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Advances in 3D-printed scaffold technologies for bone defect repair: materials, biomechanics, and clinical prospects

Jie Sun[1†], Cao Chen[1†], Bo Zhang[1], Chen Yao[1*] and Yafeng Zhang[1*]

†Jie Sun and Cao Chen have contributed equally to this work.

*Correspondence: yaochen19931021@163.com; fcius2004@hotmail.com

[1] Department of Orthopaedics, Affiliated Hospital of Nantong University, Medical School of Nantong University, Nantong 226001, Jiangsu, China

Abstract

The treatment of large bone defects remains a significant clinical challenge due to the limitations of current grafting techniques, including donor site morbidity, restricted availability, and suboptimal integration. Recent advances in 3D bioprinting technology have enabled the fabrication of structurally and functionally optimized scaffolds that closely mimic native bone tissue architecture. This review comprehensively examines the latest developments in 3D-printed scaffolds for bone regeneration, focusing on three critical aspects: (1) material selection and composite design encompassing metallic; (2) structural optimization with hierarchical porosity (macro/micro/nano-scale) and biomechanical properties tailored; (3) biological functionalization through growth factor delivery, cell seeding strategies and surface modifications. We critically analyze scaffold performance metrics from different research applications, while discussing current translational barriers, including vascular network establishment, mechanical stability under load-bearing conditions, and manufacturing scalability. The review concludes with a forward-looking perspective on innovative approaches such as 4D dynamic scaffolds, smart biomaterials with stimuli-responsive properties, and the integration of artificial intelligence for patient-specific design optimization. These technological advancements collectively offer unprecedented opportunities to address unmet clinical needs in complex bone reconstruction.

Keywords: Bone defect, 3D printing, Bone regeneration, Scaffold, Biomaterials, Bone tissue engineering

Introduction

Bone possesses remarkable regenerative capabilities; however, under certain pathological conditions, regeneration may be compromised. Bone defects, a prevalent clinical orthopedic issue, present significant treatment challenges. Trauma, infection, and pathological fractures are common causes of critical bone defects [1, 2]. Currently, bone transplantation is the predominant treatment and ranks as one of the most widely performed types of tissue transplantation globally. Autografts, derived from the same individual, exhibit superior histocompatibility, osteoconduction, and osteoinduction,

essential for bone regeneration. These grafts can rapidly and completely integrate with the defect site and exhibit a low probability of immune rejection, making them a preferred method for treating bone defects [3].

Despite their advantages, the availability of natural bone grafts does not meet the demand, and this shortage leads to challenges such as prolonged surgical times and a high incidence of donor sites [4, 5]. Pain allograft transplantation, another common approach, offers a relatively broader source availability and is not constrained by shape and size. Although allografts address some limitations of autografts, their osteoinductive properties can be diminished due to cryopreservation. Moreover, allografts often display inadequate regenerative capabilities and are associated with various challenges, including infection and immune response issues [6, 7]. In treating bone defects, the demand for innovative grafts that can replace traditional methods and foster new treatment approaches is growing. Recent advances in bone tissue engineering have seen the flourishing of bone tissue scaffolds, particularly those created using 3D printing technology. Utilizing bone-related materials, this technology has significantly impacted bone regeneration, increasing the variety of artificial bone implant substitutes. The capabilities for mass production, alongside their mechanical properties and biocompatibility, are poised to revolutionize bone defect management strategies [8, 9]. Figure 1 illustrates the procedure of 3D printing technology.

With their exogenous structures, scaffolds are designed to enhance cell viability and proliferation, forming desired tissue architectures. Recent developments in scaffold manufacturing techniques have been implemented, such as phase separation, freeze-drying, gas foaming, and electrospinning. However, these methods generally provide only an approximate control over scaffold pore size and cannot precisely adjust

