

Treatment of non-traumatic avascular necrosis of the femoral head (Review)

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Abstract. Non-traumatic osteonecrosis of the femoral head is the main cause of disability in young individuals and incurs major health care expenditure. The lifestyle changes in recent years, especially increased use of hormones and alcohol consumption, has greatly increased the incidence of femoral head necrosis. The underlying causes and risk factors of osteonecrosis of the femoral head are increasingly being elucidated, which has led to the development of novel surgical and non-surgical treatment options. Although the main goal of any treatment method is prevention and delaying the progression of disease, there is no common consensus on the most suitable method of treatment. The present review discussed the latest developments in the etiology and treatment methods for femoral head necrosis.

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1. Introduction

Non-traumatic osteonecrosis of the femoral head (NONFH) is the result of impaired blood supply to the femoral head and structural and functional disruption of local articular cartilage, subchondral bone and blood vessels (Fig. 1), which culminate in subchondral osteonecrosis, femoral head collapse and hip joint pain (1). Mont *et al* (2) estimate that the total number of patients with NONFH worldwide could reach >20 million in the next decade. The pain and limited hip joint mobility resulting from femoral head necrosis can seriously affect the quality of life of the patient.

NONFH is a chronic disease with risk factors including long-term steroid use, excessive alcohol consumption and other underlying disease (3,4). Early diagnosis is difficult and there is currently no specific diagnostic standard or treatment that can reverse early-stage femoral head necrosis. Therefore, most patients with NONFH already show substantial necrosis at the time of diagnosis. The early-stage treatments are typically palliative and experimental, rather than preventive and curative. Given the personal and social burden of NONFH, the optimal treatment method is based on the individual needs of the patients. The most suitable course of action is to perform appropriate physical and minimally invasive surgery when first diagnosed. In case the symptoms are not sufficiently relieved within a reasonable period, hip replacement surgery needs to be performed. The present review examined recent developments regarding the treatment methods of NONFH and the underlying mechanisms.

2. Epidemiology

NONFH has a complex etiology and the most common causes are hormonal disturbances and excessive alcohol consumption. The risk of osteonecrosis is significantly higher in adolescents and adult compared with children (3,4). Every year in the United States alone ~10,000-20,000 new cases of ONFH are diagnosed; it is common in individuals aged between

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Abbreviations: ARCO, association research circulation osseous; BMSCs, bone marrow mononuclear cells; CD, core decompression; ESWT, energy extracorporeal shock wave therapy; hBMSCs, human bone mesenchymal stem cells; HBO, hyperbaric oxygen; HRA, hip resurfacing; NONFH, non-traumatic osteonecrosis of the femoral head; ONFH, osteonecrosis of the femoral head; PEMF, pulsed electromagnetic fields; PRP, platelets in platelet-rich plasma; SCD, sickle cell disease; SLE, systemic lupus erythematosus; TCP, tricalcium phosphate; VAS, visual analog scale; VEGF, vascular endothelial growth factor; HHS, Harris hip score

Key words: femoral head necrosis, platelet rich plasma, core decompression, bone-marrow stem cell transplantation, joint replacement

20-50 years and 5-12% of the patients eventually undergo total hip replacement (5). In India, the mean age of onset of femoral head necrosis is 34.71 years and the male to female ratio is 5:1 (3). More than one-third (37.3%) of patients with ONFH have a history of long-term steroid usage, whereas 21.3% of the cases are idiopathic and chronic alcoholism is the underlying cause in 20.1% of the patients (3). In Japan, the incidence of femoral head necrosis is relatively low in men aged 40-49 years and significantly higher in individuals aged >50 years. Among women, the incidence rate is lower in the 16-29 years age bracket and increases markedly in the 30-39 and 60-69 age groups (4). In addition, 48 and 35% of ONFH cases among males are respectively alcohol- and hormone-induced. By contrast, 70% of the cases among females have a hormonal basis (6). Studies have shown that high-dose corticosteroids (>40 mg/day) significantly increase the risk of NONFH (7,8) and every 10 mg increase in the dose increases the incidence rate by 3.6% (9).

3. Pathogenesis

Studies have shown that femoral head necrosis is associated with several underlying diseases (Table I), including trauma or surgery of the hip joint, excessive corticosteroid production, hyperlipidemia, abnormal blood pressure, autoimmune diseases, endotoxin poisoning, smoking, excessive alcohol consumption and blood hypercoagulability (10). All of these pathological changes can eventually lead to vascular damage, bone marrow infarction and avascular necrosis.

Hormones. Long-term steroid use is the most common cause of NONFH (11), as it can lead to microthrombosis and impede blood and oxygen supply to the femoral head, resulting in osteonecrosis (12). Kuroda *et al* (13) followed up 78 systemic lupus erythematosus (SLE) patients receiving high-dose prednisolone treatment and found that 21 patients developed ONFH three months after starting treatment and that the cholesterol and triglyceride levels of the patients increased significantly within 4 weeks of hormone therapy. Wu *et al* (14) identified several non-coding RNAs involved in the development and progression of hormonal ONFH. Yue *et al* (15) found that miR-132-3p and miR-335 probably serve an important role in hormone-induced ONFH by inducing apoptosis of endothelial cells via the Wnt, Foxo and Rap1 signaling pathways.

Alcohol. Alcohol abuse is one of the main risk factors of bone deterioration. Ethanol impairs the proliferation of human bone mesenchymal stem cells (hBMSCs) and induces their differentiation into adipocytes, which eventually leads to bone loss and structural damage (16,17). Recent studies have shown that abnormal bone metabolism in patients with alcoholic ONFH is associated with the inhibition of the Akt/GSK-3 β / β -catenin pathway in bone mesenchymal stem cells (BMSCs), which is negatively affected by ethanol-induced increase in tensin homology phosphatase (18).

Other diseases. Sickle cell leukemia can lead to microthrombosis, resulting in osteonecrosis and occasionally osteomyelitis (19). Further aggravation can also lead to hemolysis, increased red blood cell activity and expansion of the

bone marrow cavity (19). Femoral head necrosis in patients with HIV is associated with hyperlipidemia and drug treatment (20). A meta-analysis conducted by Matos *et al* (20) shows that protease inhibitors can cause hyperlipidemia and ultimately lead to osteonecrosis. Mazzotta *et al* (21) conducted a multi-center case-control study wherein the highly active antiretroviral therapy significantly increased the triglyceride and cholesterol levels of patients with HIV and altered the total IgE levels in the serum. In a study on 539 patients with severe acute respiratory syndrome who received different types of steroid therapy, 39.5% of the males and 19.3% of the females were diagnosed with ONFH. In addition, ONFH was more common in patients aged 20-49 years (25.9%) compared with that in the 50-59 years group (6.3%). The incidence of ONFH in patients receiving one steroid was 12.5% as opposed to 28.6 and 37.1% in patients treated respectively with two and three types of steroids (37.1%) (22). The COVID-19 patients are also at a higher risk of developing ONFH. The COVID-19 virus is more sensitive to ONFH and the cumulative dose of steroids is smaller (23).

