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REVIEW ARTICLE

Review of various treatment options and potential therapies for osteonecrosis of the femoral head

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Summary Size and location of the lesion, subchondral collapse occurrence, and articular cartilage involvement are general disease progression criteria for direct osteonecrosis of the femoral head (ONFH) classifications. Treatment options for ONFH are usually based on individual factors and lesion characteristics. Although spontaneous repair of ONFH occurs in some cases, untreated ONFH is unlikely to escape the fate of subchondral collapse and usually ends up with total hip arthroplasty. Operations to preserve the femoral head, e.g., core decompression and bone grafting, are usually recommended in younger patients. They are helpful to relieve pain and improve function in the affected femoral head without subchondral collapse, however, poor prognosis after surgical procedures remains the major problem for ONFH. Pharmacological and physical therapies only work in the early stage of ONFH and have also been recommended as a supplement or prevention treatment for osteonecrosis. Following advances in basic science, many new insights focus on bone tissue engineering to optimize therapies and facilitate prognosis of ONFH. In this review, disease classifications, current treatment options, potential therapies, and the relevant translational barriers are reviewed in the context of clinical application and preclinical exploration, which would provide guidance for preferable treatment options and translation into novel therapies.

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Introduction

Osteonecrosis of the femoral head (ONFH) is a chronic disease that shows a complicated pathogenesis [1]. Spontaneous repair of ONFH is a slow, discontinuous, and time-dependent process that might only occur in small size lesions without concomitant joint fluid seepage [2,3]. Naw et al's [4] clinical report revealed that 94% of asymptomatic ONFH will develop to symptomatic ONFH within 5 years. Untreated ONFH is believed to carry a poor outcome and often leads to the occurrence of subchondral collapse within a short period [4,5]. Various surgical procedures are helpful to relieve pain and improve function of the affected femoral head in the early stages, however, the secondary trauma caused by surgical intervention remains an inevitable clinical problem and surgical procedures may not prevent deformity and collapse in deteriorating ONFH [6]. Therefore, how to reverse the early stage of ONFH and promote reparative bone remodelling becomes the key for maintaining the undestroyed joint adjacent to lesion areas and making available therapies to facilitate a good prognosis. Currently, the attention of surgeons and researchers is focused on: (1) enhancing the sensibility and accuracy of diagnosis to raise the rate of early diagnosis; (2) improving surgical operation technology or developing minimally invasive surgery to avoid the secondary trauma caused by surgical intervention; and (3) exploring drug or grafting products to promote reparative bone remodelling and obtain a good prognosis. This article presents a review of ONFH classification systems, current treatment options, potential therapies, and the relevant translation barriers in the context of clinical application and preclinical exploration. By addressing the relationship between ONFH pathological characteristics and various treatment options, as well as stating potential therapies and its translational barriers, we aim to provide guidance for preferable treatment options and translation into novel therapies.

ONFH classification systems

Patients with suspected ONFH would have one or more of the following criteria: (1) throbbing, deep groin pain, and one or more associated risk factors; and (2) a previous ONFH in another joint [7]. The suspected ONFH needs further validation using image detection before distinguishing lesion progression and choosing treatment options (Figure 1). ONFH classification systems are excellent tools based on imaging data that are widely used to stratify the severity and prognosis, and guide the treatment strategy [8]. There are several staging systems used for classifying ONFH, including Ficat and Arlet classification; the University of Pennsylvania (Steinberg) staging system, Association Research Circulation Osseous (ARCO), and the Japanese Orthopaedic Association (JOA) classification systems (Table 1). There are some denominators among them; the diagnostic data enable easy conversion to any of the four systems so that cross-comparison of results can be made [9].

The Ficat and Arlet system was the first classification system for ONFH and this system includes four stages [10,11]. Stage I is a transitional stage and patients are asymptomatic with a normal radiographic finding, but with increased uptake of tracer on bone scintigraphy [10]. Stage II represents the reparative stage and some diffuse sclerotic and cystic lesions can be observed before flattening of the femoral head occurs. Stage III is characterized by subchondral fracture (crescent sign). Stage IV involves the loss of the femoral head's anatomical sphericity and the occurrence of femoral head collapse and joint destruction. This damage leads to further progressive degeneration such as osteoarthritis and acetabular degeneration. There are some drawbacks in this system. Firstly, the descriptions of various stages are ambiguous and overlapping, and do not allow quantitation of the size of lesions, which makes it impossible to measure subtle degrees of progression. Next, the classification of later stages depends on invasive diagnosis techniques, such as core decompression, which would lead to secondary trauma.