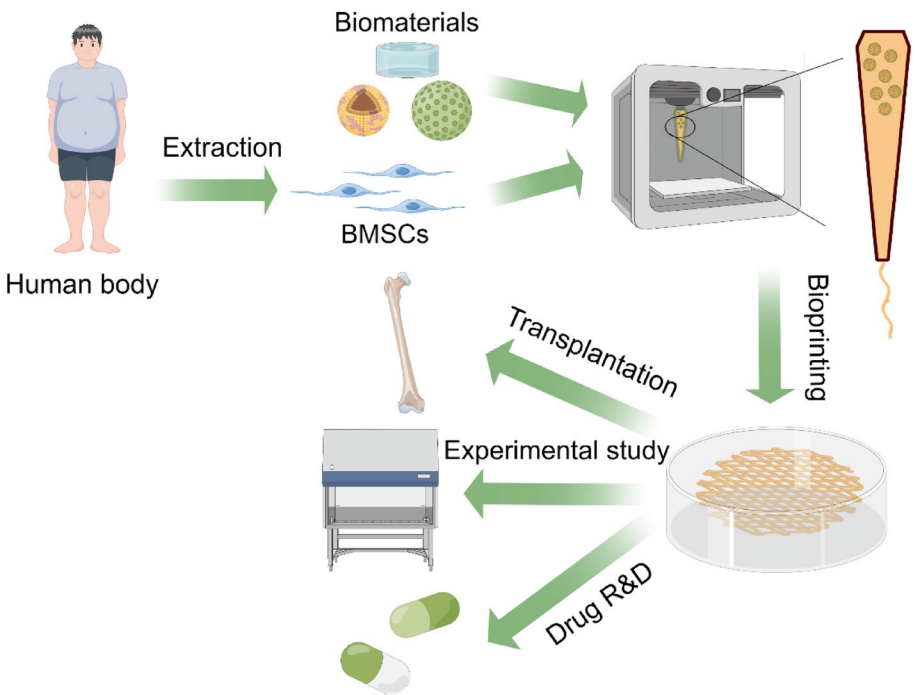

Fig. 1 The procedure of 3D printing technology. R&D: release and delivery

parameters such as porosity, thus failing to accurately emulate physiological bone structure and meet clinical needs [10–13]. In response, 3D printing technology has emerged and evolved, offering unprecedented precision in structure control and design compared to earlier scaffold technologies [14, 15]. This method manufactures three-dimensional, multi-layered structures that allow precise control over factors such as pore morphology, closely mimicking physiological bone tissue. Currently, it has shown promising preliminary clinical outcomes, particularly in dentistry. For instance, 3D-printed materials used for temporary restorations can provide sufficient mechanical properties for intraoral applications in crown and bridge restorations [16].

Given the significant clinical potential and therapeutic relevance of 3D printed scaffolds in bone defect treatment, this review will further explore the details of bone defect scaffolds, focusing on scaffold material selection and composite design encompassing metallic; structural optimization with hierarchical porosity (macro/micro/nano-scale) and biomechanical properties tailored; biological functionalization through growth factor delivery, cell seeding strategies and surface modifications. We critically analyze scaffold performance metrics from different research applications, while discussing current translational barriers, including vascular network establishment, mechanical stability under load-bearing conditions, and manufacturing scalability. The review concludes with a forward-looking perspective on innovative approaches such as 4D dynamic scaffolds, smart biomaterials with stimuli-responsive properties, and the integration of artificial intelligence for patient-specific design optimization. This systematic review aims to provide comprehensive insights into the rapidly evolving field of 3D-printed scaffolds for bone defect repair.

Overview of scaffold's properties

The performance of ideal scaffolds hinges on their ability to meet specific biological and mechanical criteria to function optimally in vivo post-implementation. The development of bone tissue scaffolds must adhere to key characteristics, as illustrated in Fig. 2.

Implant heterogeneity (biocompatibility)

Biocompatibility, a concept introduced to the biomedical field in the last century, is defined as the ability of materials to elicit appropriate host responses in specific applications [17]. This characteristic is crucial to ensure that the scaffolds do not provoke adverse immune reactions when involved in cellular behaviors such as adhesion, migration, and proliferation. The goal is to prevent severe inflammatory responses from these interactions [18, 19]. Given that scaffolds are inherently foreign objects within a biological system, they inevitably trigger immune responses, which could lead to material failure or more severe complications. Thus, selecting materials with high biocompatibility is essential for the success of any implantation [20]. For instance, in developing vascular grafts, where hemolysis reactions are prevalent, integrating natural materials such as collagen and elastin—known for their elasticity and toughness—can help simulate the physiological performance of vascular tissues [21]. Natural materials, which are integral components of human organs, theoretically exhibit superior biocompatibility compared to synthetic polymers [22]. Hence, incorporating an appropriate proportion of natural materials

