Feng WJ, Li FL, Li J, Jian LY, et al. Vascularised greater trochanter bone graft, combined free iliac flap and impaction bone grafting for osteonecrosis of the femoral head. Int Orthop 2013;37(3):391–8.
[139] Zhao D, Wang B, Liu B. Vascularized iliac bone flap transfer for early and middle stages of osteonecrosis of the femoral head. JBJS Essent Surg Tech 2019;9(1):e5.
[140] Asmus A, Vogel K, Vogel A, Eichenauer F, Kim S, Eisenschenk A. [Pedicled vascularized iliac bone graft for treatment of osteonecrosis of the femoral head]. Operat Orthop Traumatol 2020;32(2):127–38.
[141] Cao L, Guo C, Chen J, Chen Z, Yan Z. Free vascularized fibular grafting improves vascularity compared with core decompression in femoral head osteonecrosis: a randomized clinical trial. Clin Orthop Relat Res 2017;475(9):2230–40.
[142] Urbaniak JR, Coogan PG, Gunneson EB, Nunley JA. Treatment of osteonecrosis of the femoral head with free vascularized fibular grafting. A long-term follow-up study of one hundred and three hips. J Bone Joint Surg Am 1995;77(5):681–94.
[143] Chen W, Du W, Wu P, Yu F, Wang Y, Chen N, et al. Outcomes of free vascularized iliac bone flap for severe traumatic osteonecrosis of femoral head in young adults. Eur J Trauma Emerg Surg 2023;49(3):1417–24.
[144] Barla M, Polirsztok E, Peltie E, Jouve JL, Legre R, Dautel G, et al. Free vascularised fibular flap harvesting in children: an analysis of donor-site morbidity. Orthop Traumatol Surg Res 2017;103(7):1109–13.
[145] Houdek MT, Bayne CO, Bishop AT, Shin AY. The outcome and complications of vascularised fibular grafts. Bone Joint Lett J 2017;99-b(1):134–8.

[146] Cao Z, Ou Q, Pang X, Wu P, Du W, Tang J. Comparison of free vascularized iliac bone flap grafting versus pedicled iliac bone flap grafting for treatment of osteonecrosis of the femoral head. J Plast Reconstr Aesthetic Surg 2021;74(6):1261–8.
[147] Hernigou P, Beaujean F. Treatment of osteonecrosis with autologous bone marrow grafting. Clin Orthop Relat Res 2002;405:14–23.
[148] Nally FJ, Zanotti G, Buttaro MA, Diaz Dilernia F, Mansilla IG, Comba FM, et al. THA conversion rate comparing decompression alone, with autologous bone graft or stem cells in osteonecrosis. Hip Int 2018;28(2):189–93.
[149] Pepke W, Kasten P, Beckmann NA, Janicki P, Egermann M. Core decompression and autologous bone marrow concentrate for treatment of femoral head osteonecrosis: a randomized prospective study. Orthop Rev 2016;8(1):6162.
[150] Lim YW, Kim YS, Lee JW, Kwon SY. Stem cell implantation for osteonecrosis of the femoral head. Exp Mol Med 2013;45(11):e61.
[151] Kang JS, Suh YJ, Moon KH, Park JS, Roh TH, Park MH, et al. Clinical efficiency of bone marrow mesenchymal stem cell implantation for osteonecrosis of the femoral head: a matched pair control study with simple core decompression. Stem Cell Res Ther 2018;9(1):274.
[152] Hernigou P, Dubory A, Homma Y, Guissou I, Flouzat Lachaniette CH, Chevallier N, et al. Cell therapy versus simultaneous contralateral decompression in symptomatic corticosteroid osteonecrosis: a thirty year follow-up prospective randomized study of one hundred and twenty five adult patients. Int Orthop 2018;42(7):1639–49.
[153] Wang Z, Sun QM, Zhang FQ, Zhang QL, Wang LG, Wang WJ. Core decompression combined with autologous bone marrow stem cells versus core decompression alone for patients with osteonecrosis of the femoral head: a meta-analysis. Int J Surg 2019;69:23–31.
[154] Calori GM, Mazza E, Colombo A, Mazzola S, Colombo M. Core decompression and biotechnologies in the treatment of avascular necrosis of the femoral head. EFORT Open Rev 2017;2(2):41–50.
