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Advancements in 3D printing technologies for personalized treatment of osteonecrosis of the femoral head

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ABSTRACT

Three-dimensional (3D) printing technology has shown significant promise in the medical field, particularly in orthopedics, prosthetics, tissue engineering, and pharmaceutical preparations. This review focuses on the innovative application of 3D printing in addressing the challenges of osteonecrosis of the femoral head (ONFH). Unlike traditional hip replacement surgery, which is often suboptimal for younger patients, 3D printing offers precise localization of necrotic areas and the ability to create personalized implants. By integrating advanced biomaterials, this technology offers a promising strategy approach for early hip-preserving treatments. Additionally, 3D-printed bone tissue engineering scaffolds can mimic the natural bone environment, promoting bone regeneration and vascularization. In the future, the potential of 3D printing extends to combining with artificial intelligence for optimizing treatment plans, developing materials with enhanced bioactivity and compatibility, and translating these innovations from the laboratory to clinical practice. This review demonstrates how 3D printing technology uniquely addresses critical challenges in ONFH treatment, including insufficient vascularization, poor mechanical stability, and limited long-term success of conventional therapies. By introducing gradient porous scaffolds, bioactive material coatings, and AI-assisted design, this work outlines novel strategies to improve bone regeneration and personalized hip-preserving interventions. These advancements not only enhance treatment efficacy but also pave the way for translating laboratory findings into clinical applications.

1. Introduction

ONFH is a progressively debilitating condition resulting from impaired blood supply to the proximal femoral head, leading to tissue necrosis, femoral head collapse, and subsequent hip dysfunction [1]. In China, ONFH affects approximately 8.12 million people over the age of 15 [2]. ONFH predominantly affects individuals aged 41 to 60, with males being diagnosed around 7.3 years earlier than females. The male-to-female ratio is approximately 2.4: 1 [3]. ONFH can be classified into traumatic and non-traumatic categories, depending on its underlying pathogenesis. Early symptoms of ONFH include pain, often with minimal imaging abnormalities. In later stages, subchondral bone collapse and restricted hip movement become evident, significantly impairing patients' quality of life. Advanced ONFH typically necessitates artificial hip replacement, which places a considerable burden on patients and their families. The effectiveness of hip replacement can be compromised by complications such as aseptic loosening, infection, and the limited lifespan of the prosthesis. Early diagnosis and treatment are vital for ONFH.

Hip-preserving strategies can delay femoral head collapse, potentially postponing or even avoiding the need for hip replacement [4]. Surgical treatments for hip preservation currently include core decompression (CD), osteotomy, and bone grafting, with or without vascularized grafts. The primary challenges in ONFH treatment include: (1)

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impaired vascularization, which hampers long-term bone regeneration; (2) inadequate mechanical stability of traditional grafts, leading to secondary femoral head collapse; and (3) limited efficacy of hip replacement in younger patients due to the restricted lifespan of prostheses. These challenges necessitate innovative solutions. 3D printing technology, with its ability to design patient-specific scaffolds, integrate angiogenic bioactive materials, and optimize biomechanical properties, offers a promising pathway to overcome these limitations [5,6]. As a result, the search for more effective treatments for femoral head necrosis persists. Over the past decade, 3D printing has emerged as a transformative technology, offering high accuracy, speed, personalization, and cost-effectiveness. This technology enables the creation of implants that closely replicate damaged anatomy [7] and can be integrated with other modern technologies, such as the Internet and smart engineering, to advance telemedicine and digital healthcare [8]. Such innovations offer promising advancements in the treatment and diagnosis of ONFH, including the customization of surgical guides and implant stents based on postoperative patient data (Fig. 1).

2. Overview of 3D printing technology

2.1. Principles and types of 3D printing technology

3D printing (3DP), also known as "additive manufacturing" or "rapid prototyping," was pioneered by Charles Hull in the early 1980s. The process begins with a computer-aided design (CAD) program to create the initial design, which is then converted into an STL (Standard Surface Subdivision Language or STereoLithography) file. The 3D object is printed layer by layer on a 2D plane, transforming the digital model into a physical structure. In the medical field, data from laser scans, computed tomography (CT), and magnetic resonance imaging (MRI) are often converted into STL format for 3D printing [9]. There are several 3DP techniques, each selected based on the specific material and product requirements. The American Society for Testing and Materials (ASTM) International categorizes 3DP technologies into seven primary types [10,11]:(1) Material extrusion(Fig. 2A) entails heating materials such as thermoplastics to a molten state, extruding them through a nozzle, and depositing layers sequentially to fabricate three-dimensional structures [12]. (2) Vat photopolymerization (Fig. 2B) leverages light, heat, or chemical reactions to induce the polymerization of monomers, enabling the formation of intricate polymer networks [13]. (3) Powder bed fusion (Fig. 2C) involves sequentially melting metal or plastic powders using energy sources such as lasers or electron beams, followed by controlled cooling to consolidate the desired structure [14]. (4) Material jetting (Fig. 2D) precisely deposits liquid droplets, which are subsequently cured by light or heat to create solidified layers [15]. (5) Binder jetting (Fig. 2E) deposits liquid binders onto layered powder beds, where the binders fuse particles together, with subsequent post-processing enhancing mechanical strength and stability [16]. (6) Directed energy deposition (DED) (Fig. 2F) constructs three-dimensional objects by utilizing focused energy, such as lasers or electron beams, to melt metal powders or wires, which are then deposited layer by layer [17]. (7) Sheet lamination (Fig. 2G) involves stacking and bonding thin sheets of material, such as paper, plastic, or metal, to sequentially construct three-dimensional structures [18]. Among these, common medical applications include orthopedic implantable scaffolds made from metallic materials, as well as tissue and organ chips created through bioprinting. For orthopedic scaffolds, technologies like powder bed fusion, directed energy deposition, binder jetting, and sheet lamination are primarily used [19]. In contrast, 3D bioprinting uses

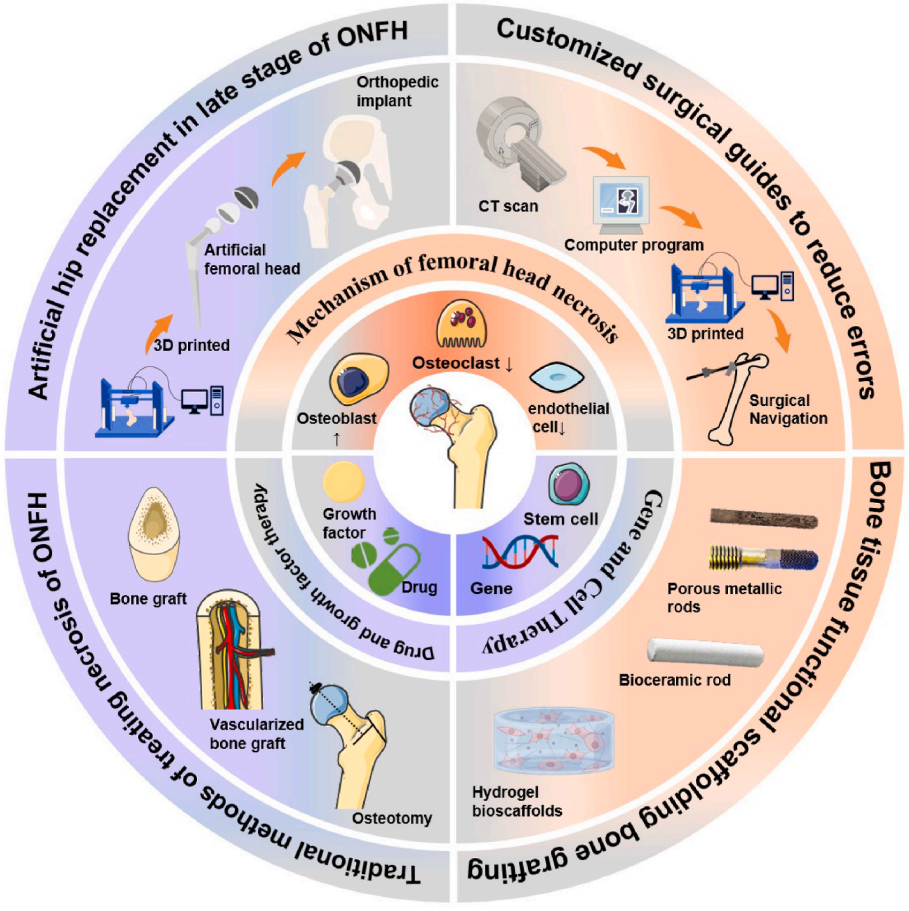

Fig. 1. Overview of the application of 3D printing technology in the treatment of femoral head necrosis.