The Steinberg system was established based on the Ficat and Arlet system, and the important modifications included the incorporation of magnetic resonance imaging findings and more clear distinction into seven stages [12]. This system is the first to incorporate the size of lesion measurements as part of a complete system [13]. The ARCO system originates from the Steinberg classification, and several amendments have been made over the years [14,15]. This system does not provide a method to evaluate either preradiographic lesions or lesions in which the joint line and the acetabulum are involved [14]. The location of ON lesion is detected and the relative information is added to each stage in ARCO system as a supplement, but its specific value is uncertain [16,17]. The JOA system originated from the Ficat and Arlet system with the location and size of the lesion added to its classification, however, this system only evaluates Ficat Stages II and III and not Stages I and IV [18,19].

The goals in treatment of ONFH are to relieve pain and preserve the femoral head as long as possible. We believe that an optimal treatment option should be based on an appropriate classification system of ONFH [7]. Currently, for treating ONFH, there is a lack of consensus regarding diagnostic methods, evaluation systems, and indications of various treatment options [8]. Thus, symptoms, imaging and histological data, size and location of lesion, and the indications of articular cartilage involvement and femoral head depression, should be incorporated together to find a preferable treatment option for ONFH.

Current treatment options for ONFH

Nonoperative treatments

Most nonoperative treatment for early stage ONFH involves restricted weight bearing using a cane and activity modification. These methods only work in the early stage, asymptomatic ONFH, but show limited success in preventing disease progression (Table 2) [5,20]. Restricted weight bearing cannot be recommended as a routine treatment, however, such therapies may have a role for patients with very limited disease or those not fit for further surgery [21,22]. Other conservative treatments, including the use of pharmacological agents (such as lipid-

lowering drugs, anticoagulants, vasodilators, traditional Chinese medicines, and bisphosphonates) and various noninvasive biophysical modalities (such as electromagnetic stimulation, extracorporeal shock-wave therapy, and hyperbaric oxygen) are advised for supplemental treatment of this disease [7,23—32]. The role of drugs for prevention or treatment is confined to specific aetiological pathways. In the right circumstances, the medical management would be able to arrest ONFH development and induce healing prior to collapse [33]. Meanwhile, these physical therapies are used to address specific physiological factors of ONFH and cannot be recommended as a routine treatment. Clinical studies have further demonstrated that conservative therapies do not achieve satisfactory clinical benefits and are not appropriate for ONFH with subchondral collapse [34].

Operative treatments

Core decompression and bone grafting

Core decompression is the leading surgical treatment for precollapse ONFH and Mont et al's [34] clinical research report showed this operation's success rate reached 70% on follow up of $\geq$ 5 years without the need for additional surgery. Core decompression involves drilling a single 8—10-mm core into the necrotic lesion that could provide pain relief and reduce intraosseous pressure [35]. Meanwhile, this procedure enhances the process of new bone creeping substitution of the necrotic area by stimulating an angiogenic response in the drill channels, therefore restoring or improving vascular flow to prevent further ischaemic episodes and progressive bone infarction [36]. However, clinical problems still exist, including incomplete reconstructive repair and weakening of the trabecular bone within and adjacent to the necrotic region [37]. Recently, Mont et al [38] described a multiple drill-hole technique using a 3.2-mm pin, and reported an 80% success rate for treatment of early stage ONFH that did not need further surgery within at least 7 years.

Core decompression combined with bone grafting produce an improved effect for ONFH through enhancing bone formation and reducing the risk of proximal femoral fracture, and this treatment has been recommended as a routine treatment for precollapse ONFH [39,40]. Allo- or auto-bone graft (cortical strut grafts taken from the ilium, fibula, or tibia; cancellous bone graft taken from the greater trochanter and proximal femur) that fill the drill channels not only offer structural support, but also provide scaffolding for repair (Figure 2) [21,41]. However, these procedures will still have potential risk of viral or bacterial infections and immune response [42,43]. Ceramic and bioglass implants are also widely used in bone surgical repairs and are able to form bone apatite-like material or carbonate hydroxyapatite on their surfaces, enhancing their osseointegration, however, brittleness and slow degradation rates of these materials are disadvantages for their use [44—46]. Metals as implant materials (such as stainless steel, titanium and its alloys, and tantalum) have advantages due to their excellent mechanical properties and porous surfaces that serve as delivery systems for special growth factors [44,47]. However, the lack of tissue adherence and the lower rate of degradation result either in a second surgery to remove the implant or in permanent