[155] Wang X, Hu L, Wei B, Wang J, Hou D, Deng X. Regenerative therapies for femoral head necrosis in the past two decades: a systematic review and network meta-analysis. Stem Cell Res Ther 2024;15(1):21.
[156] Li M, Chen D, Ma Y, Zheng M, Zheng Q. Stem cell therapy combined with core decompression versus core decompression alone in the treatment of avascular necrosis of the femoral head: a systematic review and meta-analysis. J Orthop Surg Res 2023;18(1):560.
[157] Lou P, Zhou G, Wei B, Deng X, Hou D. Bone grafting for femoral head necrosis in the past decade: a systematic review and network meta-analysis. Int J Surg 2023;109(3):412–8.
[158] Zhu S, Zhang X, Chen X, Wang Y, Li S, Qian W. Comparison of cell therapy and other novel adjunctive therapies combined with core decompression for the treatment of osteonecrosis of the femoral head : a systematic review and meta-analysis of 20 studies. Bone Joint Res 2021;10(7):445–58.
[159] Xu Y, Jiang Y, Xia C, Wang Y, Zhao Z, Li T. Stem cell therapy for osteonecrosis of femoral head: opportunities and challenges. Regen Ther 2020;15:295–304.
[160] Wang X, Zhou K, Li Y, Xie H, Wang B. Preparation, modification, and clinical application of porous tantalum scaffolds. Front Bioeng Biotechnol 2023;11:1127939.
[161] Liu ZH, Guo WS, Li ZR, Cheng LM, Zhang QD, Yue DB, et al. Porous tantalum rods for treating osteonecrosis of the femoral head. Genet Mol Res 2014;13(4):8342–52.
[162] Zhang Y, Chen W, Yang Z, Sun JN, Hu ZH, Hua ZJ, et al. Porous tantalum implant for treatment of early-stage osteonecrosis of the femoral head: a minimum 5-year follow-up study. BMC Surg 2021;21(1):360.
[163] Tsao AKRJ, Christie MJ, Dore DD, Heck DA, Robertson DD, Poggie RA. Biomechanical and clinical evaluations of a porous tantalum implant for the treatment of early-stage osteonecrosis. J Bone Joint Surg Am 2005;87(Suppl 2):22–7.
[164] Nadeau MSC, Theodoropoulos JS, Harvey EJ. Short term clinical outcome of a porous tantalum implant for the treatment of advanced osteonecrosis of the femoral head. Mcgill J Med 2007;10(1):4–10.
[165] Tanzer M, Bobyn JD, Krygier JJ, Karabasz D. Histopathologic retrieval analysis of clinically failed porous tantalum osteonecrosis implants. J Bone Joint Surg Am 2008;90(6):1282–9.
[166] Ma J, Sun W, Gao F, Guo W, Wang Y, Li Z. Porous tantalum implant in treating osteonecrosis of the femoral head: still a viable option? Sci Rep 2016;6:28227.
[167] Liu W, Hu Y, Huang Z, Shi Z, Xiao J. Analysis of peripheral bone reconstruction after the failure of hip osteonecrosis treatment with porous tantalum rod implantation. Int Orthop 2022;46(6):1323–30.
[168] Bian Y, Hu T, Lv Z, Xu Y, Wang Y, Wang H, et al. Bone tissue engineering for treating osteonecrosis of the femoral head. Exploration 2023;3(2).
[169] Song Y, Wu H, Gao Y, Li J, Lin K, Liu B, et al. Zinc silicate/nano-hydroxyapatite/collagen scaffolds promote angiogenesis and bone regeneration via the p38 MAPK pathway in activated monocytes. ACS Appl Mater Interfaces 2020;12(14):16058–75.
[170] Li F, Cao Z, Li K, Huang K, Yang C, Li Y, et al. Cryogenic 3D printing of ss-TCP/PLGA composite scaffolds incorporated with BpV (pic) for treating early avascular necrosis of femoral head. Front Bioeng Biotechnol 2021;9:748151.
[171] Horch RE, Beier JP, Kneser U, Arkudas A. Successful human long-term application of in situ bone tissue engineering. J Cell Mol Med 2014;18(7):1478–85.