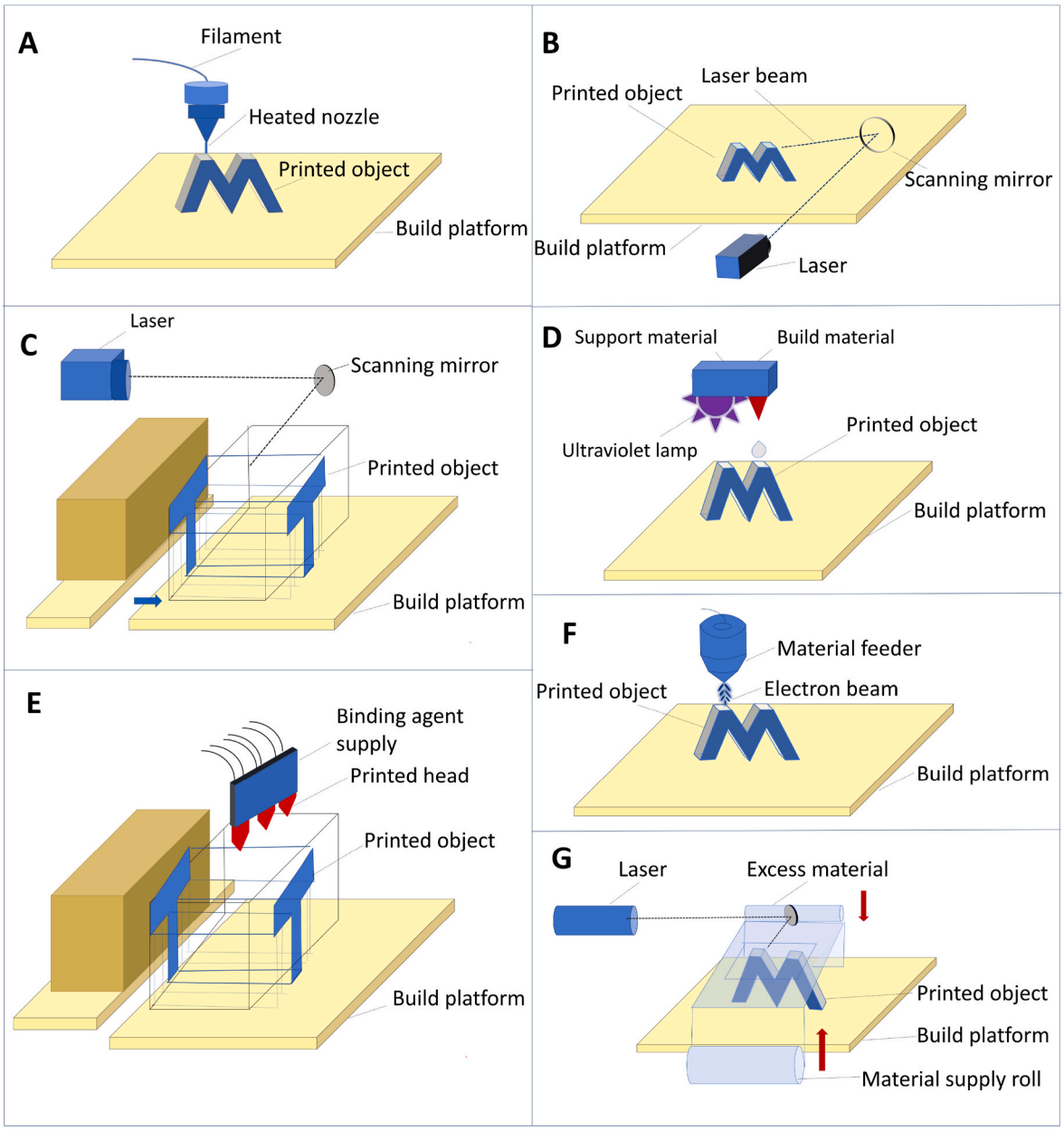

Fig. 2. 3D printing technology classification: (A) Material extrusion, (B) Vat photopolymerization, (C) Powder bed fusion, (D) Material Jetting, (E) Binder jetting, (F) DED, (G) Sheet lamination.

biomaterials, biomolecules, and living cells to print tissue structures. The choice of instrument depends on the type of bioink, with laser bioprinters, extrusion bioprinters, and inkjet bioprinters being commonly used [20].

2.2. Application and development of 3DP technology in medicine

The first significant application of 3D printing technology in medicine dates back to 1990, when Mankovich successfully replicated an anatomical model of the skull using CT scan data and Stereolithography Apparatus (SLA) [21]. Following this, a company based in San Francisco utilized 3DP technology to produce prosthetic limbs, streamlining the traditionally cumbersome manufacturing process [22]. As 3DP technology continues to evolve, it has become an increasingly pivotal tool in healthcare and medicine. Among the various medical fields, orthopedics and traumatology have seen the most substantial impact from 3DP applications. These include preoperative diagnosis and simulation, intraoperative guidance and positioning, the creation of custom implants and fixators, orthotic and prosthetic design, and clinical education [23,24]. The production of anatomical models through 3DP plays a critical role in allowing clinicians to validate and simulate preoperative strategies, significantly reducing the likelihood of medical errors and enhancing surgical outcomes. Personalized organ models generated by 3DP offer superior spatial and visual feedback during surgical simulations, thereby facilitating precise intraoperative positioning [25]. In orthopedic surgery, 3DP enables the creation of customized surgical guides, which are essential for accurate intraoperative navigation. These guides not only improve the precision, safety, and reliability of surgeries but also propel orthopedic procedures toward greater precision, intelligence, and minimally invasive techniques [26]. For example, Zhao et al. [27] designed a 3DP surgical guide for endodontic microsurgery, which precisely locates intricate anatomical structures, such as the root apex, to guide apicoectomy procedures. In bone grafting, 3DP technology offers distinct advantages by filling irregularly shaped bone defects.

This approach not only replicates the native anatomy but also incorporates biomaterials that mimic the extracellular matrix, thereby promoting tissue regeneration more effectively than traditional methods [28].

3D bioprinting has emerged as a focal point in tissue engineering and regenerative medicine research, offering the potential to fabricate biomimetic human tissues with intricate structures and functions [29]. Fang et al. [30] developed an advanced embedded 3D bioprinting technique capable of constructing complex organs with free-form vascular networks, presenting a groundbreaking strategy for tissue and organ regeneration. Additionally, 3DP orthoses have gained substantial market acceptance, with numerous studies demonstrating their ability to enhance patient satisfaction and compliance [31,32]. The scope of 3DP applications in medicine continues to expand, particularly in pharmaceutical manufacturing, where it offers significant advantages. These include the rapid and customizable production of personalized medications in various forms, doses, and appearances tailored to individual patient needs, while minimizing batch failures and quality issues associated with conventional manufacturing processes [33,34]. Furthermore, the integration of 3DP with telemedicine has led to the development of digital pharmacies [35], as well as innovations in digital diagnostics and patient care [36], thus facilitating more timely medical treatment and postoperative rehabilitation. Despite the promising prospects of 3DP technology in the medical field, challenges such as regulatory requirements, safety testing, cost assessment, and the need for ethical and legal guidance must be addressed to fully realize its potential [37,38].

3. Traditional treatment of necrosis of the femoral head

3.1. Pathogenesis and staging of necrosis of the femoral head

The etiology of ONFH is multifactorial and remains poorly understood. The femoral head's distinctive anatomy predisposes it to osteonecrosis. Blood supply to the femoral head primarily arises from the lateral and medial femoral circumflex arteries, with a region particularly susceptible to injury, obstruction, or compression [39]. This vascular vulnerability likely contributes to the increased risk of ONFH following traumatic fractures or thrombotic events. Traumatic fractures frequently involve the femoral head and neck, acetabulum, or occur during hip dislocations. Non-traumatic ONFH is frequently linked to corticosteroid use, chronic alcohol abuse, hyperlipidemia, acute lymphoblastic leukemia, bone marrow transplantation, Gaucher's disease, decompression sickness, hemoglobinopathies (e. g. sickle cell anemia, hemoglobin C disease, thalassemia), autoimmune diseases (e. g. systemic lupus erythematosus), and idiopathic factors [1,40,41]. The most common forms of ONFH are those induced by corticosteroids and chronic alcohol consumption. Corticosteroids contribute to osteonecrosis by altering lipid metabolism, promoting apoptosis, and inducing endothelial cell dysfunction. Corticosteroids enlarge and increase the number of adipocytes, leading to lipid accumulation within blood vessels, elevated intraosseous pressure, endothelial cell damage, and subsequent localized coagulation disorders and vascular embolism (Fig. 3). Alcohol impairs osteogenesis by promoting stromal cell differentiation into adipocytes [42,43]. Glucocorticoids also induce osteoporosis and osteonecrosis by downregulating HIF-1α and vascular endothelial growth factor(VEGF) expression in osteoblasts, thereby reducing their viability and function [44]. ONFH is characterized by necrotic and sclerotic zones that disrupt the balance between bone formation and resorption, with the necrotic zones exhibiting increased osteoclast activity and the sclerotic zones being dominated by active osteoblasts [45]. New blood vessels typically form around the necrotic area, but over time, new bone tissue forms a sclerotic band that impedes vascular ingrowth into the necrotic core. Excessive bone resorption in necrotic areas leads to the formation of microcavities during remodeling, which compromises the mechanical integrity and structural stability of the

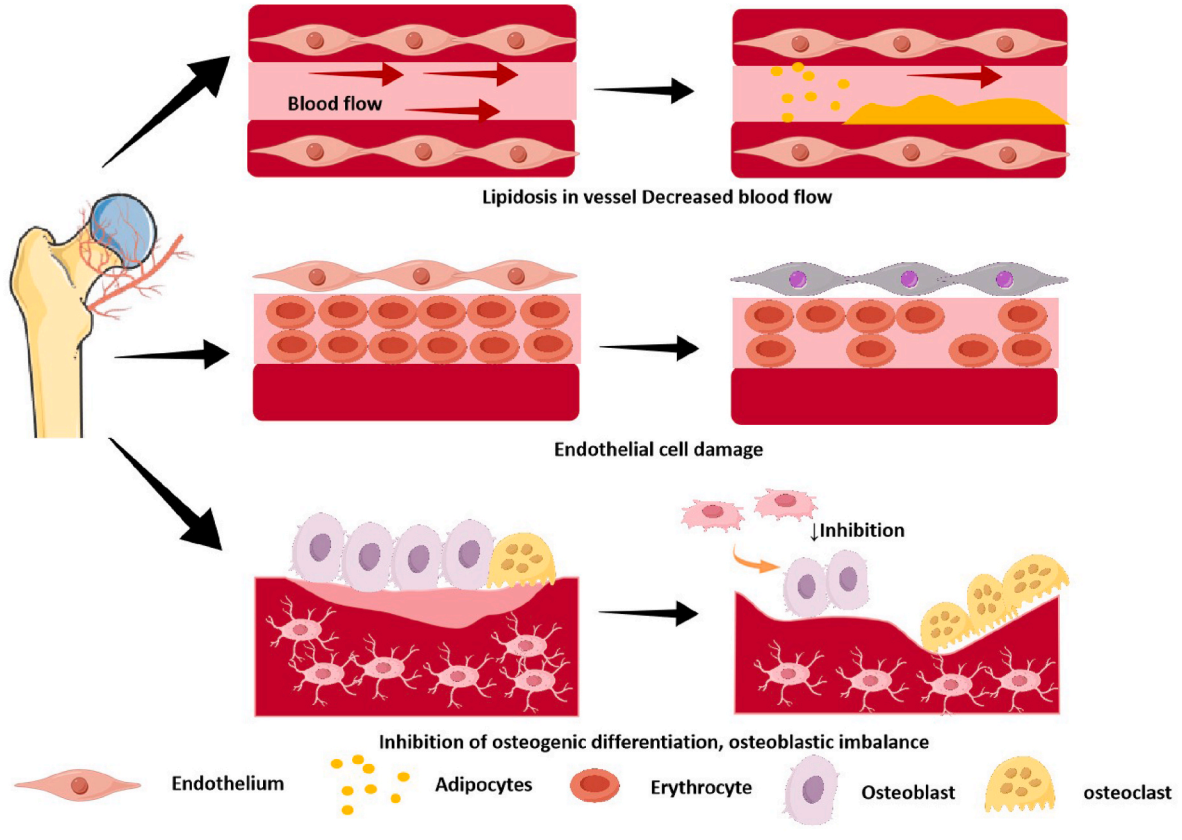

Fig. 3. Pathogenesis of femoral head necrosis.

femoral head [46,47]. These changes significantly increase the risk of fracture, making the recovery from ONFH particularly challenging.