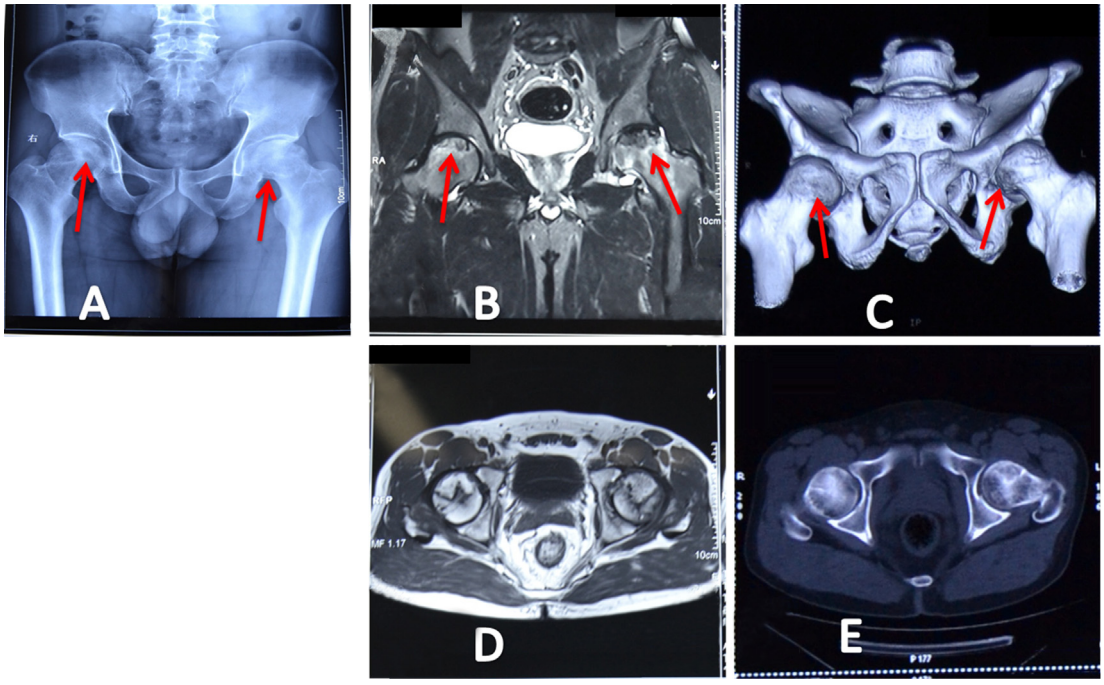

Figure 1 (A) Dual X-Ray absorptiometry, (B) magnetic resonance imaging, and (C) computed tomography of a 41-year-old man with bilateral osteonecrosis of the femoral head (red arrows), and showing the Ficat and Arlet Stage II and Stage III lesions in the right and left femoral heads, respectively. The volume, angle, and arc of osteonecrotic lesions are detected on (D) magnetic resonance imaging and (E) computed tomography for guiding further treatment.

Table 1 Classification systems of osteonecrosis of the femoral head.

Ficat and Arlet [10,11] (Radiography)		Steinberg [12,13] (Radiography; MRI; CT)		ARCO [14,15] (Radiography; MRI; CT; scintigraphy)		JOA [18,19] (Radiography; MRI; CT; scintigraphy)	
Stage	Description	Stage	Description	Stage	Description	Stage	Description
I	Normal (Patients are asymptomatic)	0	Normal physical examination (Patients are asymptomatic)	0	None	I	Demarcation line Subdivided by relationship to weight-bearing area: A: medial B: central C: lateral
II	Diffuse sclerotic and cystic lesions The integrity structure of hip (Patients have mild intermittent pain in the groin that radiates down the inner aspect of the thigh and a normal gait)	I	Normal radiography Abnormal CT and MRI (Patients are asymptomatic)	I	Normal radiography and CT and at least one of the other physical examination methods is positive Area of femoral head involvement: A: minimal $< 15\%$ B: moderate 15—30% C: extensive $> 30\%$ Length of crescent: A: $< 15\%$ B: 15—30% C: $> 30\%$ Surface collapse and dome depression: A: $< 15\%$ of and < 2 mm B: 15—30% and 2 to 4 mm C: $> 30\%$ and > 4 mm (Patients are asymptomatic)	II	Early flattening without demarcation line around necrosis area
III	Subchondral fracture Crescent sign (Patients have increased pain and crepitus during changes in position particularly when arising from sitting)	II	Diffuse sclerotic Cystic lesions Area of cystic lesions involvement: A: Mild $< 15\%$ B: Moderate 15—30% C: Severe: $> 30\%$ (Patients are asymptomatic)	II	Sclerosis Osteolysis Focal porosis (Patients have mild intermittent pain in the groin that radiates down the inner aspect of the thigh and a normal gait)	III	Cystic lesions Subdivided by site in the femoral head: A: medial B: central C: lateral
IV	Femoral head collapse Joint destruction Osteoarthritis Acetabular degeneration (Patients have pain with activity)	III	Subchondral fracture Crescent sign Area of articular surface involvement: A: Mild $< 15\%$ B: Moderate 15—30% C: Severe: $> 30\%$ (Patients have mild intermittent pain in the groin that radiates down the inner aspect of the thigh and a normal gait)	III	Crescent sign Flattening of femoral head (Patients have increased pain and crepitus during changes in position particularly when arising from sitting)		