[172] Hua KC, Yang XG, Feng JT, Wang F, Yang L, Zhang H, et al. The efficacy and safety of core decompression for the treatment of femoral head necrosis: a systematic review and meta-analysis. J Orthop Surg Res 2019;14(1):306.
[173] Li J, Mo L, Bai G, Wang Z, Zhang H, Li J. One in five patients require conversion to arthroplasty after non-vascularized bone grafts in patients with osteonecrosis of the femoral head: a systematic review. J Orthop Surg Res 2023;18(1):77.
[174] Seyler TM, Marker DR, Ulrich SD, Fatscher T, Mont MA. Nonvascularized bone grafting defers joint arthroplasty in hip osteonecrosis. Clin Orthop Relat Res 2008;466(5):1125–32.
[175] Aluisio FV, Urbaniak JR. Proximal femur fractures after free vascularized fibular grafting to the hip. Clin Orthop Relat Res 1998;356:192–201.
[176] Che Z, Song Y, Zhu L, Liu T, Li X, Huang L. Emerging roles of growth factors in osteonecrosis of the femoral head. Front Genet 2022;13:1037190.
[177] Shu P, Sun DL, Shu ZX, Tian S, Pan Q, Wen CJ, et al. Therapeutic applications of genes and gene-engineered mesenchymal stem cells for femoral head necrosis. Hum Gene Ther 2020;31(5–6):286–96.
[178] Cui Y, Huang T, Zhang Z, Yang Z, Hao F, Yuan T, et al. The potential effect of BMSCs with miR-27a in improving steroid-induced osteonecrosis of the femoral head. Sci Rep 2022;12(1):21051.
[179] Wu F, Jiao J, Liu F, Yang Y, Zhang S, Fang Z, et al. Hypermethylation of Frizzled1 is associated with Wnt/beta-catenin signaling inactivation in mesenchymal stem cells of patients with steroid-associated osteonecrosis. Exp Mol Med 2019;51(2):1–9.
[180] Basal O, Atay T, Ciris IM, Baykal YB. Epidermal growth factor (EGF) promotes bone healing in surgically induced osteonecrosis of the femoral head (ONFH). Bosn J Basic Med Sci 2018;18(4):352–60.
[181] Bu P, Xie W, Wang S, Yang Z, Peng K, Zhang W, et al. EGFL6 activates the ERK signaling to improve angiogenesis and osteogenesis of BMSCs in patients with steroid-induced osteonecrosis of the femoral head. Naunyn-Schmiedebergs Arch Pharmacol 2023.
[182] Jiang H, Lin C, Cai T, Jiang L, Lou C, Lin S, et al. Taxifolin-mediated Nrf2 activation ameliorates oxidative stress and apoptosis for the treatment of glucocorticoid-induced osteonecrosis of the femoral head. Phytother Res 2023;38(1):156–73.
[183] Okamoto M, Nakashima H, Sakai K, Takegami Y, Osawa Y, Watanabe J, et al. Cellular senescence is associated with osteonecrosis of the femoral head while mesenchymal stem cell conditioned medium inhibits bone collapse. Sci Rep 2024;14(1):3329.
[184] Gao H, Yang J, Jin X, Qu X, Zhang F, Zhang D, et al. Porous tantalum scaffolds: fabrication, structure, properties, and orthopedic applications. Mater Des 2021;210.
[185] Raina DB, Matuszewski LM, Vater C, Bolte J, Isaksson H, Lidgren L, et al. A facile one-stage treatment of critical bone defects using a calcium sulfate/hydroxyapatite biomaterial providing spatiotemporal delivery of bone morphogenic protein-2 and zoledronic acid. Sci Adv 2020;6(48).
[186] Wen Y, Xun S, Haoye M, Baichuan S, Peng C, Xuejian L, et al. 3D printed porous ceramic scaffolds for bone tissue engineering: a review. Biomater Sci 2017;5(9):1690–8.
[187] Ma H, Feng C, Chang J, Wu C. 3D-printed bioceramic scaffolds: from bone tissue engineering to tumor therapy. Acta Biomater 2018;79:37–59.
[188] Peleg K, Rozenfeld M, Radomislensky I, Novikov I, Freedman LS, Israeli A. Policy encouraging earlier hip fracture surgery can decrease the long-term mortality of elderly patients. Injury 2014;45(7):1085–90.