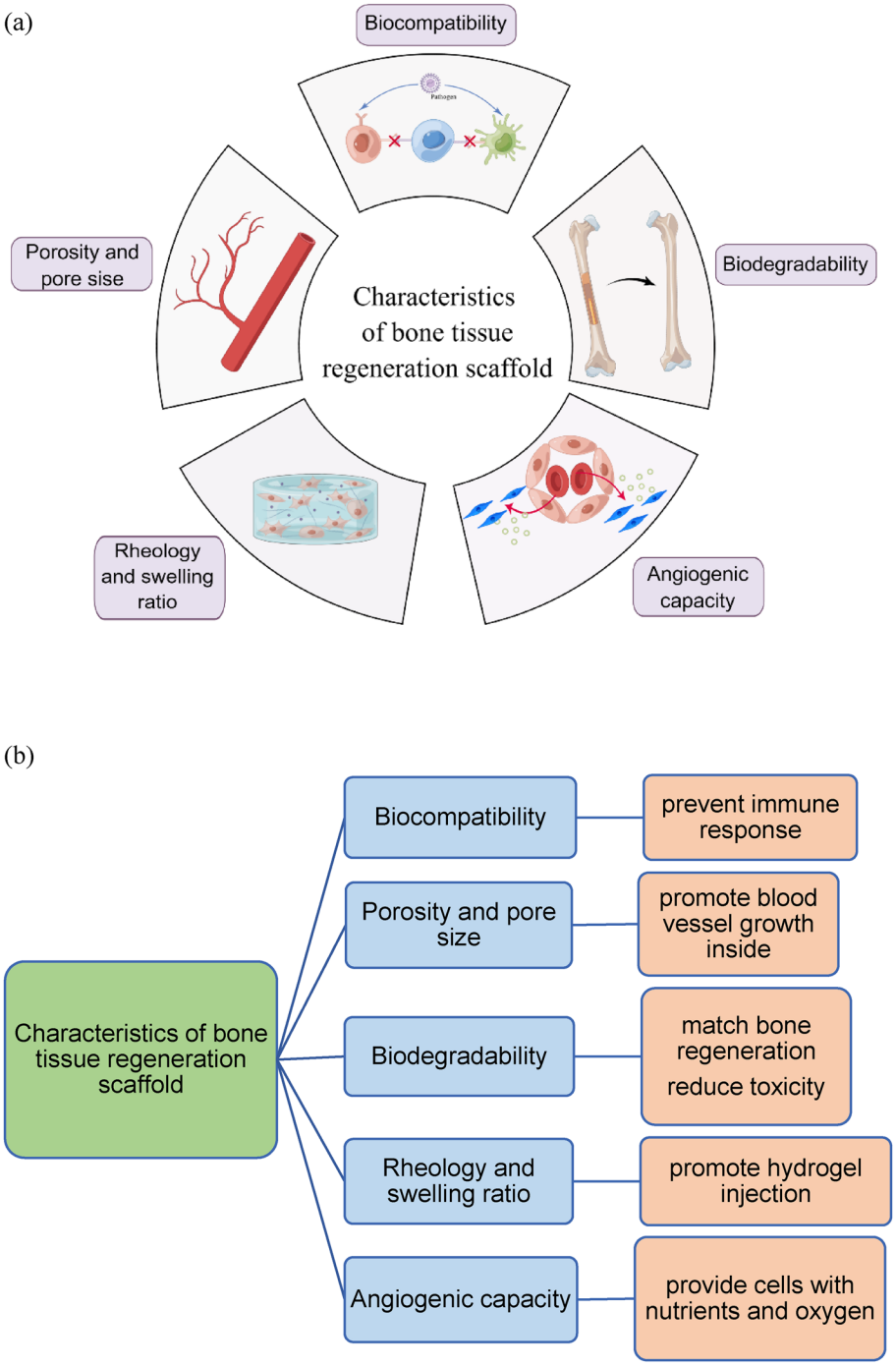

Fig. 2 Main properties required for bone tissue regeneration scaffolds. **a** Biological function of ideal bone tissue regeneration scaffold. **b** Characteristics of ideal bone tissue regeneration scaffold

into composites is crucial to enhance the biocompatibility of synthetic materials [23]. Presently, mainstream scaffold materials such as PCL and β-TCP, among synthetics, are recognized for their excellent biocompatibility, which significantly enhances cell growth and the expression of osteogenic markers. Biological experiments have

demonstrated their effectiveness in promoting bone defect healing [24]. The factors influencing the biocompatibility of therapeutic materials are varied, encompassing both the materials used for scaffolds and their fabrication processes, which can lead to different outcomes.

Structural characteristics of scaffold engineering

Biomimetic characterization is of paramount importance. Biomaterials that feature high porosity, interconnected pores, and specific surface modifications can emulate the structure of the natural extracellular matrix (ECM). Such scaffolds provide a bone-like microenvironment conducive to vascularization, stem cell recruitment, and regulation of cellular behaviors, including cell adhesion, proliferation, migration, and differentiation. Moreover, they leverage the synergistic effects of cytokines for bone regeneration [25, 26].

Specific porosity is a crucial attribute for orthopedic scaffolds. The ideal scaffold in bone tissue engineering should mimic both the biological and physical properties of natural bone. This entails a hierarchical structure with a well-defined organization spanning from the nanoscale to the macroscale. In scaffold design, achieving a structure with suitable porosity and diameter is prioritized to replicate the unique pore structure of bone tissue. The porous structure promotes cellular nutrition, proliferation, and migration and facilitates new blood vessel formation, protein absorption, and efficient waste removal [27]. Therefore, most scaffolds are designed as porous, mesh-like interconnected structures [28]. 3D printing technology excels in manipulating scaffold geometry to create interconnected pore structures and achieve specific porosity. Designing an optimal pore structure and appropriate porosity is crucial for influencing biological behavior [29]. Bone tissue comprises a unique structure of cancellous (spongy) and compact (dense) bone. Compact bone is characterized by high density and low porosity, typically ranging from 5 to 30%, whereas cancellous bone has a lower density with porosity levels between 50 and 90% [30]. Multi-level pores mimic physiological bone structures, creating favorable environments for bone tissue regeneration. Researchers have explored the effects of integrating multi-level scaffolds with controllable microporosity (< 50 μm) alongside scaffolds based on macropores. Designing scaffolds incorporating structures at both the macro- and micro-scale promotes enhanced bone and cell growth [31]. The multi-level pore structure significantly improves bone growth compared to single-level pore structures or materials lacking well-defined pore architecture [32]. Firstly, it provides a larger surface area for bone cells to adhere and proliferate, thus enhancing regeneration. Secondly, the interconnected pores facilitate improved nutrient and oxygen supply, which is crucial for the growth and survival of bone cells [33, 34]. The integration of varying pore sizes allows cells to fully interact with the scaffold [35], and designing hierarchical porosity that increases layer by layer from the exterior to the interior can enhance the differentiation capacity of bone marrow stromal cells (BMSCs), fostering both physiological and mechanical adaptation of the scaffold to the bone [36, 37].