4. Treatment strategies

The current treatments for NONFH can be classified into non-surgical and surgical methods (Fig. S1). The non-surgical approaches include protective weight bearing, physical therapy and drug therapy and examples of surgical intervention are non-vascular transplantation, osteotomy, core decompression, vascularized transplantation and joint replacement. Some therapeutic strategies developed in recent years for treating avascular necrosis of the femoral head are discussed in the following sections.

Protective load bearing. The patients are advised to lose weight, reduce the force exerted on the femoral head of the affected side, avoid mutual and reverse movement, use crutches for walking and avoid sitting or lying in bed for a long period of time (24). Studies show (21,24) that local non-weight bearing can reduce the occurrence of femoral head deformity following ischemic osteonecrosis by increasing revascularization and reducing bone resorption in the infarcted epiphysis, although it does not stimulate new bone formation. Nevertheless, it can optimize osteogenic therapies and the healing of necrotic femoral heads by controlling the rate of bone resorption (24). Therefore, weight bearing can prevent the occurrence and development of osteonecrosis, especially femoral head collapse, in subjects at the early stage of the disease [association research circulation osseous (ARCO Ia)] and with small lesions. However, this non-surgical intervention is ineffective for 80-90% of the patients with ONFH (25,26).

Pharmacological agents. Lipid-lowering agents, anticoagulants, vasoactive substances, statins and bisphosphonates have been used to prevent and treat femoral head necrosis at the early-stages. Bisphosphonates such as alendronate (trade name Fosamax) were originally prescribed to treat osteoporosis. They improve bone density by reducing osteoclast-mediated bone resorption (27-33). Animal studies and clinical trials have shown that bisphosphonates can accelerate the recovery of joint function, delay disease progression, reduce pain and lower the

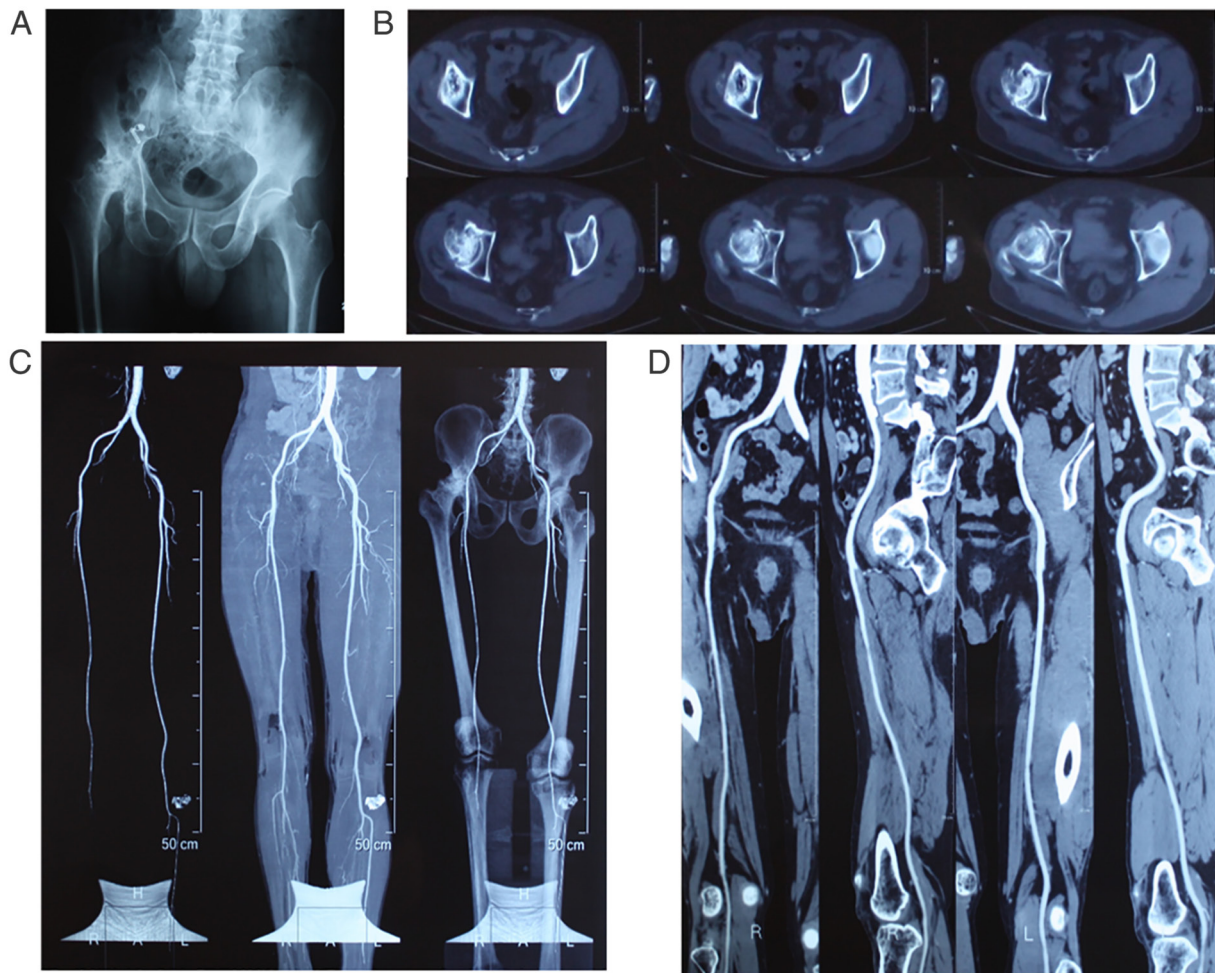


Figure 1. Imaging results of non-traumatic femoral head necrosis. (A) Representative X-ray showing lack of any joint space in the right hip joint and collapse of the acetabulum and femoral head, along with altered structure. (B) Representative computerized tomography image showing stenosis of the hip joint space, hollow femoral head and abnormal calcification. (C) Angiography of the lower extremities showing insufficient supply from blood vessels in the right femoral head. (D) Angiography of one side of the lower extremity showing properly functioning main blood vessels.

risk of femoral head collapse associated with ONFH without significant side effects (27-33). Nevertheless, the therapeutic effect of bisphosphonates against corticosteroid-induced ONFH is controversial (27) and there is no clear recommendation for the dose and duration of treatment. Overall, bisphosphonate drugs can be considered for treating femoral head necrosis caused due to metabolic disturbances.