The treatment of osteonecrosis remains a subject of debate and is strongly influenced by the stage of necrosis. Thus, precise staging is crucial for selecting the most appropriate therapeutic approach. The Ficat classification and ARCO staging system are the most widely employed methods for staging ONFH. First developed in 1964, the Ficat system primarily relies on MRI imaging to classify ONFH into four stages (I-IV). The University of Pennsylvania (Steinberg) further refined the Ficat system by adding stage 0 for cases lacking radiological evidence, subdividing stage II based on the presence or absence of the crescent sign, and introducing stages V and VI to reflect joint space alterations, such as flattening, narrowing, and occlusion [48]. The ARCO staging system, initially established in 1994, underwent its most recent revision in 2019 (Table 1). In this 2019 update, stage 0 (osteonecrosis without repair and no low-signal bands on MRI) was eliminated, and stage III was divided into IIIA (early stage, femoral head depression $\leq$2 mm) and IIIB (late stage, femoral head collapse >2 mm) [49]. The Japanese Investigative Committee (JIC) classification distinguishes three types of necrotic lesions: type 1, where the necrotic margin is medial to the femoral head tip; type 2, where the margin lies between the femoral head tip and the lateral acetabular rim; and type 3, where the margin extends beyond the lateral acetabular rim [50]. Each staging system presents distinct advantages and limitations, and no consensus has been reached regarding the most accurate, effective, and reproducibly validated method.

3.2. Conventional treatments

3.2.1. Non-surgical treatments

Non-surgical management of ONFN primarily involves protective weight-bearing, pharmacotherapy, and physical therapy [40,51]. Protective weight-bearing reduces femoral head stress and may delay surgical intervention; however, it does not stop the progression of necrosis [52]. Pharmacotherapy aims to prevent or slow the progression of femoral head necrosis and encompasses both Western and traditional Chinese medicine Western pharmacological agents, including bisphosphonates and statins, act by anticoagulation, vasodilation, lipid-lowering, osteoclast inhibition, and enhancing osteogenesis [53]. Traditional Chinese medicine is integrated throughout the treatment of femoral head osteonecrosis, predicated on the theory that blood stasis is caused by a combination of phlegm-dampness and kidney deficiency. The therapeutic approach involves activating blood circulation, eliminating blood stasis, tonifying the liver and kidneys, and dispelling phlegm-dampness [54]. However, high-quality evidence supporting the efficacy of these therapies is lacking, and many of these drugs are associated with significant adverse effects depending on their route of administration [55]. Physical therapies such as extracorporeal shock wave therapy, hyperbaric oxygen, and high-frequency electromagnetic fields aim to enhance microcirculation, accelerate vascular repair, promote subchondral bone remodeling, and prevent femoral head collapse [56,57]. Nevertheless, clinical trials of these physical therapies are heterogeneous and lack robust evidence to support their efficacy [58].

3.2.2. Surgical treatments

3.2.2.1. Core decompression. CD is a widely used intervention for ONFH prior to femoral head collapse [59]. This work by reducing intraosseous pressure (Fig. 4A), blocking the sclerotic zone, stimulating blood vessel formation around the decompression tunnel, promoting new bone formation, and slowing the progression of ONFH [60,61]. Although some studies suggest that CD is more effective than non-surgical approaches for ONFH [62], its overall therapeutic efficacy remains a subject of debate. The bone defects caused by CD drilling, along with the cavities left after necrotic tissue removal, compromise the biomechanical strength and structural integrity of the femoral head, which may adversely impact patient outcomes. Moreover, the effectiveness of CD is closely tied to the stage of the disease. For instance, Karimi et al. [63] reported success rates of 93 % for Ficat stage I and 46 % for Ficat stage II, underscoring the considerable variation in outcomes. Some studies indicate that combining CD with adjunct therapies, such as cellular therapy, bone grafting, or tantalum rod implantation, may enhance treatment outcomes compared to CD alone [64,65]. However, the results across studies remain inconsistent, and no consensus has been reached [66].

3.2.2.2. Bone grafts. Hip preservation surgery is a widely adopted strategy for ONFH, aimed at excising necrotic bone tissue and substituting it with viable, structurally sound bone. This intervention seeks to restore the integrity of the femoral head and prevent its collapse [67]. Bone grafting serves as an adjunct to CD by introducing osteoconductive or osteoinductive materials into the affected bone (Fig. 4B and D-F), thereby providing necessary mechanical and structural support to avert femoral head collapse [68]. Bone grafts are categorized into non-vascularized and vascularized types based on the presence of vascular supply. Non-vascularized bone grafts, often composed of autogenous bone (e. g. iliac, fibular, tibial cortical strut grafts, and cancellous bone from the greater trochanter and proximal femur) or allograft bone (Fig. 4E), fail to resolve the issue of insufficient blood supply to the femoral head. The predominant cause of femoral head necrosis is insufficient blood supply. Unlike non-vascularized grafts, vascularized bone grafts offer the advantage of an intrinsic blood supply, which can enhance bone regeneration. Vascularized bone grafts (Fig. 4F), including those derived from the iliac crest or fibula, provide mechanical support while maintaining vascular integrity, which may promote the healing of necrotic bone. The success of vascularized bone grafts is contingent on several factors, including patient age, procedural complexity, postoperative complications, and the duration of recovery. Vascularized bone grafting is typically recommended for patients under 50 years of age with symptomatic ARCO stages I-IIIB. Additionally, this procedure carries risks such as postoperative viral or bacterial infections, high donor site morbidity, and extended recovery periods [60].

Table 1
The 2019 revised ARCO staging criteria for ONFH.

	Imaging findings	Imaging characteristics
I	X-ray: normal	No changes are seen on plain radiographs
	MRI: abnormal	A low signal intensity band around the necrotic area is seen on MRI A cold spot is seen on bone scan
II	X-ray: abnormal	Osteosclerosis, focal osteoporosis, or cystic changes are seen in the femoral head on plain radiographs or CT scan
	MRI: abnormal	Still there is no evidence of subchondral fracture, fracture in the necrotic portion, or flattening of the femoral head
III	Subchondral fracture on X-ray or CT	Subchondral fracture, fracture in the necrotic portion, and/or flattening of the femoral head is seen on plain radiography or CT scan
IIIA (early)		Femoral head depression $\leq$2 mm
IIIB (late)		Femoral head depression >2 mm
IV	X-ray osteoarthritis	Osteoarthritis of the hip joint with joint space narrowing, acetabular changes, and destruction is seen on plain radiographs

Fig. 4. (A) The main steps of the modified Advanced CD technique under fluoroscopic guidance that includes removal of the necrotic tissue using a percutaneous expandable reamer followed by refilling of the drill hole and the defect with an injectable, hard-setting, composite calcium sulfate ($CaSO_4$)-calcium phosphate ($Ca_3(PO_4)_2$) bone graft substitute. Reproduced under terms of the CC-BY license [75]. Copyright 2017, BioMed Central. (B) Treatment of femoral head necrosis involves CD complemented by porous tantalum rod implantation. Post-implantation at 12 months, X-rays demonstrated satisfactory condition of tantalum rods. And (C) THA after femoral head collapse. Reproduced under terms of the CC-BY-NC-ND license [76]. Copyright 2020, Experimental and Therapeutic Medicine. (D) Autologous bone marrow buffy coat and angioconductive bioceramic rod grafting with advanced CD for the treatment of early femoral head necrosis. Reproduced under terms of the CC-BY license [77]. Copyright 2021, BioMed Central (E) The nonvascularized allogeneic fibula combined with CD and bone graft therapy for early osteonecrosis of the femoral head. Reproduced under terms of the CC-BY license [78]. Copyright 2020, BioMed Central. (F) Free graft of vascularized iliac bone flap based on deep circumflex iliac vessels for treatment of traumatic ONFH of the left side, and the postoperative imaging showed no collapse of femoral heads or narrowing of the hip joint spaces. Reproduced under terms of the CC-BY license [79]. Copyright 2019, BioMed Central.

3.2.2.3. Osteotomy. Osteotomy is a viable treatment option for ONFH. This surgical approach involves repositioning the necrotic segment of the femoral head away from the weight-bearing zone, substituting it with healthy bone tissue. Commonly employed techniques include transcoronal curved inversion osteotomy (TCVO) and transcoronal rotational osteotomy (TRO) [69]. Osteotomies are less frequently utilized in clinical practice, largely due to uncertainties regarding their biomechanical efficacy. Factors contributing to osteotomy failure—including patient age, body mass index, lesion location and size, and variations in surgical technique—remain poorly understood. Proximal femoral osteotomies should be contemplated only after comprehensive staging of the disease, with the chosen procedure tailored to the patient's individual needs. In older patients, the increased risk of subsequent major surgeries warrants careful consideration [70].

3.2.2.4. Hip replacement surgery. Total hip arthroplasty(THA) remains the definitive treatment for ONFH in its advanced stages (Fig. 4C). Early diagnosis, before substantial lesion progression or imaging evidence of femoral head collapse, enables non-surgical or joint-preserving interventions that significantly improve prognosis. However, in advanced ONFH—characterized by the crescent sign, femoral head flattening, and acetabular involvement—total hip arthroplasty becomes the only viable treatment option [71]. Initially, total hip arthroplasty was primarily indicated for elderly, frail patients or those with limited mobility due to comorbid conditions [72]. While younger patients are increasingly opting for hip replacement, complications such as fixation failure,

support instability, and infections remain prevalent [73]. Furthermore, given that most ONFH patients are relatively young [74], the limited lifespan of artificial joints presents a significant concern. These patients are likely to outlive their implants, necessitating potential future revisions.

4. 3D printing technology in the treatment of femoral head necrosis

4.1. 3D printing customized surgical guides

A 3D surgical template is a highly precise tool that guides the placement of internal fixations, such as screws, enabling accurate bone repositioning and precisely defining the extent of the osteotomy. The development of a 3D surgical template involves multiple steps, including acquiring patient-specific data through CT or MRI scans, segmenting the target region with advanced software, reconstructing a 3D model customized for clinical applications, and fabricating a 1:1 guide template using 3DP technology [26] (Fig. 5A). The advent of 3DP surgical guides has significantly improved the precision in localizing necrotic lesions, reduced surgical errors, and increased success rates. Bell et al. [80] systematically evaluated the efficacy of a 3D-printed drill guide specifically designed for core decompression. The device was designed with a pre-set drilling trajectory, and its feasibility was rigorously tested using femoral sawbones, advanced image processing software, and 3D modeling tools (Fig. 5B). The study conclusively demonstrated that the 3D-printed drill guide consistently directed the decompression device along the intended trajectory with exceptional precision. Cai et al. [81] employed 3DP technology to create a surgical navigation template (Fig. 5C and D), which assists in the precise intraoperative localization and excision of vascularized iliac flaps for treating ischemic femoral head necrosis. Avoiding the problems of inaccurate localization of traditional vascular bone grafting for ANFH, which mainly relies on the experience of the operator. This 3DP-based template is custom-designed to fit the unique anatomical features of each patient.