Regarding osteocyte accommodation, materials with a pore size of around 100 μm are considered more conducive to cell ingrowth and osseointegration, whereas smaller pore sizes can promote osteochondral ossification [27]. However, some researchers argue

that smaller pore sizes might impede vascular growth and cell proliferation, suggesting that a pore size greater than 300 μm can better support bone growth and angiogenesis. Additionally, fibrocartilage tissue typically requires a larger pore size of 200–300 μm for normal growth, indicating the necessity to tailor scaffold pore sizes based on specific tissue engineering requirements [38]. The mechanical properties of scaffolds, even with ideal pore sizes, are often not suitable for practical applications. While these scaffolds maintain initial structural integrity, they lack the necessary strength, stability, and durability to withstand physiological demands and forces in real-life scenarios. Although larger pore sizes and increased porosity can enhance cell ingrowth and osteogenesis, these features compromise mechanical strength and extend the duration of osseointegration. This conflict between scaffold properties may lead to implantation failures [39]. There is no consensus on the ideal pore size and porosity for optimal bone tissue regeneration [30].

In addition to pore size and porosity, mechanical strength is crucial for the effectiveness of scaffolds in supporting bone tissue growth and cell differentiation in vivo. A balance between mechanical strength and porosity is essential to provide adequate mechanical support while promoting good vascular formation within the scaffold. Many materials, particularly natural polymers, are limited in their use as bone scaffolds due to insufficient mechanical strength [40, 41]. Key mechanical properties of scaffold load-bearing capacity include Young 's modulus (elastic modulus), compressive strength (the ability of the scaffold to withstand loads that tend to compress or decrease its size, and tensile strength [42, 43]. The ideal scaffold should possess mechanical strengths similar to that of cortical bone, with Young's modulus ranging from 7 to 30 GPa along the long axis, a compressive strength of about 50 to 200 MPa, and a tensile strength of approximately 150 MPa [44, 45]. This is vital for designing the material's modulus properties to approximate those of physiological bone.

Bone tissue regeneration in vivo is a dynamic and complex process involving a two-phase composite material where minerals and collagen are intricately bound. Utilizing mixtures of materials with varied modulus properties can help scaffold designs more closely emulate the characteristics of physiological bone, enhancing both function and integration [46].

Biodegradability

The degradation rate of scaffold materials must be sufficiently aligned with the rate of bone tissue regeneration to effectively enhance the metabolic activity of osteoblasts [47]. Researchers are exploring the integration of materials with varying degradation rates to tailor scaffold degradation to the bone regeneration process. A trend in scaffold development is using composite materials to adjust performance characteristics. For instance, Miao et al. investigated a multi-parameter tunable scaffold made from strontium-doped calcium sulfate (SrCSH) and strontium-doped tricalcium phosphate (Sr-TCP). Combining two materials whose degradation rates are speedy and very slow, the degradation rate of the composite scaffold can be tuned by adjusting the porosity and specific structure of the scaffold. During bone defect repair, scaffolds with differing parameters were evaluated to identify those whose degradation profiles best matched the bone regeneration process [48].

Additionally, researchers have utilized natural materials such as chitosan to encapsulate SrCSH, further slowing the degradation rate and achieving a controlled release effect in vivo [49]. Generally, materials used in scaffold construction are selected to conform to desired tissue degradation rates, allowing for complete degradation of the scaffold as the tissue regenerates [50]. Common polymeric materials such as polycaprolactone (PCL), polylactic acid (PLA), and polylactic acid-co-glycolic acid (PLGA) are biodegradable and widely utilized in biological experiments. Using composite materials enables the production of bone tissue with varied properties tailored to different body parts [51].

The nature of degradation products also significantly impacts subsequent tissue growth and overall health. It is crucial to ensure that these products are non-toxic or have minimal toxicity to reduce potential side effects. The control of scaffold porosity is intricately linked to degradation capability; adequate porosity facilitates the removal of degradation products and metabolic waste, thus enhancing the metabolic activity of osteoblasts and promoting osteogenesis [52].