Prostacyclin is a vasodilatory agent and an antagonist of thromboxane that improves blood flow by preventing platelet aggregation. While short-term use of prostacyclin is associated with significant improvements in the clinical and radiological indices of early-stage ONFH, the long-term efficacy is still being evaluated (34). One study showed that a combination of intravenous prostacyclin and core decompression can alleviate the symptoms of osteonecrosis (35). Iloprost is a synthetic analog of prostacyclin that is routinely used to treat pulmonary arterial hypertension and has proved to be effective against bone marrow edema and ONFH (36,37). A prospective study on 30 cases of ONFH with coagulopathy showed that 53% of the patients did not progress to Ficat and Arlet stages I and II following treatment with the anticoagulant enoxaparin. In addition, the combination of enoxaparin, ginkgo biloba extract (vasodilators) and sildenafil improved

femoral head perfusion in an animal model of steroid-induced ONFH (36,37).

Studies show that the development of ONFH in the hip joint is associated with an increase in the number and size of circulating fat cells (38,39). Therefore, the lipid-lowering statins that are used to treat steroid-related inflammatory disorders (38,39) can potentially be therapeutic against ONFH. Indeed, lovastatin decreases adipogenesis and bone death in a chicken model of steroid-induced ONFH and increases the expression of osteogenic genes in bone marrow cells (40). One study on patients receiving statins and high-dose steroids showed that after a mean follow-up period of 7.5 years, the incidence of ONFH was 1% at annual follow-up, as opposed to 3% usually reported by patients receiving high-dose steroids. Therefore, statins may prevent osteonecrosis in subjects with long-term steroid use (38).

Traditional Chinese medicine formulations have been used to treat osteonecrosis for decades. Ye *et al* (41) showed that the ginsenoside Rb1 inhibits steroid-induced avascular necrosis, osteonecrosis and the elevation of serum osteocalcin in a rat model of Steroid-induced avascular necrosis of the femoral head (SANFH) by blocking the vascular endothelial growth factor (VEGF)/runx-related transcription factor 2/bone

Table I. Underlying causes of NONFH.

NONFH type	Causes
Non-traumatic osteonecrosis	Antituberculosis III deficiency, lack of protein C or S, anti-activated protein C, deficiency of the plasminogen activator, research progress of plasminogen activator inhibitor, COVID-19 and severe acute respiratory syndrome
Secondary hypercoagulable state	Steroid intake, alcoholism, myelodysplastic syndrome, pregnancy, contraceptive use, hyperlipidemia, collagen disease and Eller-Danlos syndrome, Raynaud's disease, diabetes, and antiphospholipid antibodies
Blood diseases	Hemophilia, hemoglobin disease and Erythrocytosis
Metabolic diseases	Hyperparathyroidism, gout, Cushing's disease and Gaucher's disease
Digestive diseases	Pancreatin, ulcerative colitis and chronic diseases
Other risk factors	Smoking, decompression sickness, radiation and hemodialysis

NONFH, non-traumatic osteonecrosis of the femoral head.

morphogenetic protein 2 signaling pathway. In addition, Rb1 also reduces inflammation, oxidative stress, total cholesterol and low/high lipoprotein levels, alkaline phosphatase activity and bone calcium loss in the SANFH rats.

Extracorporeal shock wave therapy (ESWT). High-energy ESWT is a non-invasive approach that has been used for treating ONFH since the end of the last century (42,43). Its potential mechanisms of action include restoration of tissue oxygenation, reduction of bone marrow edema and increased blood supply to focal lesions (42,43). ESWT is a promising alternative to the more invasive surgical methods currently used to treat ONFH at different stages. Ludwig *et al* (44) subjected 22 patients with ONFH to the shock wave treatment and assessed the visual analog scale (VAS) and HHS scores after one year follow-up. The VAS scores of the patients decreased from 8.5 points before surgery to 1.2 points and the HHS scores increased from 43.3 points to 92 points, indicating high efficacy of ESWT. Other studies have shown that ESWT is only effective against early-stage ONFH (45). Algarni and Al Moallem (46) treated 21 patients (33 hips) with early-stage ONFH using this approach and found that the VAS scores and HHS scores of 21 hip joints improved significantly after 8 months. After 5 years, 4 cases received THA treatment. Among them, 26 cases showed no significant progression from the first stage. Magnetic resonance imaging (MRI) results showed that in 23 cases, bone marrow edema was significantly reduced. Thus, ESWT significantly improved the quality of life of patients with ONFH, delayed the progression of disease and avoided the need for total hip arthroplasty (THA). Xie *et al* (43) retrospectively analyzed the data of 31 patients with ONFH (44 hips) who underwent ESWT and were followed up over an mean duration of 130.6 months. The imaging findings showed lack of disease progression in all stage I, 64.3% of stage II and 12.5% of stage III hips. Thus, ESWT is a suitable option for ARCO I and II patients.

Pulsed electromagnetic field. In 1974, Bassett *et al* (47) discovered that pulsed electromagnetic fields (PEMF) can promote fracture repair and subsequent studies have shown that PEMF can also control inflammation and repair

articular cartilage in patients with osteoarthritis and joint surgery (48,49). Seber *et al* (50) reported the cases of two Ficat II patients with ONFH who were subjected to PEMF therapy daily for 10 h over a period of 6 months and exhibited a significant improvement in their condition. Massari *et al* (51) treated 66 patients with ONFH (76 hips) with PEMF as above and followed their progress for 28 months. While 94% of the patients at Ficat stages I and II showed improvement, most Ficat stage III patients deteriorated and finally had to receive THA treatment. Thus, PEMF may be an effective option for early-stage ONFH. However, only a few studies have reported the efficacy of PEMF in the treatment of ONFH, which therefore warrants further investigation. In summary, this method can be beneficial for patients with ARCO stage I and II ONFH.

Hyperbaric oxygen therapy (HBO). HBO has proved to be highly effective against early stages of femoral head necrosis, particularly in Asian populations (52-55). In a recent study (56) on 19 patients with stage II ONFH, 12 (52.2%) underwent core decompression (CD) surgery and 11 (47.8%) received HBO treatment. Over the mean follow-up period of 34.2±18.4 months, 66.7% of patients in the CD group and 81.8% of patients in the HBO group showed satisfactory hip joint function. However, 8 patients (34.7%) progressed to a higher radiological stage during the first year of follow-up and the progression rate was similar in both groups. Studies have also shown that HBO therapy is as effective as CD for treating non-traumatic pre-collapsed femoral head AVN and therefore can be used a non-invasive alternative (52-56). The clinical efficacy of HBO depends on the synthesis of growth factors, which promote wound healing and reduce post-ischemia and post-inflammatory damage (57,58). In addition, the increase in hydrostatic pressure compresses all gas-filled spaces in the human body (Ball's law), which can reverse decompression-related diseases (59,60). HBO therapy reduces edema, increases tissue oxygenation and restores venous drainage in the affected bone area by inducing proliferation of endothelial progenitor cells, promoting neo-angiogenesis and improving local microcirculation (57,61-65). A 2017 systematic review found that HBO therapy is effective against early-stage ONFH and may reduce cellular ischemia by increasing the

Table II. Non-surgical treatment of NONFH.