[189] Wang Y, Zhu W, Xiao K, Li Z, Ma Q, Li W, et al. Self-healing and injectable hybrid hydrogel for bone regeneration of femoral head necrosis and defect. Biochem Biophys Res Commun 2019;508(1):25–30.
[190] Wang L, Xu L, Peng C, Teng G, Wang Y, Xie X, et al. The effect of bone marrow mesenchymal stem cell and nano-hydroxyapatite/collagen I/poly-L-lactic acid scaffold implantation on the treatment of avascular necrosis of the femoral head in rabbits. Exp Ther Med 2019;18(3):2021–8.
[191] Wang G, Li Y, Sun T, Wang C, Qiao L, Wang Y, et al. BMSC affinity peptide-functionalized beta-tricalcium phosphate scaffolds promoting repair of osteonecrosis of the femoral head. J Orthop Surg Res 2019;14(1):204.
[192] Lu Y, Wang Z, Lu X, Lu J, Chen X, Niu D, et al. [Minimally invasive treatment for osteonecrosis of the femoral head in ARCO stage II and III with bioceramic system]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2019;33(10):1291–8.
[193] Aoyama T, Goto K, Kakinoki R, Ikeguchi R, Ueda M, Kasai Y, et al. An exploratory clinical trial for idiopathic osteonecrosis of femoral head by cultured autologous multipotent mesenchymal stromal cells augmented with vascularized bone grafts. Tissue Eng Part B Rev 2014;20(4):233–42.
[194] Yang P, Bian C, Huang X, Shi A, Wang C, Wang K. Core decompression in combination with nano-hydroxyapatite/polyamide 66 rod for the treatment of osteonecrosis of the femoral head. Arch Orthop Trauma Surg 2014;134(1):103–12.
[195] Lu Y, Lu X, Li M, Chen X, Liu Y, Feng X, et al. Minimally invasive treatment for osteonecrosis of the femoral head with angioconductive bioceramic rod. Int Orthop 2018;42(7):1567–73.
[196] Hernandez A, Nunez JH, Sallent A, Gargallo-Margarit A, Gallardo-Calero I, Barro V. Core decompression combined with implantation of autologous bone marrow concentrate with tricalcium phosphate does not prevent radiographic progression in early stage osteonecrosis of the hip. Clin Orthop Surg 2020;12(2):151–7.
[197] Liang D, Pei J, Zhang L, Ling H, Liu Y, Chen X. Treatment of pre-collapse non-traumatic osteonecrosis of the femoral head through Orthopdische Chirurgie Munchen approach combined with autologous bone mixed with beta-tricalcium phosphate porous bioceramic bone graft: a retrospective study of mid-term results. J Orthop Surg Res 2021;16(1):492.

[198] Zhang L, Zhang J, Liang D, Ling H, Zhang Y, Liu Y, et al. Clinical study on minimally invasive treatment of femoral head necrosis with two different bone graft materials. Int Orthop 2021;45(3):585–91.
[199] Jameel J, Sinha S, Kumar A, Qureshi OA, Kumar S, Aggarwal N, et al. Effectiveness of calcium sulfate and hydroxyapatite composite in collapse prevention in osteonecrosis of femoral head. Cureus 2022;14(4):e24408.
[200] Wan J, Hu Y, Li J, Zeng Y, Ren H. Comparison of the outcome of different bone grafts combined with modified core decompression for the treatment of ARCO II stage femoral head necrosis. Int Orthop 2022;46(9):1955–62.
[201] Li D, Xie X, Yang Z, Wang C, Wei Z, Kang P. Enhanced bone defect repairing effects in glucocorticoid-induced osteonecrosis of the femoral head using a porous nano-lithium-hydroxyapatite/gelatin microsphere/erythropoietin composite scaffold. Biomater Sci 2018;6(3):519–37.
[202] Phipps MC, Monte F, Mehta M, Kim HK. Intraosseous delivery of bone morphogenic protein-2 using a self-assembling peptide hydrogel. Biomacromolecules 2016;17(7):2329–36.
[203] Wang J, Mi R, Zhao G, Shi J, Chen J, Liu C, et al. A silk-based high impact composite for the core decompression of the femoral head. J Mater Chem B 2020; 8(42):9734–43.