Scaffold swelling ratio

The swelling property is a critical attribute in scaffold fabrication, primarily influenced by the hydrophilicity and permeability of the material. Different bone scaffold materials and application scenarios necessitate varied swelling rates. For instance, injectable hydrogel scaffolds, used to fill small bone defects, may require a higher swelling rate to adequately fill the defect and integrate seamlessly with surrounding tissues. Conversely, scaffolds that provide long-term mechanical support, such as those used for repairing significant segmental bone defects, should have a lower swelling rate to maintain stability throughout the bone repair process [53, 54]. Expanding scaffolds upon water uptake can lead to structural changes such as altered pore architecture, which impacts cellular growth and the effective exchange of nutrients, oxygen, and other metabolites. While hydration-mediated expansion can increase pore size and scaffold volume, which is beneficial for filling bone defects, post-implantation swelling may negatively affect the scaffold's degradation process [30].

For example, Zhang XT et al. observed that in hydrogel-based bone scaffolds, water molecule ingress during swelling disrupts the interactions between polymer chains, accelerating degradation [55]. Additionally, Mehdi Ebrahimi et al. explored several factors affecting the hydrophilicity of a nanocomposite collagen/nanobiphasic calcium phosphate scaffold (collagen/nBCP). They determined that a higher Tween ratio (the ratio of Tween content to other materials in the scaffold), faster quenching rate (the rate at which excited matter returns to its ground state), and a greater collagen ratio enhance the scaffold's hydrophilicity. Over time, interactions with the environment, such as water molecule adsorption and surface chemical alterations, can modify the hydrophilicity, increasing or decreasing it based on the surrounding conditions [56].

Rheological properties also play a significant role in the practical application of implant materials. For instance, injecting gel-like substances into non-gel material scaffolds requires specific rheological coefficients to achieve successful outcomes [57]. Control over the swelling rate of hydrogels is thus crucial for developing hydrogel-wrapped scaffolds. Common bioinks, which are formulations of acellular matrix particles and gels in specific ratios, exemplify materials that achieve desirable swelling rates. These

rates support essential functions such as the exchange of water and nutrients necessary for cell survival and proliferation without compromising the mechanical integrity and degradation properties of the scaffold [58].

Angiogenic capacity

As highlighted previously, large porosity within scaffolds provides an optimal environment for endothelial cell ingrowth and the formation of blood vessels, which are vital for bone defect regeneration. A robust blood supply is crucial as it delivers essential nutrients and oxygen to bone cells, promoting effective tissue regeneration [59, 60]. The failure of many bone graft scaffolds is often attributed to inadequate vascularization [61]. Fine-tuning the pore size and controlling the microstructure of bone scaffolds can enhance angiogenesis and bone tissue regeneration [62].

The regulation of angiogenesis-related factors such as HIF-1α and VEGF is key in promoting angiogenesis [63]. Modifications to the scaffold's surface coating and increases in porosity can significantly boost the expression levels of these angiogenic factors, indirectly aiding bone tissue healing by fostering angiogenesis and osteocyte differentiation [64]. Many scaffold materials possess inherent vascular-promoting functions, an important consideration in material selection. For instance, Gao et al. investigated magnesium-coated Ti6 Al4 V scaffolds and found that they could enhance the expression of HIF-1α and VEGFs, thus improving the proliferation and migration of endothelial cells [65].

HIF-1α plays a central role in controlling angiogenesis, and its overexpression can notably enhance the expression of various angiogenic factors, thereby influencing angiogenesis within scaffolds [66]. Moreover, the sustained release of VEGF from the scaffold has been shown to significantly promote angiogenesis in areas of bone defect, thereby improving bone regeneration [67]. VEGF not only promotes vascularization indirectly, but also directly influences osteogenesis [68, 69], highlighting its critical dual role in bone regeneration. Furthermore, the synergy between osteogenic factors such as BMP-2 and angiogenic factors indicates the intricate interplay and significance of angiogenesis in the context of bone scaffolds, affirming the vital link between vascular and bone regeneration [70, 71].

Addressing refractory bone defects remains a substantial clinical challenge due to the dual hurdles of insufficient osteogenesis and angiogenesis. Lai et al. explored a Herin microenvironment-responsive scaffold composed of poly-L-lactic acid (PLLA) and manganese dioxide (MnO2) nanoparticles. This scaffold enhances bone regeneration and modulates the immune microenvironment in situ by scavenging endogenous reactive oxygen species. Targeting the bone microenvironment to micro-regulate bone regeneration processes and achieve precise, effective interventions is a promising research direction [72]. Additionally, Li et al. developed a novel bioinspired double-network hydrogel scaffold via 3D printing, characterized by its incorporation of tissue-specific acellular extracellular matrix (dECM) and exosomes derived from human adipose-derived mesenchymal stem cells (MSC). This scaffold ensures a continuous and stable release of exosomes, profoundly influencing the bone microenvironment and enabling the concurrent regeneration of cartilage and subchondral bone tissue in

a preclinical rat model. This technology facilitates cell-free delivery and represents a potential therapeutic approach for treating injuries or degenerative joint diseases [73].