First author/s, year	Treatment method	Quantity (hip)	Follow-up time (month)	Indications	(Refs.)
Xie K, 2018	ESWT	44	130.6	ARCO I-III	(43)
Algarni AD, 2018		33	8	ARCO I-II	(46)
Massari L, 2006	PEMF	76	28	Ficat I-II	(51)
Moghamis I, 2021	HBO	11	34.2	Steinberg II	(56)

NONFH, non-traumatic osteonecrosis of the femoral head; ESWT, energy extracorporeal shock wave therapy; PEMF, pulsed electromagnetic fields; HBO, hyperbaric oxygen.

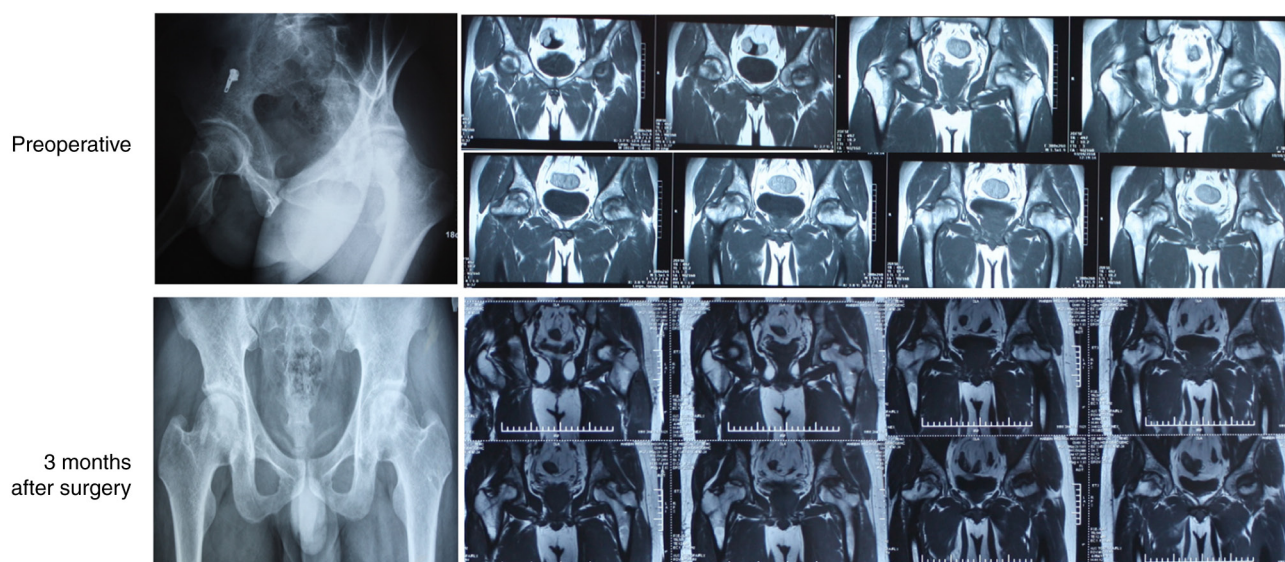


Figure 2. Typical imaging results of non-traumatic osteonecrosis of the femoral head after pure core decompression.

concentration of extracellular oxygen (66). In summary, HBO therapy can be considered for the prevention and treatment of early-stage femoral head necrosis.

The literature related to the non-surgical treatment methods for NONFH are summarized in Table II.

CD. CD is the commonest surgical procedure for early-stage osteonecrosis and is used to relieve pain and promote bone regeneration and repair (67,68). As shown in Fig. 2, pure CD can repair and delay the progression of NONFH (67) by reducing intramedullary pressure on the inside of the femoral head, accelerating bone regeneration, reversing femoral head necrosis and improving blood flow. However, the clinical results so far are inconclusive and indicate that CD may have an improved effect on early-stage ONFH (68).

In one study, CD surgery prevented further deterioration of the hip joints of 87-90% of Ficat I patients with NONFH, whereas only 59-70% of stage IIa patients derived a clinical benefit from this procedure (69,70). CD surgery can also significantly reduce hip pain in patients with stage I and II avascular necrosis of the femoral head and increase the range of motion of the hip joint (69,71). Simank *et al* (72) found that the therapeutic effect of CD can be weakened in case of corticosteroid usage, smoking, drinking and other risk factors.

In addition, some studies report that CD can only exert a short-term therapeutic effect and the long-term curative effect is poor and does not preclude the need for total hip replacement (73-76). Multiple drilling cannot effectively reduce the rate of THA conversion in early-stage NONFH. In fact, the risk of conversion to THA is increased after multiple drilling in case of larger necrotic lesions, presence of bone marrow edema and higher postoperative workload (74,75). Furthermore, Sadile *et al* (76) report lower efficacy of CD against NONFH compared with that of other palliative surgical techniques in terms of clinical status, imaging characteristics and the need for total hip replacement.

Despite the inconsistencies regarding the therapeutic effects of CD alone, the combination of CD with other treatment methods has shown encouraging results. For instance, the HHS score, hip function recovery and imaging performance of patients with NONFH that received bone marrow mesenchymal stem cell therapy are superior compared with patients who underwent CD, although the combination treatment had the optimal effect. Tabatabaee *et al* (77) subjected 28 cases of early NONFH to CD or a combination of CD with concentrated bone marrow implantation and found that the VAS pain index and MRI results improved to a significant greater extent in the combination treatment group. In a recent study conducted