IV	Flattening of femoral head Area of femoral head involvement: A: Mild < 15% of surface affected and < 2 mm of depression B: Moderate 15–30% surface affected and 2–4 mm of depression C: Severe: > 30% surface affected and > 4 mm depression (Patients have increased pain and crepitus during changes in position particularly when arising from sitting)	IV	Acetabular changes Joint destruction Osteoarthritis (Patients have pain with activity)
V	Joint narrowing or acetabular changes (Patients have pain with activity)		
VI	Advanced degeneration changesanges (Patients have pain with rest)		

ARCO = Association Research Circulation Osseous; CT = computed tomography; JOA = Japanese Orthopaedic Association; MRI = magnetic resonance imaging.

implantation in the body with the related risks of toxicity due to accumulation of metal ions caused by corrosion [48,49]. In addition, patients who continue steroid therapy after decompression have a worse prognosis [50]. Recently, pure magnesium and its alloy coated with microarc oxidation and electrophoresis deposition have been shown to reduce the degradation rate of magnesium and have great potential as promising biodegradable implantation materials and internal fixators [51]. Although core decompression seems to be more effective than purely symptomatic treatment, it must be performed in the precollapse stage, because it will not restore femoral head sphericity or remove the collapsed segments from the weight-bearing area [34,36].

Osteotomy

Osteotomies are used to rotate the necrotic or collapsing segment of the hip out of the weight-bearing zone or to move the segments of necrotic bone away and replace them with a healthy viable bone [6,22,52]. This procedure could change the biomechanical effect, and reduce venous hypertension and intramedullary pressure [52]. Osteotomies are usually recommended to younger patients (aged $<$ 45 years) [53]. These surgical procedures include transtrochanteric rotational osteotomy and intertrochanteric angular osteotomy [54,55]. However, the prognosis of these two procedures is difficult to compare because there are ethnic differences [7]. Transtrochanteric rotational osteotomy only applied to Asian countries because the posterior capsule of the hip in Asians may be more lax and may allow for better rotation of the anterior portion of the femoral neck. On the contrary, the intertrochanteric angular osteotomy has been more successful in Caucasians due to above anatomic difference [7,56]. However, poor fixation with screws may cause increased various deformity, delayed union, and even secondary collapse of the femoral head [57]. Osteotomy is used rarely, because this procedure is only suitable for patients with the following criteria: (1) aged $<$ 45 years; (2) not being treated with long-term steroids; (3) with minimal osteoarthritic changes; (4) a small necrotic angle; and (5) without acetabular involvement [53,58].

Arthroplasty

Limited femoral resurfacing with cement fixation is usually used in younger patients. In this procedure, the damaged cartilage on the femoral side is removed, the viable acetabular cartilage is retained, and bone stock is preserved [59]. However, this limited femoral resurfacing surgery requires years of rigorous training and great skill, because these procedures have high failure rates and are closely related to femoral neck fracture [60,61]. Mont et al [59] recommend that patients with the following criteria are chosen for limited femoral resurfacing: (1) Ficat and Arlet Stage III; (2) necrotic angle of $>$ 200° or necrotic area $>$ 30%; (3) femoral head collapse of $>$ 2 mm; and (4) the acetabular cartilage has not been damaged.

In addition, full resurfacing arthroplasty has become an increasingly popular choice for younger patients with end-stage arthritis [62,63]. Parsons and Steele [22] considered that all operations were performed in special patients with the following criteria: (1) necrotic area $<$ 35%; (2) femoral head neck junction integrity remains preserved; and (3) the

Table 2 Treatment options and their advantages and disadvantages.