4.2. 3D printed bone grafts

With the progressive development of biomaterials and basic research, the therapeutic application of bone tissue engineering in femoral head necrosis further optimizes the effectiveness of bone graft in the treatment of femoral head necrosis [48]. However, there still exists a gap between material design and clinical application before clinical translation, including mismatched mechanical properties, poor osteogenic and integrative properties, and unreasonable degradation rates, which need to be adjusted to overcome these problems by adjusting the material properties, optimizing the structure, and taking into account the underlying patient diseases [82]. 3DP technology has great potential to optimize structural design and material utilization, and it can create versatile bone tissue engineering scaffolds by selecting the most suitable printing technique using the advantages of different materials.

Compared to conventional methods such as non-vascularized and vascularized bone grafts, 3DP offers several advantages, including the ability to create patient-specific scaffolds with controlled gradient porosity that closely mimics natural trabecular bone. Table 2 illustrates a direct comparison of 3D-printed scaffolds with traditional grafting techniques, highlighting improvements in mechanical stability, osseointegration, and vascularization. These features address long-standing challenges, such as inconsistent mechanical support and suboptimal angiogenesis, which are common in traditional grafting approaches.

4.2.1. Metallic biomaterials

While autografts remain the gold standard, compared to conventional methods such as non-vascularized and vascularized bone grafts, 3DP offers several advantages, including the ability to create patient-specific scaffolds with controlled gradient porosity that closely mimics natural trabecular bone [28]. Table 3 shows examples of clinical applications of 3D printed metal scaffolds, highlighting improvements in mechanical stability, osseointegration, and vascularization. 3DP is highly versatile, accommodating a wide range of materials. Among these, metals are predominantly utilized in orthopaedic implants and prostheses due to their superior toughness, fatigue resistance, biocompatibility, and machinability. Consequently, metals such as tantalum, titanium, magnesium, nickel, and their alloys are the materials of choice for load-bearing applications in clinical practice [83,84]. Nevertheless, metallic materials are not without limitations. A prominent drawback is stress shielding, which arises from their high mechanical strength and mismatch with the mechanical properties of human bone tissue. To address these challenges, a range of modification strategies has been explored, including elemental doping, surface plasma treatments, pore structure engineering, and the incorporation of reactive coatings [85–87]. Moreover, surface modification techniques have been shown to not only alleviate stress intensity but also enhance osseointegration, thereby improving implant performance [88]. Leveraging 3DP technology in conjunction with computer-aided design facilitates the precise engineering of porous metal scaffold structures, thereby enhancing their biological performance [89]. Porous titanium scaffolds fabricated via 3DPachieve a substantial reduction in elastic modulus (96 %–93 %) and strength (96 %–91 %), closely replicating the mechanical properties of human bone [90]. Moreover, the porous architecture provides an osteoconductive surface that supports cell attachment and bone formation, while fostering regeneration and promoting inward bone growth [91]. Luo et al. [92] revealed that Ti-6Al-4V scaffolds with 65%–90 % porosity and 600 μm pore size effectively emulate the architecture of natural cancellous bone, characterized by fully interconnected trabeculae. Mofazali et al. [86] demonstrated that Ti-6Al-4V scaffolds enhanced with gelatin/alginate-IGF-1 surface coatings significantly increased cell viability (80.7 %–104.1 %) and proliferation. Nonetheless, stents alone fail to resolve the underlying pathology of femoral head osteonecrosis. As a result, extensive research has focused on integrating drugs, cells, and growth factors with metal stents to augment the recovery process of femoral head osteonecrosis. For instance, Cheng et al. [93] utilized polydopamine to embed strontium (Sr), a bioactive element known to enhance angiogenesis and bone formation, into porous tantalum scaffolds. Lei et al. [94] employed 3D-printed titanium reconstruction rods (Fig. 6A–C) loaded with therapeutic agents to treat femoral head necrosis, yielding substantial therapeutic benefits as evidenced by 3D reconstructions and coronal gray value analysis. Li et al. [95] utilized porous scaffolds as carriers for grafted vascular bundles, effectively promoting angiogenesis and tissue recovery (Fig. 6D and E). However, metallic materials may release toxic ions and particles during corrosion or wear, which could elicit hypersensitivity reactions, thereby hindering healing and jeopardizing the long-term stability of implants. Therefore, future efforts should prioritize the development of advanced metal synthesis methods, innovations in 3DP technologies, and optimized scaffold surface modifications.

4.2.2. Bioceramics and bio-glasses

Bioceramic materials, such as calcium phosphate, calcium carbonate, calcium sulfate, and Bioglass, have emerged as widely utilized bone grafts for the clinical management of femoral head necrosis. These materials exhibit osteoconductive and osteoinductive properties, thereby serving as effective substitutes for bone repair. Nevertheless, their application is constrained by inherent limitations, including uncontrollable degradation rates and the potential for immune rejection after implantation. To overcome these challenges, the integration of 3D printing technology with diverse materials and coatings has been proposed to optimize the functionality of bioceramics in bone grafting applications [104,105]. β-tricalcium phosphate (β-TCP) is extensively employed as a scaffold material after core decompression, with numerous studies substantiating the effectiveness of bioceramics in

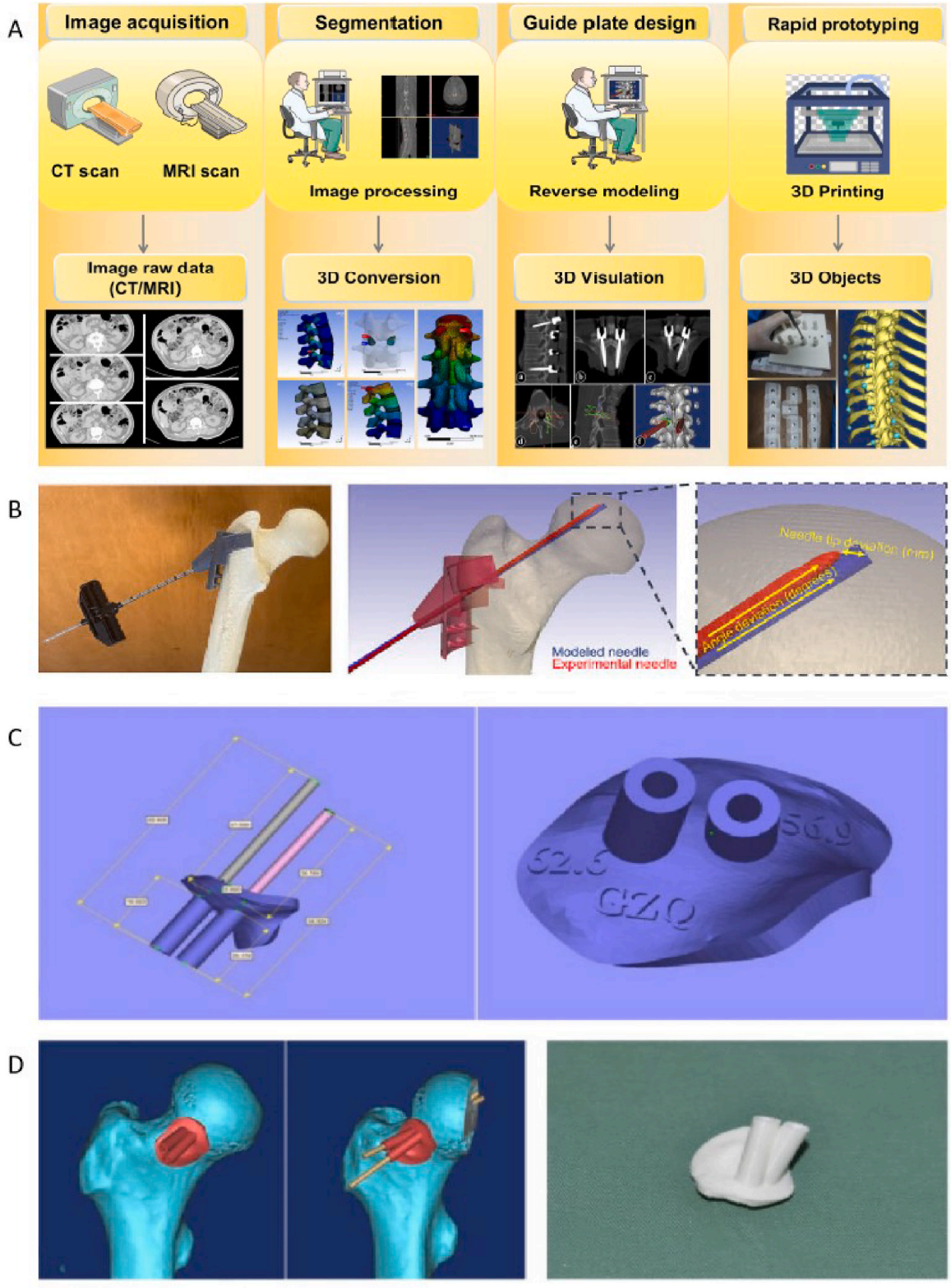

Fig. 5. (A) The creation of a 3D-printed surgical guide involves acquiring imaging data from CT or MRI scans. This data is then analyzed, reconstructed into a 3D model, and subsequently printed. Reproduced with permission [26]. Copyright 2022, Elsevier. (B) Bell et al. designed a drill guide with a predetermined path, demonstrating its precision in guiding a decompression device along this specified trajectory. Reproduced under terms of the CC-BY license [80]. Copyright 2024, 3DP in Medicine. (C) and (D) Cai et al. utilized 3DP technology to develop a personalized navigational template, enabling precise positioning and resection of an iliac bone flap with a vascular pedicle for the treatment of avascular necrosis of the femoral head. Reproduced under terms of the CC-BY-NC-ND license [81]. Copyright 2020, Annals of Plastic Surgery.

Table 2
Comparison of 3D-printed scaffolds with traditional grafting techniques.

Features	Traditional Bone Grafts	3D-Printed Scaffolds
Mechanical Stability	Limited, especially in non-vascularized grafts	Gradient porous designs optimize strength and reduce stress shielding.
Angiogenesis	Relies on graft integration	Enhanced with bioactive coatings (e.g., VEGF, BMP-9).
Personalization	Generic grafts	Patient-specific scaffolds based on imaging data.

treating ONFH (Fig. 4D) [77,106,107]. A key advantage of β-TCP is its capability to promote the uniform filling of porous ceramic particles within necrotic areas. Porous ceramic rods effectively direct blood flow from healthy to necrotic tissue, whereas the ceramic particles serve as scaffolds for reconstructing the necrotic bone bed, thereby promoting vascularization and bone regeneration [108]. Similar to metallic implants, bioceramics alone fail to adequately address the critical issue of impaired blood supply in femoral head necrosis. Consequently, they are often combined with effectors such as autologous bone marrow or stem cells to augment therapeutic efficacy [77,109]. For instance, Lyu et al. [110] introduced platelet-rich plasma combined with β-TCP into necrotic regions of the femoral head following core decompression surgery. Their findings revealed that this strategy significantly alleviated pain, improved joint function, and decelerated the progression of femoral head necrosis over the short term.