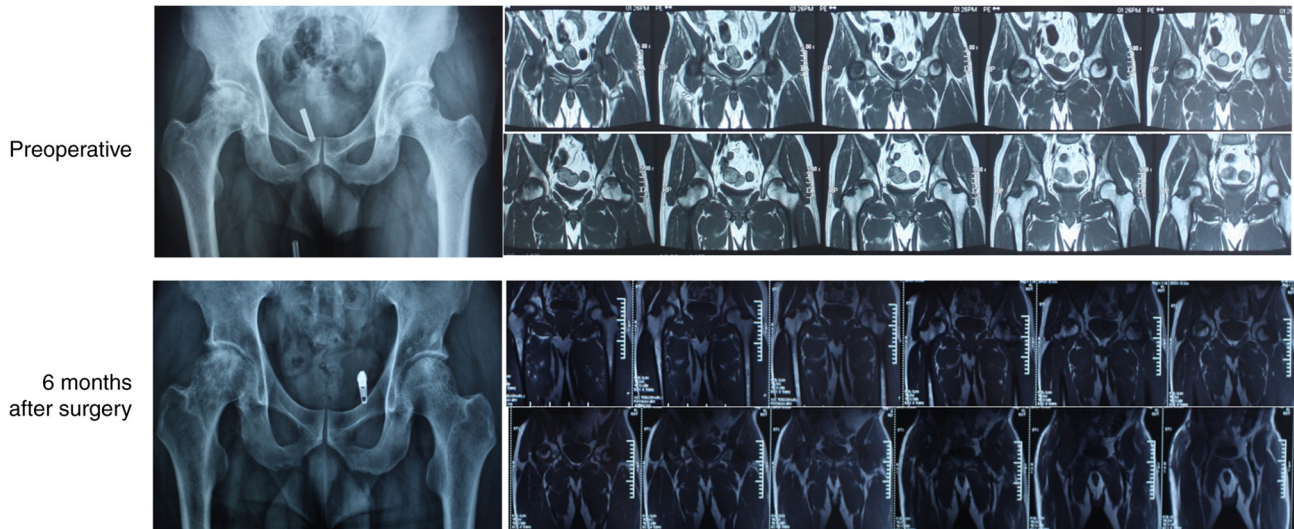


Figure 3. Imaging results of patients with non-traumatic osteonecrosis of the femoral head 6 months after the combination treatment of core decompression and platelets in platelet-rich plasma.

on 52 hips (65%) with Ficat IIa and 28 hips (35%) with Ficat IIb ONFH, 46 hips (30 Ficat IIa and 16 Ficat IIb) received HBO therapy and 34 hips (22 Ficat IIa and 12 Ficat IIb) were treated with a combination of CD and HBO. Although the VAS and HHS scores improved in each group compared with the pre-treatment scores ($P < 0.001$), the recovery was markedly higher in the CD + HBO group ($P < 0.001$). Furthermore, the functional and pain scores as per the SF-36 scale (78) were also significantly different between the two groups ($P < 0.005$). HBO treatment can reduce the degree of pain in Ficat II patients and increase their functional scores. The combination of CD and HBO treatment achieves greater pain reduction in stage IIa patients compared with stage IIb patients (78). The BMSCs-bone morphogenetic protein 2 (BMP-2) complex on the magnesium alloy rod was implanted into the metaphysis of the left femur of the rabbit to the femoral head, BMP-2 coated magnesium alloy can promote the expression of bone growth factor in rabbit bone marrow implants, thereby delaying femoral head necrosis and promoting repair (79).

Platelet-rich plasma (PRP). PRP has 8-fold higher load of platelets compared with whole blood, along with high levels of regenerative cytokines such as platelet-derived growth factor, transforming growth factor β , basic fibroblast growth factor, endothelial growth factor, insulin-like growth factor and VEGF (80). Karakaplan *et al* (81) found that PRP alleviates the symptoms of early-stage hormonal ONFH in a rabbit model. Zhang *et al* (82) further showed that the fusion of PRP with tricalcium phosphate (TCP) promotes the formation of new bone and inhibited inflammation in the rabbit model of ONFH. In addition, the triple combination of CD surgery, PRP fusion and autologous granular bone transplantation relieves traumatic ONFH with a success rate of 80% (83). Houdek *et al* (84) treated 22 steroid-induced patients with ONFH (35 hips) with BMSCs and PRP and found that the mean HSS increased from 57 points pre-transplantation to 85 points over an mean follow-up duration of 3 years and 93% of the patients were stable without any disease progression or

complications. Although PRP cannot reverse the pathophysiological process of ONFH, it can induce osteogenic activity and stimulate the differentiation of stem cells in ARCO stage I and II patients when used in conjunction with CD and stem cell transplantation or bone grafting (85).

Previous studies (86,87) have shown that PRP can alleviate the symptoms of ONFH by the following mechanisms: i) Induction of angiogenesis and osteogenesis to promote bone healing, ii) inhibition of the inflammatory response in necrotic lesions, iii) prevention of GC-induced apoptosis and iv) activation of GC-induced osteogenesis and autophagy (87). While combination therapies incorporating PRP have achieved potent therapeutic effects (88), further prospective randomized clinical trials must be conducted to determine the optimal concentration of PRP and the proportion of stem cells (86). Platelet lysates can also treat femoral head necrosis by promoting the proliferation of osteoblasts and endothelial cells and reducing cell apoptosis and bone resorption (89). As shown in Fig. 3, CD combined with PRP therapy can accelerate the treatment of femoral head necrosis and promote healing of the decompression tunnel. Therefore, for patients with early-stage femoral head necrosis, a combination of PRP and CD is recommended.

Stem cell therapy. Studies increasingly show that femoral head necrosis is associated with a weakened regenerative ability of the affected tissue, which can be attributed to the decrease in the number of BMSCs and lower osteogenic differentiation (90-92). Since BMSCs support angiogenesis, transplantation of bone marrow MSCs can potentially achieve clinical resolution of ONFH. However, there are several challenges in the practical application of stem cell therapy, such as patient selection, standardization of procedures, safety assessment and the fate of transplanted cells *in vivo*. Further studies are needed to identify ideal sources of cells, the appropriate transplantation methods, as well as the optimal number of cells (90-92).

Hernigou and Beaujean (93) performed CD and autologous bone marrow transplantation on 116 patients (189 hips) with

NONFH and followed them up for 5-10 years. The treatment effect was evaluated using HHS score, imaging and the necessity for THA. Among the 145 early-stage hips, 136 achieved the desired results, whereas 25 out of the 44 hip joints with advanced femoral head collapse eventually underwent THA. Autologous bone marrow transplantation is a reliable method for treating NONFH and the therapeutic effect is proportional to the number of transplanted progenitor cells. The success rate of CD in combination with autologous bone marrow mononuclear cell transplantation is 79.7% in the patients with NONFH and this method can significantly relieve pain and stall femoral head necrosis in the early stages (94-96).