Treatment options		Criteria	Advantages	Disadvantages	References
Untreated		Asymptomatic ONF	Spontaneous repair in exceptional cases	Poor outcome Developing to symptomatic	[2—5]
Nonoperative therapy	Restriction of weight-bearing	The early stage of ONFH (Ficat and Arlet Stage I)	Giving pain relief	Very limited for preventing disease progression	[20—22]
	Drugs	With known aetiological pathway	As prevention treatment	Very limited benefits	[23—26,30—32]
	Physical therapy	With known physiological factors	Supplement treatment for operation	Not appropriate for collapse	[27—29]
Core decompression	Drill a single 8—10 mm core	Ficat and Arlet Stage II Patients have mild intermittent pain	Giving pain relief Reducing intraosseous pressure	Lower mechanical strength Secondary trauma	[35—37]
	Drill a single 3.2 mm core	Precollapse ONFH	Stimulating angiogenesis and osteogenesis	NA	[38]
Bone grafting	Allo-bone grafting Auto-bone grafting Ceramics Bioglass		Giving pain relief Offering structural support Stimulating angiogenesis and osteogenesis	Infections Immune response Higher brittleness of implants Slow degradation rates Secondary trauma	[21,41—43] [44—46]
	Metal implants Stainless steel Titanium Tantalum			Lower tissue adherence Lower rate of degradation Metal ions toxicity Secondary trauma	[44,47—49]
Osteotomy	Transtrochanteric rotational osteotomy Intertrochanteric angular osteotomy	Ficat and Arlet Stage II and III Patients have increased pain Patients $<$ 45 years old No long steroids using history A small necrotic angle	Giving pain relief Changing biomechanical effect in lesion region Reducing intramedullary pressure	Ethnic differences Poor fixation Delayed union Secondary deformity Secondary collapse	[7,52—58]

		Minimal osteoarthritic changes Without acetabular involvement			
Arthroplasty	Limited femoral resurfacing	Ficat and Arlet Stage III Patients have increased pain or crepitus during changes in position Necrotic angle of $>$ 200° Necrotic area $>$30% Femoral head collapse $>$2 mm Without acetabular cartilage involvement	Retaining the viable acetabular cartilage Retaining the bone stock	Higher failure rates Femoral neck fracture Dislocation of femoral head Secondary trauma	[59—61,67]
	Full resurfacing	Ficat and Arlet Stage III and IV; Necrotic area $<$35%; Femoral head neck junction integrity remains preserved; Bone stock providing a stable foundation for other components.	Best choice for younger patients with end stage arthritis	Dislocation of femoral head Secondary trauma Groin pain Limited implants lifespan	[22,62—67]
	Total hip arthroplasty	Ficat and Arlet Stage IV; Femoral head quality is very poor Continuing defective on bone mineral metabolism With acetabular cartilage involvement	The only choice for degenerated hip joint	Greater mechanical failure rate Limited implants lifespan Dislocation of femoral head Secondary trauma	[6,22,59,63,67]

ONFH = osteonecrosis of the femoral head.

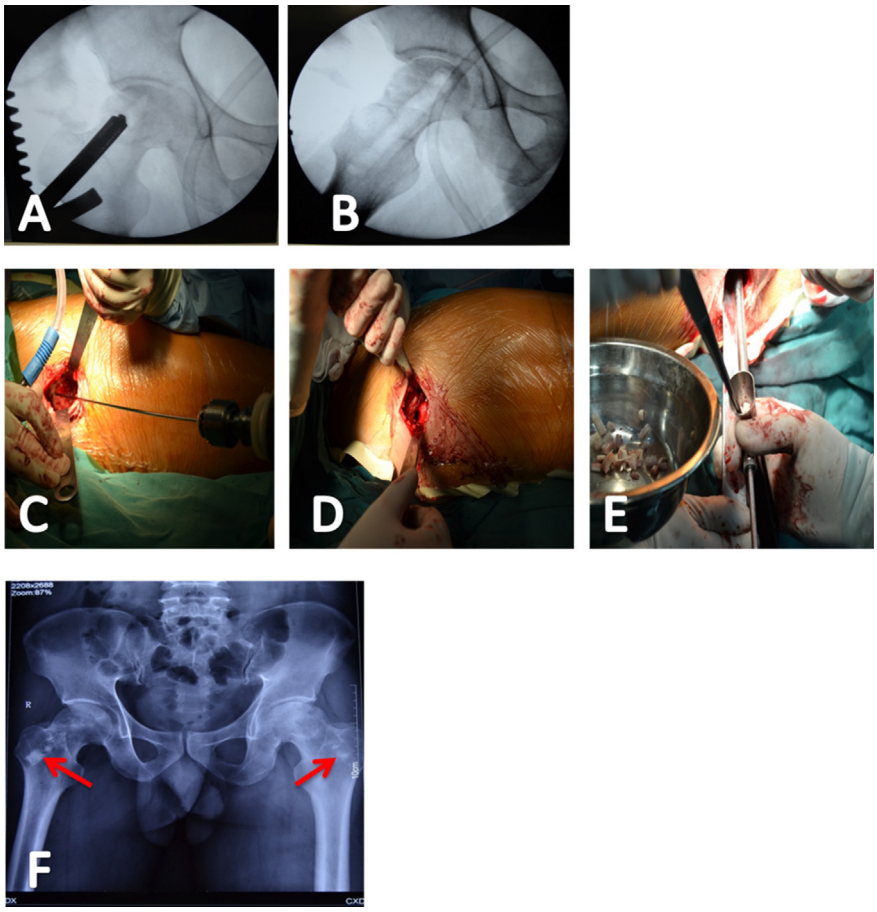

Figure 2 (A—E) The same patient as described in Figure 1 treated using core decompression and allo-bone grafting. (F) The condition on the first postoperative day was delineated by dual X-ray absorptiometry; allo-bone implants were seen in the tunnel (red arrows).