4.2.3. Hydrogel and other polymer materials

Polymers are generally categorized into natural variants, such as chitosan, gelatin, and alginate, and synthetic counterparts like polycaprolactone (PCL) and polylactic acid (PLA), which are valued for their high plasticity, tunable degradation rates, and exceptional biocompatibility [111]. Nevertheless, their mechanical strength is often inadequate compared to other materials, and the safety as well as biocompatibility of synthetic polymers require meticulous evaluation [104]. The advent of 3D bioprinting has markedly expanded the scope of polymer applications in tissue engineering, providing innovative avenues for material design and fabrication. Specifically, bioprinting utilizes bioinks, comprising biomaterials, cells, and other biological constituents, to fabricate hydrogel-based structures with defined geometric and structural characteristics that foster cell proliferation and guide lineage-specific differentiation [112]. Consequently, researchers have directed substantial efforts toward optimizing degradation kinetics, improving mechanical robustness, and augmenting biological functionality by synthesizing advanced materials and incorporating bioactive agents such as cells or growth factors [113–115]. For instance, Kawai et al. [116] leveraged 3D printing to construct functionally graded scaffolds composed of PCL and (β-TCP) (Fig. 6F and G). These scaffolds, loaded with genetically modified bone marrow stromal cells, were utilized for femoral head necrosis treatment, combining biologic delivery with structural and mechanical reinforcement. Similarly, Bai et al. [117]. revealed that Zn-modified metal-organic framework 818 (Zn-MOF-818), integrated with desferrioxamine, gelatin methacryloyl hydrogel, and demineralized bone matrix, effectively neutralizes excess reactive oxygen species, stimulates angiogenesis, and modulates immune responses.

In conclusion, the distinct advantages and limitations of each material, coupled with the variability in scaffold performance depending on the chosen manufacturing method, highlight the critical importance of material-method synergy. Tables 4 and 5 comprehensively compare the advantages and drawbacks of various materials and printing techniques, providing essential guidance for informed decision-making. Moreover, the judicious selection of materials and printing techniques tailored to the pathological conditions of femoral head necrosis and the inherent differences in anatomical structures is pivotal for advancing the development of personalized therapeutic strategies.

4.3. Artificial hip prosthesis

The artificial hip joint prosthesis replicates the structure of the human hip joint, with its stem inserted into the medullary cavity. The prosthesis head articulates with the acetabular socket or metal cup, facilitating the flexion, extension, and overall mobility of the femur. Postoperative infection and aseptic loosening remain the primary complications associated with prosthetic implants, similar to those seen with stent implantation. A common strategy to enhance bone anchorage involves engineering rough surfaces on the prosthesis, utilizing methods such as porous coatings, nanostructured layers, and biomimetic modifications [153]. Naghavi et al. [154] designed a low-stiffness polyether ether ketone (PEEK) hip prosthesis using fused deposition modeling

Table 3
Clinical use of porous metal scaffolds for the treatment of femoral head necrosis.

	ONFH Staging	Treatments	Groups	Clinical outcome (Joint preservation success rate)
Zhao et al. [96]	ARCO II-IV	Tantalum rod implantation + vascularized iliac grafts	52 cases	95 % at ARCO II, 92 % at ARCO III, and 63.6 % at ARCO IV
Liu et al. [97]	ARCO II and III	Porous tantalum rod implantation	149 cases (168 hips: II 79 hips, III 89 hips)	69 % in the whole group
Zhao et al. [98]	ARCO IIIc and IV	Tantalum rod implantation + autologous bone marrow mesenchymal stem cells (ONFH end stage)	24 cases (31 hips: IIIC 19 hips, IV 12 hips)	89.47 % at ARCO stage IIIc, 75 % at ARCO stage IV
Zhang et al. [99]	ARCO II	3D Printed Titanium Trabecular Bone Reconstruction System	30 hips (IIA 2 hips, IIB 26 hips, IIC (B) 2 hips)	100 % in the ARCO IIA, 100 % in the IIB group, and 50 % in the IIC group
Zhao et al. [100]	ARCO II-IV	Tantalum rod implantation + vascularized iliac grafts	61 cases (66 hips: II 21 hips, III 30 hips, IV 15 hips)	The whole group was 77.2 %.
Fang et al. [76]	Ficat I and II	Non-surgical treatment and tantalum rod implantation	60 cases (30 non-surgical: Ficat I 7cases, Ficat II 23 cases; 30 surgica: Ficat I 10 cases, Ficat II 20 cases)	4.9 % in the non-operative group and 36.7 % in the operative group.
Peng et al. [101]	ARCO I and II	Porous tantalum rod implantation	60 cases (30: CD + bone implantation, 30: CD + tantalum rod implantatio)	Harris scores were higher in patients with porous tantalum rod implants than in patients with bone grafts at 12 months after treatment ($p < 0.05$)
He et al. [102]	ARCO II and III	Porous tantalum rod implantation	40 hips (II 27 hips, III 13 hips)	With an overall survival rate of 75 % at 96 months (ARCO stage II: 81.5 %; stage III: 38.5 %; JIC type C1: 83.3 %; C2: 30 %).
Zhang et al. [103]	ARCO I and II	Porous tantalum rod implantation	52 hips (I 22 hips, II 30 hips)	Success rate of joint preservation 53.8 %

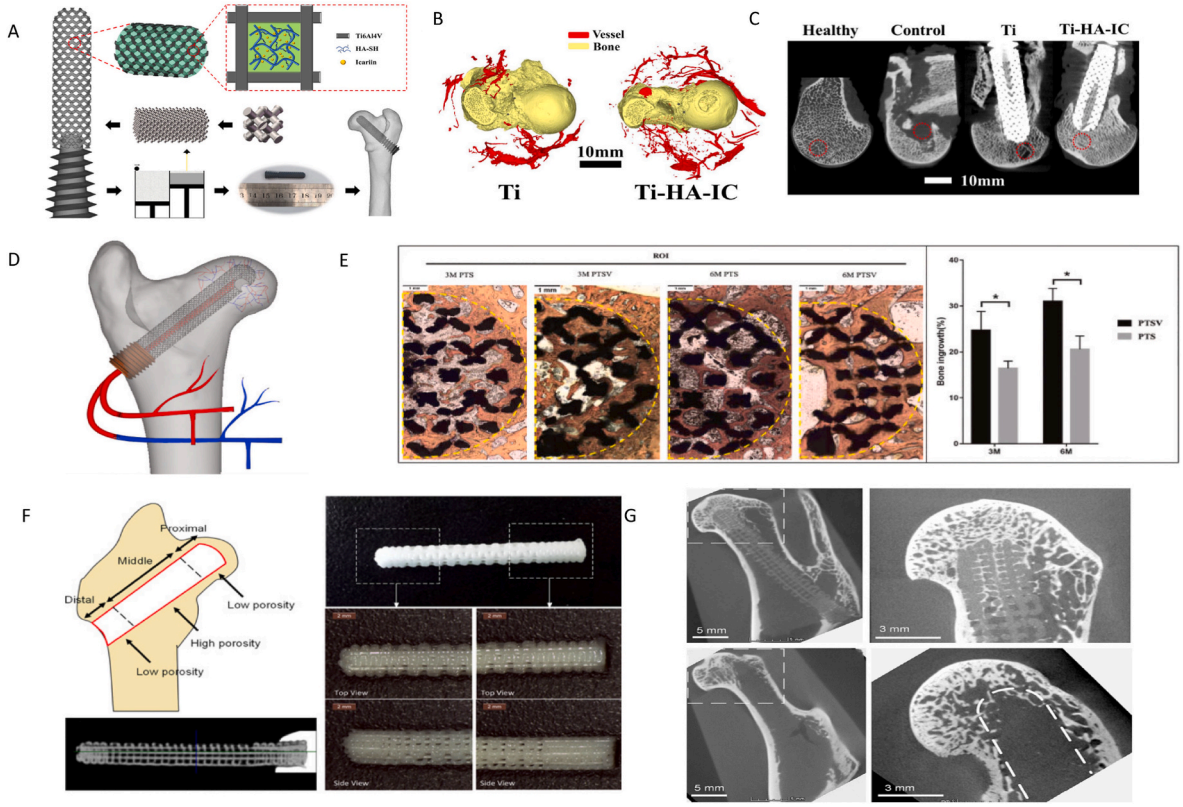

Fig. 6. (A)–(C) Lei et al. developed a drug-loaded 3D-printed titanium rod for the treatment of femoral head necrosis. The therapeutic efficacy was evidenced by significant improvements in 3D reconstruction images and coronal gray values. Reproduced with permission [94]. Copyright 2023, Elsevier. (D)–(E) Li et al. utilized a porous scaffold as a carrier for grafted vascular bundles. Histological analysis confirmed that this approach significantly enhanced bone growth rates. Reproduced with permission [95]. Copyright 2021, Elsevier. (F)–(G) Kawai et al. designed a customized, biodegradable, functionally graded scaffold, which was implanted in a rabbit model of femoral head necrosis. Micro-CT analysis demonstrated that this scaffold effectively promoted bone tissue regeneration within the bone tunnel. Reproduced with permission from Ref. [116]. Copyright 2017, John Wiley and sons.

(Fig. 7A and B), aiming to mitigate stress discrepancies following hip arthroplasty. Bai et al. [155] provided evidence that sintered bionic porous titanium alloys and 3D-printed titanium alloys exhibit superior performance compared to HA-coated titanium alloys in promoting osseointegration at the bone-implant interface (Fig. 7C–E). Notably, the elastic modulus mismatch between metallic implants and adjacent bone tissue remains a critical factor in aseptic loosening, often culminating in stress shielding and eventual prosthesis failure. Accordingly, contemporary research on artificial joint materials has focused on advancing osseointegration while mitigating elastic modulus mismatches at the bone-implant interface. The integration of 3D printing technology has demonstrated substantial potential. Naghavi et al. [156] systematically compared the stress shielding effects, bone resorption characteristics, stiffness, and fatigue properties of solid versus porous hip implants using in vitro physiological experiments and finite element analysis (Fig. 7F and G). Their findings revealed that porous hip implants achieved a 70 % reduction in stress shielding and a 60 % decrease in bone loss compared to solid hip implants.