Mao *et al* (97) devised a technique for the directional delivery of autologous bone marrow mononuclear cells (BMMCs) enriched in MSCs through the medial femoral circumflex artery for the treatment of ONFH. They followed-up on 62 patients (78 hips) with ONFH for 5 years and found that the failure rate of the treatment was 3/68 for Ficat I-II hip joints and 3/10 in the stage III cases. Thus, targeted delivery of bone marrow cells can effectively delay the progression of ONFH, especially at the early-stage. Yoshioka *et al* (98) performed bone marrow transplantation on 9 patients with SLE complicated by ONFH, of which 8 did not require THA. During the follow-up period of ≤ 3 years, the patients reported significant pain relief and an improvement in HHS scores, indicating that this method is also effective for ONFH complicated by SLE. Autologous BMMC transplantation was also used to treat ONFH caused by sickle cell leukemia. At the last follow-up, the patients reported significant pain relief and improvement in HHS score and the quality of life. Imaging further showed a marked reduction in bone marrow edema around the necrotic area and the lesion area, indicating that BMMC implantation is a safe and effective treatment method (99,100).

Nandeesh *et al* (101) treated 48 patients with ONFH with autologous bone marrow stem cells combined with PRP-derived growth factor concentrate. During the 2-year follow-up, 93% of the patients had increased hip joint space and MRI results showed cartilage regeneration. The joint function of the patients also improved significantly and the overall satisfaction was high. Nevertheless, the findings need to be validated on a larger cohort. Emadedin *et al* (102) subjected 9 patients with ONFH to CD surgery and injected autologous bone marrow-derived CD133+ cells derived into the necrotic area of 9 patients in combination with CD therapy. During the 12-month follow-up, all patients recovered considerably and the necrotic area was significantly smaller. Due to the small number of patients however, further validation is required. Pak (103) treated two patients with ONFH by transplanting adipose tissue-derived stem cells and recorded a marked improvement in the VAS score, HHS score and MRI results, which coincided with regeneration of the medullary bone tissue in the femoral head. Mardones *et al* transplanted 5 patients with ONFH with hBMSCs expanded *in vitro* and observed significant recovery after 19 to 54 months (34).

Migration technology. Bone transplantation has been the mainstay of early NONFH treatment for more than 70 years (104). The common methods included simple bone transplantation, osteochondral transplantation and vascularized bone flap

transplantation, all of which have exhibited good clinical effects.

Simple bone transplantation. Bone impaction grafting prevents the development of osteoarthritis by restoring the collapsed spherical head and remodeling the necrotic area using autologous bone tissue (105). Guo *et al* (106) performed allogeneic fibula transplantation in patients with early-stage femoral head necrosis and recorded rapid recovery of joint function, low level of trauma and significant improvement in clinical symptoms, indicating that this method is ideal for short-term management (107,108).

Bednarek *et al* (109) treated 63 patients with NONFH (72 hips) with autogenous or artificial bone transplantation. After 5 years of follow-up, 45 hips (63%) had less pain and did not exhibit any change in the shape of the femoral head. The degree of pain in 16 hips (22%) was lower, although the movement was still limited. X-ray images showed that the femoral head had collapsed significantly and this method created mechanical and biological conditions suitable for bone graft fusion and produced obvious long-term effects. Vahid Farahmandi *et al* (110) performed iliac crest auto-cortical bone grafting on 96 cases (132 hips) and followed the patients for an mean duration of 48.5 months. The shape of the femoral head did not change in 120 hips (90.9%) and the degree of pain was significantly lower and only 12 cases progressed to grade IV. Therefore, this method can treat patients with early-stage NONFH and prevent total hip replacement. However, some studies have shown that the efficacy of bone transplantation is not ideal. Bakx *et al* (111) performed tibial bone grafting on 16 patients (20 hips) with femoral head necrosis. During the 3-year follow-up, 15 cases reported improvement without any significant changes in the imaging characteristics. The treatment failed for 2 cases and further surgical intervention was required, indicating overall low efficacy of this method for NONFH.

Bone transplantation with blood vessels. Vascularized bone grafts have been developed to restore the blood supply to the necrotic femoral head and improve the ischemic state. Zhu and Zhou (112) subjected 6 patients with NONFH to vascularized iliac periosteum transplantation and detected significant recovery during the follow-up period of 3 to 7.5 years. The patients reported complete cessation of pain in the hip joint and were able to move freely. X-ray images showed that the shape of the femoral head was normal with a clear outline and the bone density was also restored. Thus, vascularized bone transplantation improves the blood supply of the femoral head, which is conducive to its revascularization and may reverse early-stage avascular necrosis of the femoral head (113).

For vascularized iliac bone transplantation with femoral head necrosis, medium and short-term therapeutic effects that can effectively delay the need for total hip replacement have been observed (114,115). Scully *et al* (116) compared the therapeutic effects of vascularized fibula transplantation and cord decompression in patients with ONFH at different stages. The combination of both treatments had a significant curative effect in the Ficat I patients. In patients at Ficat stages II and III, the success rate of vascularized fibula

transplantation was 89 and 81% respectively compared with only 65 and 21% with CD, indicating that vascularized bone transplantation is superior to CD against both early and late stage ONFH. Heinrich and McBeath (117) used the gluteal muscle pedicle bone grafting technique to treat 16 patients (20 hips) with Ficat II-III NONFH. After an mean follow-up duration of 47 months, X-ray imaging showed recovery in 12 cases whereas no obvious progress was seen in 8 cases.

Cartilage transplantation. Cartilage transplantation, including autologous chondrocyte implantation, autologous osteochondral transplantation and allogeneic osteochondral transplantation (118), is widely used for treating talus osteochondral disease and knee cartilage injury (119,120). Gagala *et al* (121) treated 7 early stage patients with NONFH via osteochondral transplantation and 13 advanced-stage patients with a combination of autologous osteochondral and allogeneic bone transplantation. The mean follow-up duration was 46.14 months. At the final follow-up, the HHS scores of both groups had improved significantly, especially in patients with early-stage NONFH, indicating that osteochondral transplantation can significantly slow the progression of NONFH and delay the need for THA. However, due to lack of relevant research, the curative effect of cartilage transplantation is not completely clear.

Porous tantalum or other implants transplantation. A porous tantalum rod is a biocompatible material with an elastic modulus similar to the human fibula and can therefore provide structural support for the femoral head. Tantalum implants have been widely used for treating orthopedic diseases. Studies show that porous tantalum implants can effectively slow the progression of femoral head necrosis (122) and that its therapeutic effect on early-stage NONFH is superior to that of traditional bone transplantation (123). Nadeau *et al* (124) used porous tantalum implants for treating 15 patients with NONFH (18 hips), of which 3 cases were at Steinberg stage III and 15 cases were at stage IV. Most patients did not need further surgical treatment after 12 months and the success rate was 77.8%. The postoperative HHS score of the patients had improved significantly over an mean follow-up period of 23 months, which was indicative of good short-term effects. At the last follow-up however, the total success rate dropped to 44.5%, indicating that the long-term treatment effect requires further resolution. Liu *et al* (125) compared the postoperative hospital stay, number of days of PCA, HHS score and survival rate of the hip joint in patients who underwent traditional bone transplantation (control group) and patients who had received porous tantalum implants. The HHS score of the tantalum rod implantation group was significantly higher compared with the control group and the hip joint survival rate was 74.1% compared with only 49% in the bone-transplanted controls. Thus, implantation of tantalum rod can have a significant therapeutic effect in patients with NONFH without bone marrow edema and can delay or even avoid the need for THA. Likewise, Liu *et al* (126) found that whole tantalum rod implantation can effectively treat early-stage to mid-term NONFH. However, they observed high-density metal particles remnants in the femoral bone marrow cavity on X-ray images, which may be the cause of post-treatment pain and treatment failure.