These biomimetic strategies represent a leap in innovation, paving the way for the design of structured and functionalized 3D bio-inspired scaffolds that target complex tissue regeneration.

In summary, the primary considerations for characterizing bone tissue scaffolds encompass biocompatibility, porosity and pore size, biodegradability, swelling rate, and angiogenic capabilities [9]. The foremost consideration is using biocompatible materials, such as commonly employed natural polymers, to prevent severe reactions such as rejection soon after implantation [74]. Additionally, the scaffold's porosity and pore size are critical for vascularization and mechanical strength, facilitating successful implantation and sufficient support for bone regeneration and the temporary replacement of the weight-bearing or specific mechanical requirements of bone [27]. However, striking a balance between enhancing bone cell activity and maintaining mechanical properties with existing technology presents a significant challenge. Thus, prioritizing material selection and manufacturing considerations for scaffold development is imperative [75].

Moreover, the type of cells loaded on the scaffold significantly influences the effectiveness of implantation due to the direct repair impact of cells on bone defect regeneration [76]. Table 1 lists the common cells used in bone scaffolds, with stem cells playing a predominant role in regenerative behaviors in bone tissue engineering [76]. Stem cells are noted for their remarkable regenerative and differentiation capabilities, such as embryonic stem cells, which can differentiate into various cells for regeneration and repair [77]. Once harvested from autologous or allogeneic sources, these cells can proliferate in vitro and be encapsulated onto pre-fabricated bone tissue materials. Post-implantation, they can further differentiate and proliferate, integrating to form new

Table 1 Related cells in bone scaffold

Commonly used cells in bone scaffolds	Characteristics	Related articles
ASCs	It has an osteogenic ability similar to BMSC and can also produce bone matrix. The number of donors is relatively abundant, which does not require in vitro amplification and can be obtained relatively easily, the incidence rate of donors is low	[194, 195]
BMSCs	Has the ability to differentiate into osteoblasts and other cells, can form intact bone tissue, and is the gold standard cell for bone tissue engineering	[196, 197]
iPSC	Can differentiate into BMSCs with strong proliferation and differentiation abilities, also with powerful osteogenic and angiogenic abilities	[198, 199]
Osteoblast	Can synthesize and deposit ECM of bone cells, but has weaker differentiation ability than mesenchymal stem cells	[200–202]
HUVECs	Originating from the umbilical vein, it is an important source of cells for bone tissue vascular regeneration and also has anti-inflammatory properties	[203, 204]
DPSCs	With great potential to reconstruct mineralized tissues, including bone and dentine/pulp complex	[205]
Human PDLSCs	Express PDGF-BB to promote the bone growth of alveolar bone defects	[206]

ASCs: adipose-derived stem cells; BMSCS: bone mesenchymal stem cells; iPSCs: induced pluripotent stem cells; HUVECs: human umbilical vein endothelial cells; DPSCS: dental pulp stem cells; PDLSCs: periodontal ligament stem cells

Table 2 Commonly used materials and their characteristics for the treatment of bone defects

Materials	Advantages	Disadvantages	Examples
Metals	Biocompatible superior strength	Toxic of metal ions stress-shielding poor tissue adhesion poor biodegradability	Ti6 Al4 V magnesium tantalum
Natural polymers	Biocompatible biodegradable low toxicity low cost adhesion sites for cells	Low mechanical properties low controllability endotoxin and other pathogenic substances	Collagen chitosan alginate
Synthetic polymers	Multiple ways of compositioneasy to modify	Some may produce acidic degradation products low biological activity hydrophobic	PCL, PLGA
Ceramics	Biocompatible high compressive modulus delivering bioactive ion osteoinductive and osteoconductive Anti-corrosion	Brittle	HA, β-TCP bioglass zirconia

PCL: polycaprolactone; PLGA: polylactic acid-co-glycolic acid; HA: hydroxyapatite; β-TCP: β-tricalcium phosphate

Table 3 Comparison of 3D printing materials and traditional transplantation techniques

	Autograft	Allograft	Metal	Polymer	Ceramic
Osteoinductive	●●●●	●●●●	●●	●●●	●●●
Osteoconductive	●●●●	●●●●	●●	●●●	●●●
Economic	●●	●●	●●●●	●●●●	●●●●
Biocompatible	●●●●●	●●●●	●●●	●●●	●●●
Young's modulus	●●●●●	●●●●●	●●	●●●●	●●●
Personalized manufacturing	●	●	●●●●	●●●●	●●●●

tissue at the defect site [78]. Utilizing these bone-related cells for bone transplantation offers several benefits: firstly, obtaining bone cells directly from the patient mitigates rejection risks; secondly, scaffolds designed for bone cell implantation can foster new bone growth more effectively [79]. Employing different types of loaded cells under specific conditions can optimize regenerative outcomes [80].