4.4. Frontline exploration of 3D printing in the treatment of femoral head necrosis

Early intervention in ONFH is essential to prevent the progression to hip replacement. Despite its importance, there is currently no standardized consensus or established guidelines for the early treatment of ONFH. Recent advancements in 3DP technology have empowered researchers to engineer diverse biomaterials and optimize manufacturing techniques for producing porous bone tissue scaffolds, thereby enhancing treatment strategies for femoral head necrosis [157]. Related investigations, as summarized in Table 6, offer essential insights into the evolving therapeutic landscape. 3D bioprinting represents a state-of-the-art approach to fabricating tissue-engineered materials. This technology not only facilitates the construction of polymer composite scaffolds with biomimetic architectures but also integrates nanomaterials, cells, drugs, cytokines and small-molecule amines (SMAs) [158] into bio-inks [159]. Furthermore, 3D bioprinting allows for the precise fabrication of bone tissue engineering scaffolds with layered structures for repairs at different interfaces [160]. These advancements collectively enable multifunctional strategies to enhance scaffold performance, approximating natural bone characteristics and meeting the structural requirements of bone regeneration [161]. For example, Long et al. [162] employed 3D printing to construct scaffolds comprising black phosphorus (BP)-infused poly(lactic-co-glycolic acid) (PLGA) copolymers (Fig. 8). These scaffolds exhibited superior biocompatibility, biodegradability, and mechanical properties, while facilitating bone regeneration in the distal femur defect of a steroid-associated osteonecrosis (SAON) rat model by regulating macrophage M2 polarization. Nonetheless, the mechanical properties of bioprinted scaffolds remain considerably weaker than those of metallic counterparts, motivating researchers to investigate composite material strategies. For instance, Che et al. [163] designed a 3D-printed porous titanium scaffold incorporating a thermosensitive collagen hydrogel loaded with VEGF and bone morphogenetic protein-9 (BMP-9) (Fig. 9). This system enhances angiogenesis and osseointegration by enabling the continuous release of angiogenic and osteogenic growth factors at the bone defect site. Likewise, this approach offers significant potential for improving osteogenic-angiogenic repair in femoral head necrosis and serves as a promising alternative to conventional therapies.In addition, the

Table 4
Comparison of advantages and disadvantages of 3D printing materials in femoral head necrosis applications.

Materials		advantages	disadvantages
Metals [104]	Titanium alloy	Low density, excellent mechanical properties, corrosion resistance, excellent biocompatibility [118]	Mechanical Properties mismatch with Natural Bone leads to stress shielding, stiffness can Be reduced by 3D printed porous structures [119]
	Magnesium alloy	Degradable [120], bone has better biomechanical compatibility [121]	Corrosion is faster and hydrogen may be released during degradation [122]
	Tantalum alloys	Corrosion resistance, excellent mechanical properties and bioactivity for bone regeneration [123]	High cost, high density Young's modulus comparable to titanium alloys [123]
	Memory alloy (NiTi. etc)	Proximity to body transition temperature, proximity to bone elastic modulus, corrosion resistance and biocompatibility [124]	Release of Ni ions due to corrosion may cause safety issues [125]
bioceramics [104]	hydroxy-apatite (HA)	Biological activity, osteoconductivity and lack of immune response [126]	High brittleness, low compressive and flexural strength [127], mechanical properties and biocompatibility; dependent on interaction with other metals, minerals [128]
	Calcium beta-phosphate(β-TCP)	Bone conductivity, β-TCP is resorbable and easily replaced by new bone [129]	Brittle at high temperatures, need to optimize printing techniques [130]
	Bioactive Glass	Multifunctional, can be used in combination with other biomaterials, and is biocompatible [131]	Brittleness, temperature and print speed control [132]
Polymers [104]	Natural polymers (collagen, gelatin hydrogels, silk proteins, etc.)	Bioactive and biocompatible, inherent functionality of the polymer, promotes cell adhesion [133]	Complex rheological properties (viscosity and shear-thinning behavior) with relatively low mechanical strength and stability [133]
	Synthetic polymers (polycaprolactone, polylactic acid, etc.)	Chemical sensitivity [134], plasticity, controlled degradation [104]	Mechanical constraints, biocompatibility, demanding printing technology [135, 136]

Table 5
Comparison of advantages and disadvantages of 3D printing technology in the application of femoral head necrosis.

Materials	Printing technology	Advantages	Disadvantages
metals	Powder bed fusion (laser powder bed fusion (LPBF), electron beam powder bed fusion (EBPBF) [19]	High precision, complex geometries, internal structural design for functional integration [137]	High residual stresses, thermal deformation and stress issues, powder management issues, post-processing issues [138]
	Directed energy deposition [19]	Surface repair and modification, multi-material switching, high mechanical properties, high build rate, large build volume [139]	Residual stresses, low resolution and high surface roughness, limited accuracy, and post-processing needs [140]
	Binder jetting [19]	Prints complex structures, reduces costs, is highly scalable, and is applicable to a wide range of materials [141]	Relatively low density, low mechanical properties and need for post-treatment [141]
	Laminated object manufacturing (LOM) [19]	For printing of multi-metal parts [142]	Large amounts of waste and low print speeds (especially for complex objects) [143]
Bioceramics/ Polymers	Fused deposition modeling (FDM) [144]	Material versatility, ability to print complex geometries, and low waste generation [145]	Poor surface quality, mechanical constraints, limited precision, and long time [146]
	Stereolithography (SLA) [144]	High resolution, printable complex structures [147]	Hardening of the resin may lead to the occurrence of brittleness and fracture [147]
	Selective laser sintering (SLS) [144]	Printed parts have excellent mechanical properties and high durability [148]	Poor surface smoothness, high cost, and long printing time [148]
	Inkjet 3D printing [133,144]	High resolution, rapid prototyping, material diversity [149]	Inadequate mechanical properties, reprocessing needs [150]
	Digital Light Processing (DLP) [133,144]	High precision, fast print speeds, smooth surfaces [151]	Material limitations, small build volume, curing process issues [152]

proposed mechanically-assisted bioprinting post-strategy can improve the inherently poor mechanical properties of bioprinted cell-carrying scaffolds to achieve mechanical responsiveness to load sensors [164]. There have also been studies on the preparation of novel scaffolds with different bioinks and printing strategies, which can replace the drawbacks of 3DP post-processing solvent residues and difficult to control 3D surface roughness [165]. For example, Chen et al. [166] for example proposed a printing strategy inspired by the stone hut, customized a composite polymer consisting of PLGA microspheres as "Stone" and alginate (Alg) hydrogel as "Mortar". Ink, and the width of the groove-ridge microstructure (identified as W) between the "Stone" can

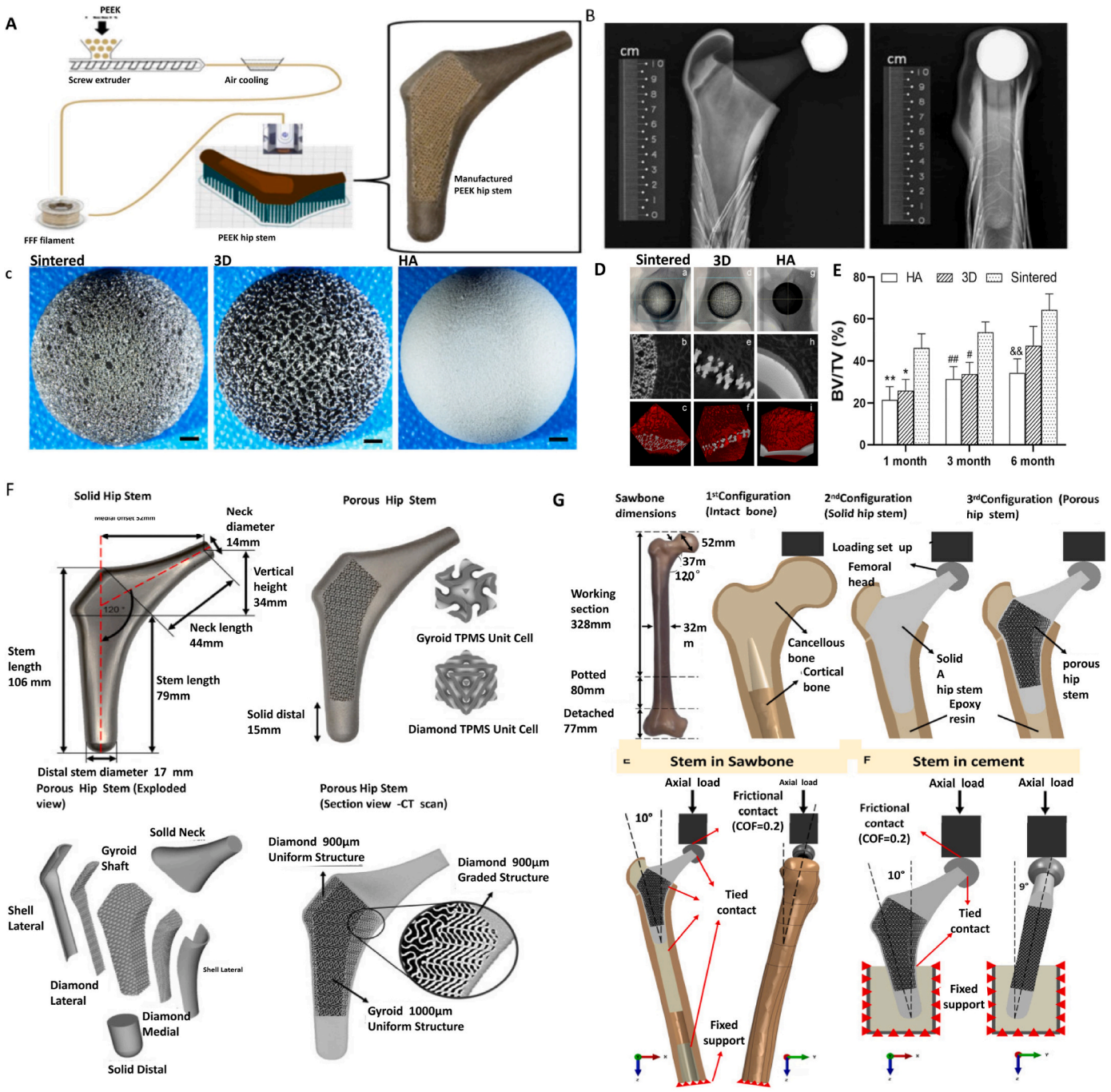

Fig. 7. (A) Manufacturing process and 3D printing of PEEK hip stems with porous surface linear scaffold cells,and(B)X-rays of PEEK prosthesis after implantation. Reproduced under terms of the CC BY 4.0 license [154] Copyright 2022, Polymers (Basel). (C) Sintered porous titanium alloy acetabular cup, (D) MicroCT images of different materials during the follow-up for 6 months. And (E) BV/TV analysis of three materials at different times.These results indicate that both sintered bionic porous titanium and 3D-printed titanium alloys outperform HA-coated titanium alloys in promoting osseointegration. Reproduced under terms of the CC-BY license [155]. Copyright 2022, Frontiers in Bioengineering and Biotechnology. (F) 3D-printed porous hip rods, and (G) Analysis of different artificial hip implants and finite element loading forces Reproduced under terms of the CC-BY license [156]. Copyright 2023, Frontiers in Bioengineering and Biotechnology.

be precisely adjusted by varying the size of the "Stone" to give the 3D printed scaffolds adjustable roughness morphology. In recent years, smart scaffolds prepared by 3DP technology, which mimic native extracellular matrix (ECM) by sensing ex vivo stimuli and initiating targeted biological responses, have been used to enhance the efficacy of bone repair and regeneration as well as to achieve desired therapeutic outcomes. This also provides new strategies for the treatment of femoral head necrosis [167].