The composite scaffold is expected to be a promising device for regulating the microenvironment of osteonecrosis and overcoming the challenges related to bone regeneration. A number of organic [for example, poly(lactide-co-glycolide) (PLGA), poly(ϵ -caprolactone), polylactide and chitosan], inorganic (for example, nano-hydroxyapatite, β -tricalcium phosphate and ceramics) and composite materials have attracted increasing attention as the matrix of bone tissue engineering scaffolds. This is due to their excellent biocompatibility, controllable degradation, easy processing, excellent mechanical properties, osteoconductivity and the ability to promote bone regeneration (127-130). The combined application of polymers and various other substances utilizes the advantages of various substances and the advantages of polymers to meet the needs of a wider range of osteonecrosis research. The addition of various substances improves the biological activity and mechanical support performance of the pure polymer. Various biologically active substances are added to polymers to produce functionalized polymers. The addition of stem cells, growth factors, small molecule drugs and metal ions in polymer bone substitute materials give the polymer bone-forming and vascular properties, which is conducive to repairing osteonecrosis (129-131). The research on functionalized polymer bone substitute materials has become a development trend and the production of various functionalized polymer biomaterials may improve the treatment of osteonecrosis (131).

Magnesium powder, PLGA and β -TCP are elements used to formulate novel porous PLGA/TCP/Mg (PTM) scaffolds using low temperature-rapid prototyping technology. The biological safety assessment from 0-12 weeks after implantation did not cause an increase in the serum magnesium ion concentration and the immune response and liver and kidney function parameters were at normal levels. These findings indicate that PTM scaffolds have osteogenic and angiogenic capabilities and they have a synergistic effect in enhancing the formation of new bone and enhancing the quality of newly formed bone in ONFH (132).

Osteotomy. Osteotomy can effectively delay the need for THA in patients with NONFH and the most common type is intertrochanteric valgus flexion osteotomy. The postoperative situation is related to the degree of the femoral head necrosis (133,134). Portigliatti Barbos *et al* (135) performed flexion osteotomy on 19 patients with avascular necrosis of the femoral head and followed them up for 8 years. Almost 85% of patients showed significant recovery, indicating that osteotomy is an ideal choice for treating NONFH (136). Mont *et al* (137) followed up 37 patients with Ficat II-III NONFH who underwent intertrochanteric osteotomy for an mean of 11.5 years and found that 28 showed good recovery with improved HHS score, while 9 had to undergo THA. Among the 17 patients with hormonal NONFH, the treatment failed in 6 cases, of which 5 had a necrosis angle exceeding 200 degrees. Thus, intertrochanteric osteotomy can be effective against Ficat II-III NONFH, but is not recommended for patients with long-term corticosteroid usage or excessive necrosis. Inao *et al* (138) and Masui and Hasegawa (139) performed transtrochanteric osteotomy on patients with NONFH and confirmed good recovery of the femoral heads during the mean follow-up of 13.2 years, with <2 mm collapse over 15 years after surgery.

Table III. Effectiveness of CD-based treatments for non-traumatic NONFH.

First author/s, year	Treatment method		Quantity (hip)	Follow-up time (month)	Indications	Treatment effect (rate)	(Refs.)
Leder K, 1993	CD	CD-alone	47	≥24	Ficat I-II	I 87.0% II 59.0%	(69)
Specchiulli F, 2000			20	60	Ficat I-IIa	I 90.0% IIa 70.0%	(70)
Etemadifar M, 2014			22	12	Ficat I-IIa	/	(71)
Hernigou P, 2002		Stem Cell	189	84	Ficat I-II	I+II 93.8% III+IV 43.2%	(93)
Wang BL, 2010			59	27.6	ARCO I-IIIa	76.3%	(94)
Xian H, 2020		PRP	46	36	ARCO II-III	91.7%	(83)
Houdek MT, 2018			35	36	Pennsylvania Stage 1-2	93.0%	(84)
Tomaru Y, 2017		Simple bone graft	50	48.5	ARCO II-III	90.9%	(100)
Bakx PA, 1991			20	36	FICATII-IV	30.0%	(111)
Lau HW, 2021			50	≥60	FICAT II-III	56.0%	(115)
Zhang NF, 2003		Vascular bone graft	26	31.5	ARCO I-II	56.5%	(114)
Scully SP, 1998			614	50	FICAT II-III	81.0%	(116)
Heinrich JT, 1995			20	47	FICATII-III	60.0%	(117)
Gagala J, 2013		Cartilage transplantation	7	46.14	ARCO II	61.5%	(121)
Nadeau M, 2007		Porous tantalum transplantation	18	23	Steinberg III-IV	44.5%	(124)
Liu Y, 2016			42	48	SteinbergI-II	84.6%	(125)

NONFH, non-traumatic osteonecrosis of the femoral head; PRP, platelets in platelet-rich plasma.

Motomura *et al* (140) conducted a long-term follow-up study on 16 patients (25 hips) with SLE complicated by NONFH who had undergone transtrochanteric anterior rotation osteotomy. The hip survival rate was 73.7% on the 25th year post-surgery, indicating long-term therapeutic effect. However, osteotomy has certain disadvantages that preclude it as the first choice for NONFH treatment. Schneider *et al* (141) compared the therapeutic effects of different osteotomies, including flexion osteotomy, rotational osteotomy, variant osteotomy, intermediate osteotomy and extension osteotomy, on 106 patients that were followed-up for an mean of 69 months. Only flexion osteotomy achieved the desired effect, with the 5-year and 10-year hip survival rates reaching 89.2 and 60.7% respectively. The other groups, particularly rotary osteotomy, the success rate was very low and the frequency of complications was high. Thus, the current consensus is that flexion osteotomy is the only effective method for NONFH provided it is only applied when the necrotic area is small enough to guarantee a satisfactory therapeutic effect. Nevertheless, one study reported development of osteoarthritis 5 years after osteotomy and extremely poor long-term effect (142).

The adaptation period and therapeutic effects of non-traumatic NONFH with non-replacement surgery are summarized in Table III.