Material selection (mainstream material classification)

The selection of scaffold materials is pivotal for maximizing the efficacy of scaffolds in treating bone defects. These materials must align with the previously described characteristics; only when these fundamental characteristics are met can the scaffold's performance be fully realized, which is critical for clinical interventions in bone defects. Different materials exhibit unique properties, as outlined in Table 2, which details the main advantages and disadvantages of primary bone tissue engineering materials. Table 3 systematically compares 3D printing materials and traditional transplantation techniques. The number of points in the table represents the degree of superiority of various performance indicators. The more points there are, the better the performance.

In 3D printing materials, natural biological substances such as collagen offer distinct benefits [81]. Derived from natural cellular components, these materials harmonize

with tissue structures in their biological functions and elicit lower immunogenic responses [74]. Yun-Jeong Seong and colleagues developed chitin–hydroxyapatite–collagen composite scaffolds (CHCS) to repair tibial defects, which are biocompatible and biodegradable porous scaffolds. In vivo experiments on tibial repair demonstrated significant bone regeneration in the CHCS group, thereby accelerating bone repair. Collagen enhances the scaffold's biocompatibility and promotes osteogenic differentiation [82]. Natural polymers exhibit superior capabilities in promoting cell viability, proliferation, and differentiation compared to synthetic polymers. However, natural polymers present challenges such as insufficient mechanical strength and low controllability [83–85]. In contrast, synthetic materials such as PLGA and PCL offer significant mechanical strength, enhanced processability, and controllable degradation rates. Nonetheless, synthetic polymers often suffer from low bioactivity and high hydrophobicity, which can impede cellular behavior.

Researchers have developed new composite scaffolds to mitigate these drawbacks and leverage the strengths of both material types. These composites combine natural and synthetic polymers or blend metals with natural polymers, thus integrating both advantages. Such scaffolds meet bioscaffold requirements, including bioactivity, ease of fabrication, mechanical strength, and controlled degradation [86, 87]. They support the growth of bone cells, osteogenic differentiation of bone tissue, angiogenesis, and other biological behaviors [88]. Given the various limitations of using a single material, composite materials represent a promising research direction [89] due to their ability to compensate for individual deficiencies.

Xing Wang and colleagues created a functional, insulin-loaded nHAC/PLGA composite scaffold that acts both as a drug delivery system and a three-dimensional scaffold to sustain cell activity in bone defect repair. The insulin release kinetics were effectively controlled. This composite scaffold exhibited robust mechanical and structural properties, facilitating BMSC adhesion, proliferation, and differentiation into osteoblasts. The combined biocompatibility, mechanical properties, and slow release of the materials were fully utilized, demonstrating excellent bone repair performance in a rabbit critical-size bone defect model.

Reflecting on recent trends, scaffold materials can be categorized into metals, polymers, and bioceramics. These categories can be further refined based on the origin of the materials, such as natural versus synthetic [90–92].

Metals

Metallic materials, including stainless steel and titanium alloys, have been used in bone replacement for over a century due to their outstanding mechanical strength and compatibility. They are extensively employed in orthopedic surgeries, such as fracture surgery, enhancing bone strength and support [93]. Moreover, metal ions contribute to bone defect repair by promoting osteoblastogenesis, inhibiting osteoclastogenesis, enhancing angiogenesis, and providing antibacterial properties [94]. However, metal scaffolds present limitations such as lack of biodegradability and potential harm to tissue growth, which restrict their application in bone tissue engineering. These materials exhibit a high elastic modulus and may also lead to biological issues such as metal ion poisoning, poor tissue adhesion, and the stress shielding effect [95, 96].

In joint replacement scenarios, most of the load is borne by the metal implant, resulting in insufficient stress on the bone tissue and a lack of stimulation for bone regeneration, a phenomenon known as the stress shielding effect [97]. In the rapidly evolving field of dentistry involving metal implants, contemporary implants are often fabricated from titanium alloys and zirconia. These materials are characterized by a slightly rough surface, good biocompatibility, and rapid osseointegration, as evidenced by numerous animal and human studies [98]. Research indicates that surface modifications of titanium alloys, specifically Ti6 Al4 V, can enhance feedback, demonstrating effective integration capabilities in tooth defect models [99].

Metal materials, particularly titanium alloys, have long been fundamental in bone tissue implants. Titanium alloys are particularly noted for their excellent biocompatibility, high strength, and corrosion resistance, making them crucial for bone growth and defect tissue reconstruction with broad prospects in orthopedics and dentistry [100, 101]. Ti6 Al4 V, a common titanium alloy, is particularly suited for orthopedic surgery. Compared to other alloys, it has a slightly lower elastic modulus and a relatively minor stress-shielding effect, facilitating the regeneration of bone tissue within the scaffold [102, 103]. Leveraging the mechanical strength of titanium alloys while compensating for their lack of biodegradability remains a priority in their application. Tao Yang's team devised a bilayer scaffold to promote cartilage regeneration, featuring a subchondral bone compartment made of 3D-printed titanium alloy and a cartilage compartment composed of a freeze-dried collagen sponge. This design provides the necessary mechanical support from the titanium alloy, whereas the collagen ensures sufficient biodegradation. In a rabbit femoral trochlear osteochondral defect model, titanium alloy scaffolds accelerated osteochondral formation and integration with adjacent host tissues, highlighting the importance of continuous mechanical support in scaffold printing technology for bone support [104].