Advances in materials, bioinks, and 3DP technologies have greatly expanded the possibilities for personalized treatments of osteonecrosis of the femoral head. Traditional in vitro bioprinting technologies remain limited by their inability to fabricate and implant irregularly shaped scaffolds efficiently and their restricted suitability for rapid clinical applications. In situ material deposition technology has emerged as a transformative approach, overcoming these barriers by facilitating the direct on-site fabrication of complex tissues with biomaterials, cells, and bioactive factors, thereby enabling highly personalized treatment strategies [168,169]. For example, Brito et al. [170] employed a portable 3D

Table 6
3D printed scaffolds have been applied in ONFH treatment in recent years.

	Scaffold	Animal Models	ONFH Type	In vitro experiment	Image analysis	Histological analysis
Zhu et al. [185]	porous titanium + gelatin	Rabbit	Ischemic type	Cell adhesion, proliferation, osteogenesis, with low cytotoxicity.	Micro-CT revealed substantial bone growth and higher bone volume in the treatment group vs. control.	Treatment group showed mature bone along scaffold edges, with incomplete differentiation of neoplastic bone and soft tissue.
Wang et et al. [186]	3D printed Cervi cornus Colla deproteinized bone scaffolds	Rat	Hormone type	Scaffolds promote osteoblast accumulation and adhesion, stimulating osteoclast proliferation.	X-ray analysis revealed smooth articular surfaces, recovery of necrotic and cystic regions, with mild degeneration observed in some rat femoral heads.	Treatment rats exhibited reduced chondrocyte damage, ossification of femoral head, cement lines, and minimal inflammatory cell infiltration in the medullary cavity.
Wang et et al. [187]	Diamond lattice porous titanium alloy rod	Sheep	Ischemic type	–	X-ray and Micro-CT showed tight bone-rod integration, no radiolucent lines, and new bone growth in Rod group. BV/TV ratio was 930 % and 452 % higher in Rod vs. CD group at 3 months.	BV/TV ROI in Rod group was 647 % and 422 % higher than CD group at 3 and 6 months, respectively.
Wang et al. [188]	Biological trabecular porous titanium rods with laminar structure.	Sheep	Ischemic type	–	X-ray confirmed tight scaffold-bone integration. Micro-CT showed new bone growth in Rod group, reaching rod center at 3m. BV/TV in Rod group was 890.0 % and 438.1 % higher than CD at 3 and 6 months, respectively.	BV/TV in Rod group was 881.0 % and 413.3 % higher than CD group at 3 and 6 months, respectively.
Gao et al. [189]	3D porous titanium stent + daily trans-cinnamaldehyde (TCA) injection.	Beagle dog	Ischemic type	–	Micro-CT results indicate improvement in femoral head necrosis among treated patients.	3DP Ti alloy scaffold + TCA treatment improved pathological ONFH in femoral head, reducing immature bone & collagen.
Maruya et al. [190]	Functional gradient PCL/β-TCP porous scaffold.	Rabbit	Hormone type	–	Micro-CT: 30 % porosity FGS had higher bone long entry (73.9 % ± 15.8 %) than CD (39.5 % ± 13.0 %, $p < 0.05$). 60 % porosity FGS (61.3 %) showed no significant difference.	HE staining: Thick, mature trabeculae around 30 % porosity FGS vs. thinner, less mature trabeculae in 60 % porosity FGS.
Li et al. [95]	Porous titanium scaffolds with internal U-shaped channels (carrying vascular bundles)	Small Tailed Han sheep	Ischemic type	–	Micro-CT: More bone tissue grew into experimental scaffold vs. control (3m: 29.66 % vs. 20.35 %, $P < 0.05$; 6m: 30.47 % vs. 25.10 %, $P < 0.05$).	Histology: Higher bone ingrowth in experimental vs. control at 3 months (24.71 % vs. 16.45 %, $P < 0.05$) & 6m (31.01 % vs. 20.60 %, $P < 0.05$).
Lei et al. [94]	3D printed porous Ti-6Al-4V reconstruction rods	Beagle dog	Ischemic type	Titanium reconstruction rods enhance MC3T3-E1 cell proliferation and promote cell adhesion and spreading	Micro-CT: Ti-HA-IC femoral head resembled healthy group with better appearance, structure, & bone preservation. BV/TV similar to healthy. Angiography: Dense vessel distribution, higher vessel counts in Ti-HA-IC group.	HE staining: Ti-HA-IC group showed abundant new bone growing into rod holes, adhering tightly with no gaps.
Li et al. [191]	Cryogenic 3D Printing of β-TCP/PLGA Composite Scaffolds Incorporated with BpV (Pic).	Rat	Alcoholic type	Sustained bpV(pic) release from bPTCP scaffolds promotes osteogenic differentiation, inhibits adipogenesis, and enhances osteogenesis & angiogenesis via autophagy-mediated apoptosis prevention in BMCs.	Micro-CT results confirmed that the bPTCP stent significantly alleviated the progression of Avascular Necrosis of Femoral Head (ANFH) in rats.	Istologic analysis confirmed that the bPTCP stent significantly alleviated the progression of ANFH in rats.
Tsubosaka et al. [192]	3D-printed β-TCP/PCL FGS for targeted cell delivery with IL-4-PDGF-pMSC integration.	Rabbit	Hormone type	–	Micro-CT: CD group had more bone in CD region than both FGS groups.	IL-4-PDGF-pMSCs & FGS + PDGF-MSCs showed fewer cavities, accelerated osteoclastogenesis. VEGF staining area similar across groups.
Lai et al. [193]	Cryogenic 3D printing of PLGA/TCP/patchouli glycoside (PTI) scaffolds.	Rabbit	Hormone type	Caffolding promotes proliferation, differentiation and mineralization of MC3T3	Micro-CT: New bone formed in bone tunnel at 2, 4, 8 weeks; stent-implanted group had enhanced bone formation at 8 weeks.	Histology: New bone grew into stent holes at 4 & 8 weeks, significant difference between implanted & unimplanted groups.

printer to fabricate scaffolds directly at bone defect sites in rats. Likewise, Qin et al. [171] demonstrated enhanced repair of osteochondral defects in a rabbit knee joint model through the in situ deposition of a double-layer MOF hydrogel. Low-temperature deposition manufacturing (LDM), recognized as an environmentally friendly process due to its avoidance of heating liquefaction, represents a promising advancement in rapid prototyping. Scaffolds produced via LDM exhibit multi-scale, controllable pore architectures and interconnected micropores, which collectively enhance bone regeneration. Furthermore, LDM allows for the seamless incorporation of various cell

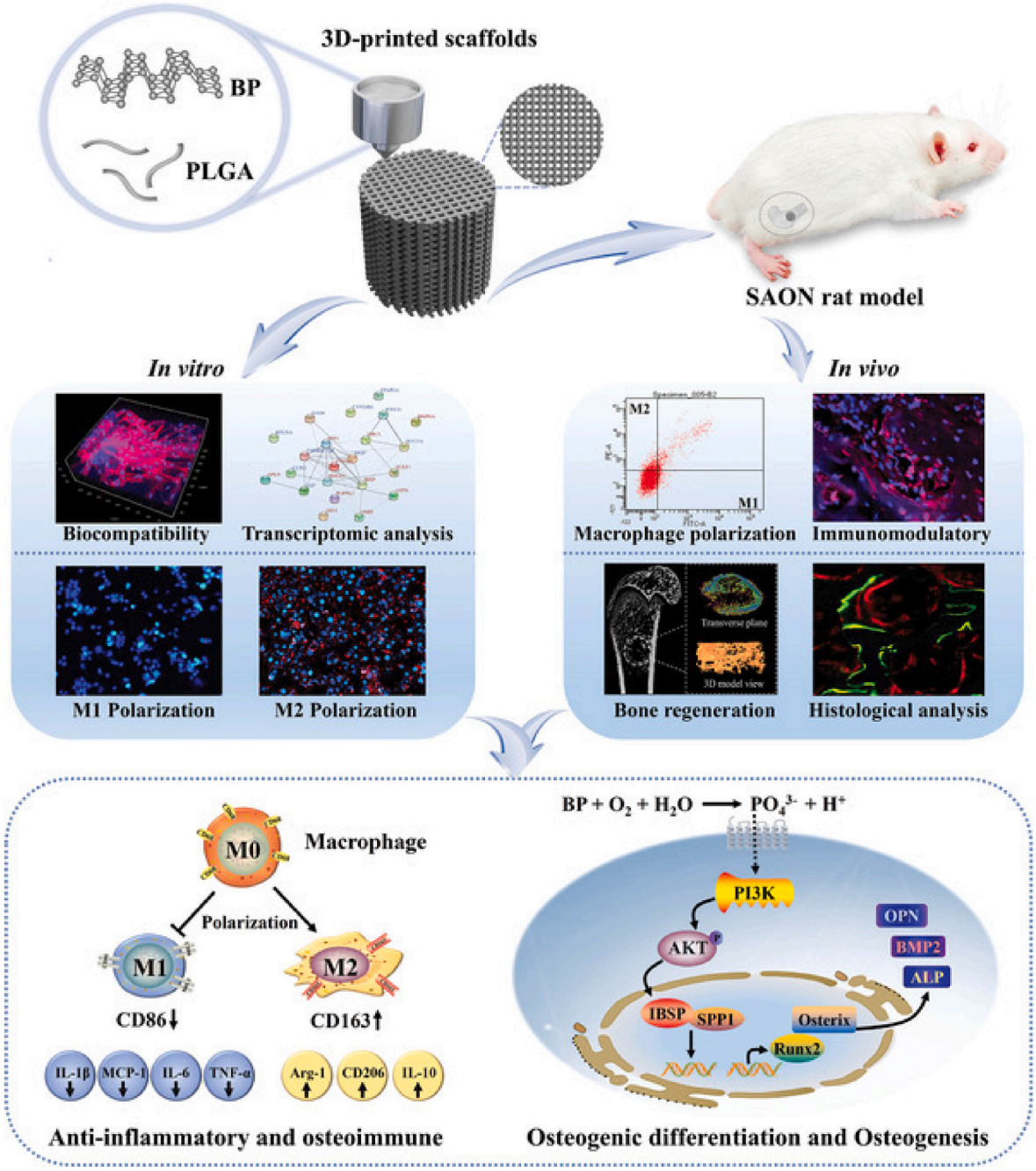

Fig. 8. Schematic illustration of PLGA/BP scaffolds fabricated by 3DP and proposed mechanism of osteoimmune environment induced by BP degradation to accelerate bone regeneration.Reproduced under terms of the CC BY 4.0 license [162]. Copyright2023,WILEY.

types and bioactive factors into 3D scaffolds, thereby broadening its utility in bone tissue regeneration [172]. For instance, Yang et al. [173] utilized cryogenic deposition 3DP to fabricate manganese dioxide scaffolds, which promoted osteogenic-angiogenic coupling by remodeling the bone regeneration microenvironment in a femoral head necrosis model. Moreover, the variability in bone volume, trabecular thickness, and trabecular count within necrotic regions, combined with the structural disparities between the femoral neck and head, presents considerable challenges [174,175]. The advent of 3D-printed gradient porous scaffolds offers a promising solution to overcome these obstacles in the treatment of femoral head necrosis. Numerous studies have focused on the development of scaffolds with multi-gradient functionalities. For example, Talukdar et al. [176] developed a functionally graded porous (FGP) titanium fusion device featuring three distinct porosities (48 %, 65 %, and 78 %). Their findings revealed that FGP scaffolds effectively balance mechanical strength and porosity, outperforming solid and uniformly porous titanium scaffolds.