remains of bone stock could provide a stable foundation for femoral components. This procedure involves replacing a limited portion of the femoral head by a thin cemented polyethylene acetabular component or the renaissance of a large head [64,65]. The use of these devices for necrotic hips has led to some concerns regarding vascular insult to the femoral head and lower osteointegration rate of fixation components [66], and the design of devices does not address pathology progression at the acetabular surface in the later-stage ONFH, along with many complications including wear, loosening, and groin pain [67]. However, research has found that if good results are seen at an early stage, they would be maintained for a long time.

Once the hip joint has degenerated (the articulation was compromised), total hip arthroplasty (THA) will be needed. However, there is no consensus regarding the utilization of total hip replacement in particular patients with sickle cell disease, systemic lupus erythematosus, postrenal transplant and ongoing steroid use or alcohol abuse [22]. Mont et al [6,59] and Parsons and Steele [22] also recommend that patients considered for total hip replacement should meet the following criteria: (1) the femoral head quality is very poor; (2) there may be continuing defective bone mineral metabolism; and (3) hip is subjected to continuing insults. However, there is a greater mechanical failure rate in patients aged $\geq$ 50 years; wearing and loosening are major complications of THA [63,67]. Currently, the use of contemporary cementing techniques or uncemented components combined with improved bearing surfaces could reduce wear and improve longevity of implants [22]. In addition, coupled with the larger head combinations made possible by hard-on-hard bearing surfaces, this should reduce the loosing or dislocation risk [22]. Recently, metal-on-metal and ceramic-on-ceramic bearing surfaces have become more popular in clinical application. Correctly, the potential advantages of resurfacing over THA are lower dislocation rates, preservation of bone stock, and THA conversion could be performed if necessary [63,67].

Potential therapies for ONFH and their translational barriers—scaffold-based bone tissue engineering combined with biofactors

Bone is in a constant state of osteoclasts resorbing the matrix and osteoblasts forming the matrix during the adult stage [68], and this well-balanced state is associated with cellular and vascular events [69,70]. Various cellular mediators (growth factors, differentiation factors, cytokines, and hormones) are sequestered in vascular and bone matrix, and regulate bone metabolism, function, and regeneration [71,72]. Currently, evidence implies that the ONFH

deterioration is associated with the follow issues [73—77]: (1) aberrant osteoclastic resorption activity; (2) continuous higher vascular permeability; (3) sluggish reparative angiogenesis and osteogenesis; (4) irreversible connective tissue formation; (5) subsequent lower mechanical properties; (6) necrosis area diffusion; (7) severe joint fluid seepage; and (8) necrosis spreading to joints. Vascular, cellular, and matrix events are all involved in this advanced pathological progression and affect each other [77]. To date, biologics involving antiapoptosis, angiogenesis, and osteogenesis pathways have been screened [78]. Selected biologics (cellular mediators, osteogenic, and angioblastic cells) were injected directly into necrotic regions or seeded in scaffolds and then implanted in the bone defect site where the lesion tissue was removed; these procedures were performed in various preclinical models to test the efficacy [79,80]. The scaffold combined with biologics serves as a template to facilitate cell interactions and the formation of bone-extracellular matrix that could be more favourable to enhance reparative angiogenesis and osteogenesis compared with signal scaffold implant and cellular mediator injection (Figure 3) [81—84].

The ideal material or composite used as the component of the scaffold should be nonimmunogenic, nontoxic, controllable, inexpensive, and readily available. A number of scaffold components are currently available [44,84,85] and include inorganic materials, organic materials, and biologics. Through control of a variety of different but inter-related parameters, there is the potential to develop novel and increasingly advanced composites [44,85]. For example, polymers have the advantage of biocompatibility, however, their low mechanical strength and high rates of degradation often affects their use, chemical modification, or other materials participation to improve these polymers implants physical properties and bioactivity. Furthermore, composite scaffolds could also incorporate some biofactors to make a potential bone graft substitute available [44,86,87]. In 1998, the first implantation of a porous ceramic seeded with *in vitro*-expanded autologous osteogenic cells was performed in a bone segmental defect of a patient and it exhibited a good integration and repair process at the interface with the host bone [88,89]. Since then, a few other similar cases were treated using the same approach [80]. In the last 15 years, bone marrow