Joint replacement. For the Ficat stage III or IV patients with NONFH with femoral head depression measuring >2 mm and large lesions, it is frequently difficult to achieve the desired therapeutic effect using palliative surgery and the patients often require total hip replacement or hip resurfacing. The number of cases opting for THA is increasing, which can be attributed to the improvements in long-term efficacy. Furthermore, younger patients with ONFH are unwilling to undergo joint-sparing surgery that requires long-term hospitalization (143). Thus, joint replacement surgery is currently the most preferred treatment method for advanced NONFH.

Total hip replacement. Kirschenbaum *et al* (144) followed up 87 patients who underwent THA for a mean of 5.7 years. The respective scores of prosthesis loosening, revision and pain were <5 at the endpoints and survival rates were 0.61, 0.94 and 0.81 respectively. As of the revision study, there were no differences between men and women who were <50 years old, ≥50 years old, or patients weighing <185 pounds and patients weighing ≥185 pounds. Therefore, THA is a viable option for the treatment of NONFH.

Ritter *et al* (145) compared acetabular prosthesis loosening, femoral prosthesis loosening and revision rates of

Table IV. Revision rates of total hip arthroplasty and hip resurfacing in patients with NONFH.

First author/s, year	Treatment method	Quantity (hip)	Follow-up time (month)	Revision rate (%)	(Refs.)
Kirschenbaum IH, 1991	Total hip replacement	87	5.7	11.5	(144)
Dong W, 1997		50	8.5	20.0	(146)
Al Mousawi F, 2002		35	9.5	20.0	(148)
Beaulé PE, 2001		37	6.5	30.0	(156)
Calder PR, 2004		15	1.9	60.0	(157)
	Hip resurfacing				

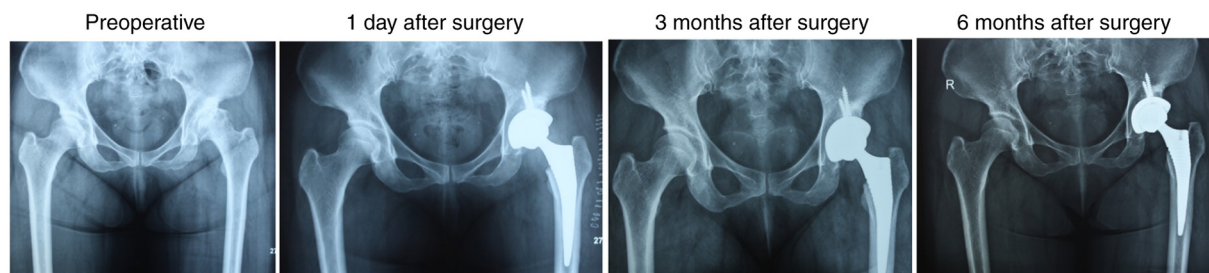


Figure 4. Representative image of total hip arthroplasty on a non-traumatic osteonecrosis of the femoral head patient.

115 patients with NONFH who underwent THA with that of 202 patients who had undergone THA due to osteoarthritis. Postoperative pain scores were similar in both groups, which further confirms the efficacy of THA against NONFH. Dong *et al* (146) performed cemented THA on 40 steroid-induced patients with NONFH (50 hips) and recorded significant improvement in HHS scores during the mean follow-up duration of 8.5 years. The revision rate was 2% after 4 years, while the renovation rate after 18 months was 18%. The authors holds the view that cemented THA is a suitable option for treating younger patients. Yuan *et al* (147) conducted a 7.6-year follow-up on 19 alcoholic patients with ONFH (24 hips) who underwent THA and detected significant improvements in the VAS and HHS scores. The 5-year and 10-year survival rate of the prosthesis was 96 and 64% respectively, which shows that THA is a reliable choice for alcoholic patients with ONFH as well. The study also found that chronic alcoholism can significantly increase the risk of revision.

Al-Mousawi *et al* (148) performed THA on 28 patients (35 hips) with ONFH secondary to sickle cell disease (SCD) and followed them up for an mean of 9.5 (5-15) years. One case developed infection and 6 cases developed aseptic loosening. SCD patients are at a higher risk during and post-THA. However, despite the higher failure rate in SCD patients, THA is still the most reliable option. As shown in Fig. 4, after 3 months of follow-up, THA led to significant recovery of ONFH.

The aforementioned studies underscore the influence of age on femoral head necrosis and that of various underlying diseases on joint function. The surgical approach of joint replacement has no significant impact on the lifespan of joint replacement and rather depends on individual differences (149-153).

Hip resurfacing. Compared to THA, hip resurfacing (HRA) can preserve more femoral bone mass and maintain normal biomechanics with similar outcomes (154,155). Therefore, HRA can be used as an alternative to total hip replacement. Beaulé *et al* (156) performed half-face replacement therapy on 37 patients with Ficat stage II, III or IV NONFH. The clinical, imaging and functional indices showed considerable improvement during the mean follow-up duration of 6.5 years and the 5-, 10- and 15-year survival rates were 79, 59 and 45% respectively. However, some studies have reported suboptimal outcomes of HRA. Calder *et al* (157) performed HRA on 12 patients with NONFH (15 hips; 1 stage II, 9 stage III and 5 stage IV), of which 9 had to undergo revision surgery within two years during the mean follow-up period of 22.8 months. In addition, the overall results were not satisfactory. In addition, Hsieh *et al* (158) found that temperatures $>50^{\circ}\text{C}$ prolonged bone cement polymerization during HRA, resulting in higher heat loss compared with normal bone. Therefore, more research is needed to determine the therapeutic efficacy of HRA. As summarized in Table IV, THA has a significantly lower revision rate compared with HRA.

5. Conclusion

Femoral head necrosis is a slow progressive disease that causes irreversible structural changes in the hip joint, leading to chronic pain and disability. However, there are no standard criteria for early screening and diagnosis, thus making early treatment less likely. Based on the current literature, the present review recommended CD combined with bone transplantation, PRP, HBO therapy, stem cell therapy, high-energy ESWT and PEMF for patients at ARCO stage I or II following the failure of non-surgical treatment. For

patients at ARCO stage III, these methods may be effective, although there is currently lack of evidence. THA must be performed for the ARCO stage IV patients. However, this surgical plan does not consider patient age, comorbidities and other influencing factors. Therefore, an individualized plan based on the patient's condition and the mechanisms of the therapeutic strategy should be developed.

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Authors' contributions

NL and QW collected images from clinical work. NL performed literature review and wrote the manuscript. CZ performed literature review of pathophysiology and diagnosis. QW edited the manuscript and figures. ZH designed the study and wrote the manuscript. NL and ZH confirm the authenticity of all raw data. All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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