Furthermore, integrating AI with 3DP allows for precise design adjustments based on individual patient anatomy [177,178], thus offering a personalized and effective solution for ONFH treatment. Combining 3D printing with artificial intelligence makes the image processing after CT scanning more efficient, and also predicts the print applicability of materials, optimizes the printing parameters, and intelligently monitors the printing, which comprehensively ensures the high efficiency and high quality of the printed products [179,180]. 3DP combined with AI is enough to construct in vitro models with fine control and complex microstructure for drug screening and disease modeling [181]. For example, recent innovations have demonstrated the potential of AI to

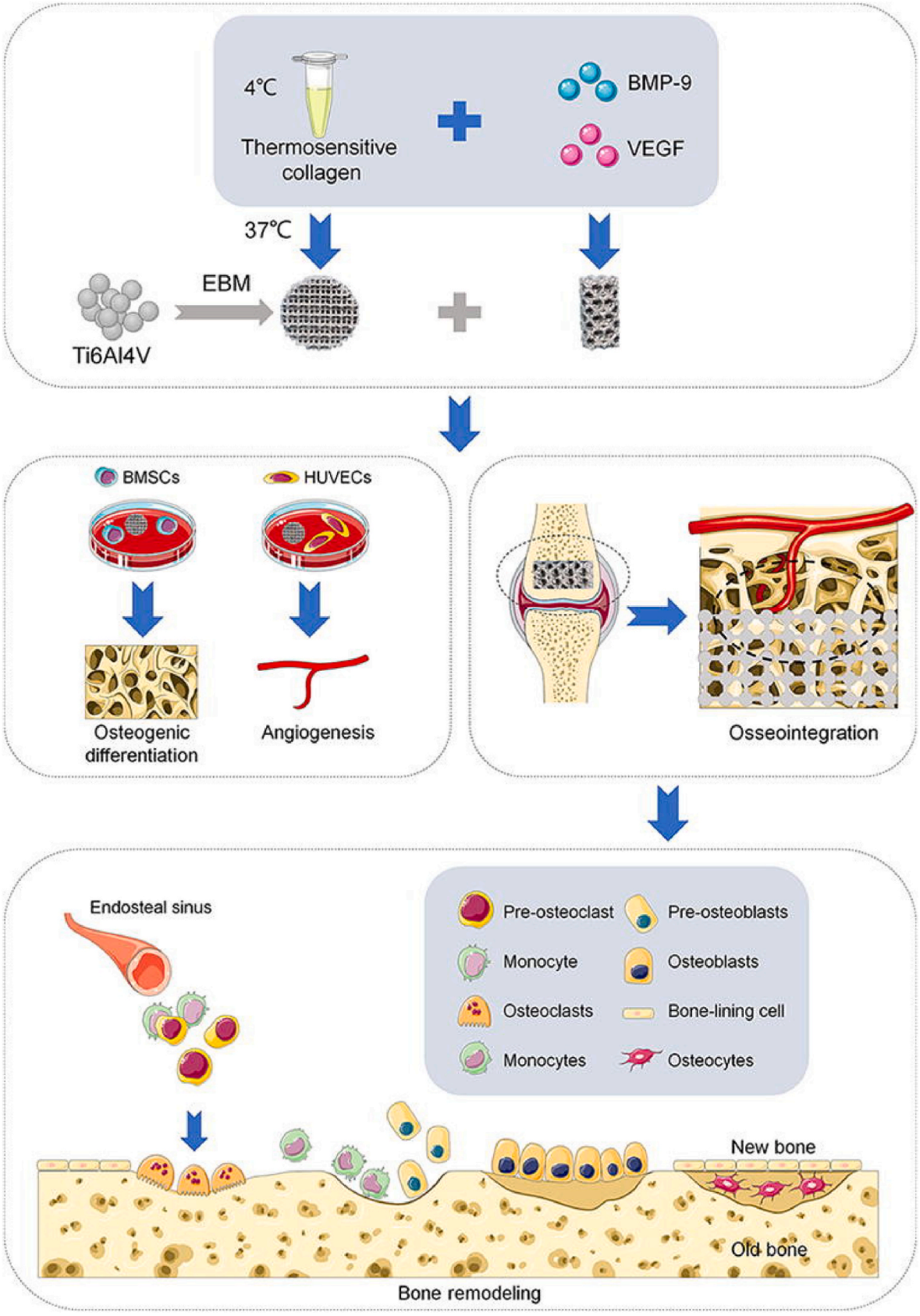

Fig. 9. 3D printing created a porous titanium scaffold with a heat-sensitive collagen hydrogel containing VEGF and BMP-9 to enhance angiogenesis and bone integration.Reproduced with permission [163]. Copyright 2022, Elsevier.

enhance the bioactivity and structural integrity of 3D-printed scaffolds [182]. AI algorithms can assist in fine-tuning scaffold porosity, material composition, and biomechanical properties [183,184].

5. Perspectives

3DP offers great potential for treating osteonecrosis of ONFH, addressing unique challenges like mechanical instability, vascularization, and patient-specific needs. However, significant barriers still exist in adapting these innovations to ONFH treatment. Specific challenges for 3D printing in ONFH treatment include ensuring mechanical stability with gradient porous scaffolds, enhancing vascularization through bioactive coatings, enabling customization with patient-specific designs using AI, and achieving controlled degradation that aligns with bone regeneration. Future research for ONFH should focus on: (1) Optimizing Gradient Scaffolds for better mechanical properties and bone integration. (2) Incorporating Bioactive Materials to promote angiogenesis and bone regeneration. (3) Personalized Scaffold Designs using AI-driven processes for patient-specific treatments. (4) Improving Biodegradable Materials that synchronize degradation with bone healing.

However, significant barriers remain in adapting these innovations to clinical practice. Future research should focus on integrating artificial intelligence (AI) with 3DP technology to optimize scaffold design and improve treatment outcomes. AI algorithms can analyze patient-specific imaging data, predict optimal scaffold properties (e.g. porosity, mechanical strength, and degradation rates), and model long-term implant performance. These capabilities ensure scaffolds match anatomical needs while promoting better bone regeneration and reducing complications like stress shielding. Advancing in-situ material deposition technologies further enables precise integration of bioactive molecules and mechanical reinforcements during scaffold fabrication, addressing the dual challenges of vascularization and mechanical stability. Additionally, research into gradient porous scaffolds and biodegradable materials is critical for improving mechanical compatibility and synchronizing scaffold degradation with bone healing.

Despite advancements, several challenges must be addressed. High manufacturing costs and limited access to 3DP equipment hinder widespread adoption, particularly in resource-constrained settings. Developing cost-effective printing techniques and materials or optimizing production processes will facilitate commercialization and broader use. Additionally, achieving superior precision and resolution in scaffold manufacturing is essential, as even minor deviations can compromise implant functionality. Regulatory frameworks for 3D-printed medical products also remain underdeveloped. Collaboration across research, clinical, and regulatory sectors is key to overcoming the challenges of ONFH treatment with 3DP. By addressing issues such as mechanical stability, vascularization, and scalability, 3DP can significantly improve ONFH treatment outcomes.

6. Conclusions

As medical technology advances, 3DP has emerged as a valuable tool in orthopedic surgery, offering innovative solutions for the treatment of ONFH, a condition that significantly impacts patients' quality of life. By addressing limitations of traditional approaches, such as poor vascularization and mechanical instability, 3DP enables earlier interventions and improved long-term outcomes through highly customized treatment protocols. The integration of advanced imaging, design software, and AI has further enhanced scaffold personalization, ensuring optimal fit, functionality, and precision. These innovations contribute to reduced complications, such as prosthesis failure, and shorter recovery times. Incorporating advancements in materials science and biology, 3DP has facilitated the development of biocompatible and functional scaffolds, promoting effective bone regeneration and integration within the body. However, achieving widespread clinical adoption requires overcoming significant challenges, including high costs, technical limitations, and underdeveloped regulatory frameworks. Collaborative efforts among researchers, clinicians, industry stakeholders, and policymakers are critical to translating this technology from the laboratory to clinical practice. Future research should focus on improving the biocompatibility, mechanical properties, and biological functions of printed materials, as well as developing cost-effective and scalable manufacturing processes. Additionally, enhancing surgical planning software with AI-driven algorithms can further refine treatment strategies, ensuring precise and reliable interventions tailored to individual patient needs. By addressing these challenges, 3DP has the potential to revolutionize traditional ONFH treatments, offering safer, more effective, and personalized solutions. Its continued advancement underscores the broader trajectory of medical technology development, providing critical insights for improving healthcare outcomes and shaping the future of regenerative medicine.

CRediT authorship contribution statement

Tingting Chen: Writing – original draft, Investigation, Data curation. **Lincong Luo:** Writing – review & editing, Visualization. **Jiaying Li:** Methodology. **Jiamin Li:** Data curation, Conceptualization. **Tao Lin:** Investigation, Data curation. **Mingrui Liu:** Software. **Hang Sang:** Investigation. **Xinyu Hong:** Data curation. **Jiahao Pu:** Data curation. **Wenhua Huang:** Writing – review & editing, Supervision.

Declaration of Competing interest

The authors declare no conflict of interest.

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Data availability

The authors do not have permission to share data.

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