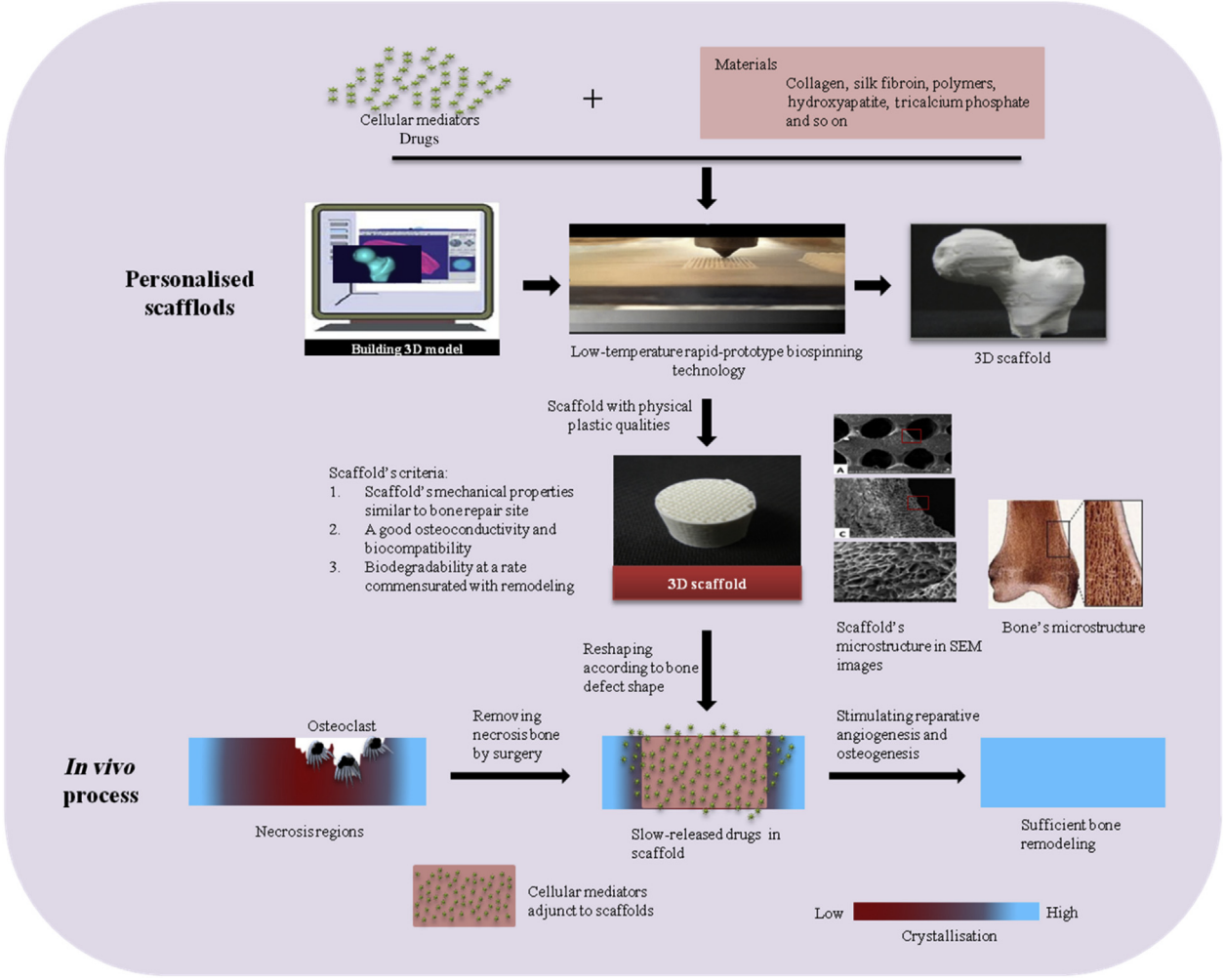

Figure 3 Potential therapy for osteonecrosis using biodegradable three-dimensional scaffolds with biofactors. 3D = three dimensional; SEM = scanning electron microscopy.

mesenchymal stem cells, bone marrow cells, periosteal cells, platelet-rich plasma, and/or recombinant human bone morphogenetic proteins 2 and 7 (rhBMP-2 and rhBMP-7) have been incorporated into degradable porous scaffolds as implants for bone defect and necrotic cartilage repair in orthopaedic patients [90—95]. However, the use of scaffolds combined with biofactors in clinical practice has several major inconveniences [80]. The contribution of the biofactors to the bone formation was difficult to evaluate due to the lack, or inadequacy, of control group patients [96—98]. The success rate is higher, but complications or nonunions are common, especially in large shaft reconstructions [80,99]. rhBMP-2 has been the most commercially successful bone tissue engineering product, being utilized in up to 25% of all spinal fusion procedures [99]. However, there have been significant complications with rhBMP use, including patient death, dysphagia, airway compression in spine fusion, and heterotopic bone formation in the spinal canal [100,101]. In addition, clinical trials of rhBMP-2 incorporation showed risks of cancer, causing the Food and Drug Administration (FDA) to halt its clinical study [102]. The clinical gold standard remains the vascularized free-fibular graft. Although billions of dollars in research funding has been input to explore novel available scaffolds, translation of scaffold-based bone tissue engineering therapies to clinical use is required in the future [103]. Technical and business barriers are critical issues resulting in failed translations and there is a need to address this long-term development.