[204] Wang Y, Shen S, Hu T, Williams GR, Bian Y, Feng B, et al. Layered double hydroxide modified bone cement promoting osseointegration via multiple osteogenic signal pathways. ACS Nano 2021;15(6):9732–45.
[205] He D, Zhuang C, Xu S, Ke X, Yang X, Zhang L, et al. 3D printing of Mg-substituted wollastonite reinforcing diopside porous bioceramics with enhanced mechanical and biological performances. Bioact Mater 2016;1(1):85–92.
[206] Katiella KA, Yanru Z, Hui Z. Magnesium alloy transfected BMSCs-BMP-2 composite in repair of femoral head necrosis with assessment of visceral organs. SpringerPlus 2016;5(1):1857.
[207] Wang Y, Mei X, Bian Y, Hu T, Weng X, Liang R, et al. Magnesium-based layered double hydroxide nanosheets: a new bone repair material with unprecedented osteogenic differentiation performance. Nanoscale 2020;12(37):19075–82.
[208] Zhao D, Huang S, Lu F, Wang B, Yang L, Qin L, et al. Vascularized bone grafting fixed by biodegradable magnesium screw for treating osteonecrosis of the femoral head. Biomaterials 2016;81:84–92.
[209] Cheng Q, Shan C, Pu L, Xu Y. [Clinical study of a new biodegradable magnesium internal fixation screw in treatment of osteonecrosis of the femoral head]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2022;36(11):1343–50.
[210] Sun J, Li Z, Liu S, Xia T, Shen J. Biodegradable magnesium screw, titanium screw and direct embedding fixation in pedicled vascularized iliac bone graft transfer for osteonecrosis of the femoral head: a randomized controlled study. J Orthop Surg Res 2023;18(1):523.
[211] Zhu W, Zhao Y, Ma Q, Wang Y, Wu Z, Weng X. 3D-printed porous titanium changed femoral head repair growth patterns: osteogenesis and vascularisation in porous titanium. J Mater Sci Mater Med 2017;28(4):62.
[212] Wang C, Liu D, Xie Q, Liu J, Deng S, Gong K, et al. A 3D printed porous titanium alloy rod with diamond crystal lattice for treatment of the early-stage femoral head osteonecrosis in sheep. Int J Med Sci 2019;16(3):486–93.
[213] Wang C, Xie Q, Yang L, Liu J, Liu D, Li Z, et al. A 3D printed porous titanium alloy rod with biogenic lamellar configuration for treatment of the early-stage femoral head osteonecrosis in sheep. J Mech Behav Biomed Mater 2020;106:103738.
[214] Gao R, Ji W, Xia T, Fan Y, Wei W, Shi L, et al. Three-dimensional-printed titanium alloy porous scaffold combined with trans-cinnamaldehyde for repairing osteonecrosis of the femoral head in a dog model. Am J Transl Res 2020;12(3): 1070–9.
[215] Li B, Yu L, Huang Z, Liang Y, Li G, Zhao Y. A novel device for treatment of osteonecrosis of femoral head: feasibility and preliminary efficacy of animal study. J Orthop Translat 2021;31:20–5.
[216] Chen XT, Tan XY, Liu YW, Zhang XD, Liu LY, Jia YD. [Application of minimally invasive, decompression bone graft implantation combined with metal trabecular bone reconstruction system for early stage osteonecrosis of femoral head]. Zhong Guo Gu Shang 2015;28(5):422–5.
[217] Zhang Y, Zhang L, Sun R, Jia Y, Chen X, Liu Y, et al. A new 3D printed titanium metal trabecular bone reconstruction system for early osteonecrosis of the femoral head. Medicine (Baltim) 2018;97(26):e11088.
[218] Chen XT, Zhu YJ, Liu YW, Chen K, Xu WW, Zhang LL, et al. Metal trabecular bone reconstruction system better improves clinical efficacy and biomechanical repair of osteonecrosis of the femoral head than free vascularized fibular graft: a case-control study. J Cell Physiol 2019;234(11):20957–68.
[219] Wei QS, Hong GJ, Yuan YJ, Chen ZQ, Zhang QW, He W. Huo Xue Tong Luo capsule, a vasoactive herbal formula prevents progression of asymptomatic osteonecrosis of femoral head: a prospective study. J Orthop Translat 2018;18: 65–73.