Dr Scott Hollister [102] provided the *4Fs* overview of scaffolds, which served as the fundamental framework for bone tissue engineering, and should be considered in the design of an effective scaffold. The 4Fs are *Form*, *Function*, *Fixation*, and *Formation*. Form refers to the ability to conform the 3D shape and fill the bone defect site. Function refers to the mechanical properties of the scaffold and requires that scaffolds provide temporary mechanical load bearing within a bone defect. Fixation refers to the ability of the scaffold to integrate and attach to the existing neighbouring bone and soft tissue with good biocompatibility. Formation indicates that scaffolds have a good osteoconductivity, features which are related to porosity, permeability, diffusivity, and delivering osteoinductive factors, including cells, proteins, and genes. Finding a scaffold that addresses all the 4Fs quantitative requirements is an extremely challenging task. There is a common trade-off between the 4Fs during scaffold design, because a strategy priority to promote formation needs special materials or participation of biofactors, which requires a preferable manufacturing technique that intrinsically limits scaffold physical properties related to form, function, and fixation [104]. In general, a scaffold development undergoes two phases [85]: (1) scaffold fabrication needs to entail its physical properties (elasticity, permeability, diffusivity, and degradation) meet functional and formation requirements through regulating the distribution and participation of various materials and micropore structure in three-dimensional space [44,105—108]; and (2) innovative biomaterials with controlled biofactor release, combined with a structural device such as surface creating to cater for individual clinical design [109—111].

Karageorgiou and Kaplan [44] systematically analysed potential porous 3D biomaterial scaffolds according to their physical properties and biological functions and provided guidance regarding design choices of available bone grafts. However, many successful scaffolds in preclinical models may be implausible in some clinical applications due to technical barriers. Firstly, the sequential fabrication technology needed to address all the 4Fs is difficult to achieve due to the limitation of engineering and materials science domain development [112,113]. Secondly, the safety and efficacy of key parameter allocation involving trade-off of the 4Fs are difficult to validate before a wide application in clinics, because the assessment of patient responses is a more complex task for heterogeneity of genetic background and dissimilarity of bone defect types and bone loss patterns [114]. Finally, the controlled biologic release system in a scaffold makes it difficult to match desirable delivery dose and time scale; existing biologic carriers use a very higher dose delivered over a relatively short timescale, which has led to many side effects such as oedema, heterotopic bone and vascular formation, and increased cancer risk [101,115]. The above issues require more investigation in preclinical and clinical trials.

In addition, the business barrier is another critical issue that needs to be addressed in scaffold-based bone tissue engineering translation. The business challenges to translation include regulatory approval, obtaining external funding support, obtaining surgeon acceptance, and obtaining approval for insurance reimbursement [102]. This procedure is very long and uncontrollable, with a need to invest a lot of time, energy, and money. The first step is to establish a quality system covering the scaffold design and manufacturing, as well as a biofactor attachment [116,117]. This would further assure scaffold biosafety and reduce the investment risk to extend the scaffold product to a combination product. The second step in conducting a scaffold from discovery to the clinic is to assure the material components used in the scaffold have been approved by the FDA or China FDA. In parallel, the preclinical studies required in a Class II or Pre-Market Approval application, and the preclinical trials performed, should match International Standards Organization 10993 guidelines [117,118]. The last but the most important part is clinical trials. In general, the clinical trial consists of 4 difference research phases (Phase I, II, III, IV), and a commercially scaffold need to require approvals from phase I to phase IV. Unfortunately, many scaffolds fail to pass Clinical Trial Phase II approval and then the relevant study is halted by the FDA [102]. The failed cases imply that the successful translation of scaffold-based bone tissue engineering still requires more innovation techniques and preferable biofactors.

Future perspectives

Despite the challenges in bone tissue engineering being very frustrating, there remains tremendous optimism concerning the potential to replace damaged and degenerated structures and tissue. The integration of multiple disciplines, such as cell biology, molecular biology, biomechanics science, immunology, structure engineering

science, computer science, three-dimensional printing technology, and translational science, may accelerate bone tissue engineering development and product translation. These advances might improve bone healing by alternative approaches in surgery and facilitate the prognosis of ONFH.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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