The insufficient surface activity of titanium alloys significantly contributes to suboptimal bone implantation effects [105]. Since copper plays a vital role in the normal physiological structure of bones and the maturation of bone tissue, a coating can be applied to titanium surfaces to increase the roughness of titanium alloys, thus aiding in their stabilization in vivo [106]. In research focused on the surface activity of macroporous Ti6 Al4 V scaffolds, a silicon-substituted hydroxyapatite (SiHA) coating was employed alongside VEGF to enhance surface activity. Studies have demonstrated that the adsorption of VEGF stimulates endothelial cell proliferation. In vivo experiments in sheep revealed that only the simultaneous presence of these two components significantly boosts bone tissue regeneration. Osteogenesis facilitated by SiHA coating alone or VEGF alone proved unsatisfactory. However, the combined adsorption of a SiHA-coated scaffold and VEGF enhances the functionality of titanium alloys, displaying a synergistic effect. Surface coating titanium alloys with active factors can alter their characteristics and enhance their active function in vivo [67]. Titanium metal possesses a high elastic modulus, significantly surpassing that of bone tissue, which leads to a stress-shielding effect when in contact with bone. In addressing this issue, Takashi Takizawa et al. demonstrated a titanium fiber plate that, subjected to compressive and shear stress, achieved a thickness of 0.2 mm and Young's modulus as low as 30 Gpa, nearing the typical cortical bone range of 10–30

Gpa. Even after prolonged implantation in the defect area, this titanium plate does not induce stress shielding. It demonstrates an outstanding osteogenic effect when engineered with appropriate pore size and porosity [107].

Infectious bone defects present a significant clinical challenge, and traditional approaches for their prevention and treatment are suboptimal. Techniques such as autologous bone transplantation, the Ilizarov technique, and the Masquelet technique may compromise local blood supply, resulting in diminished local antibiotic concentrations following systemic administration. The cornerstone of treatment involves the reconstruction of bone defects, anti-infection measures, and osteogenesis. Teng Zhang et al. developed a hydrogel encapsulating vancomycin, designed with an optimized molecular chain structure to degrade over 25 days, aligning with the healing timeline of infectious bone defects. This hydrogel exhibits bacterial-responsive release properties. The implant surface, modified with submicron pores via micro-arc oxidation (MAO), enhances osteogenic activity and integrates effectively with the hydrogel drug delivery system. In infected rabbit bone defects, osteogenesis confirmed the implant's effective antibacterial and osteogenic capabilities. The results indicate that MAO 3D printed porous Ti6 Al4 V composite with vancomycin hydrogel can repair infectious bone defects, offering excellent anti-infection and bone integration outcomes [108].

This strategy provides a promising approach for clinical surgery with antibacterial properties. By refining the gel wrapping system and incorporating a range of antibacterial drugs, precise, quantified, timed, and targeted release can be achieved, promoting excellent antibacterial effects and bone regeneration.

Many metal materials, including aluminum alloys, exhibit sufficient mechanical strength but generally lack effective biodegradability. In recent years, magnesium alloys and ions, notable for their relatively superior biodegradability and biological activity, have garnered interest in the research of bone scaffolds. Magnesium plays a crucial role in bone metabolism as a regulator, influencing intracellular calcium and sodium channels, catalyzing various enzymes, and stimulating cell growth and proliferation. It can enhance bone density by impacting the functions of osteoblasts and osteoclasts [109].

Compared to other conventional metallic materials, magnesium has an elasticity modulus that is more akin to that of bones. This property is advantageous as it helps reduce the stress shielding effect that occurs post-implantation and aids in promoting bone stress regeneration. To compensate for the strength deficiencies of hydrogel scaffolds, Xintao Zhang et al. incorporated magnesium ions into a double crosslinked hydrogel through the Mg-S coordinate covalent bond. This addition enhances mechanical strength and cell adhesion and boosts biological activity, thereby endowing the hydrogel with robust, comprehensive performance. The synergistic properties of these composite scaffolds have been effectively utilized [110].

These advancements demonstrate comprehensive performance in bone scaffolds through Mg ion loading, which could address clinical challenges such as large segmental bone defects that require robust scaffold strength for effective bone regeneration.

Despite its numerous advantages in bone tissue engineering, magnesium has a significant drawback: it corrodes rapidly in physiological solutions. This high

corrosion rate can lead to a direct loss of mechanical and physiological properties during bone healing [111].

Currently, tantalum, a distinct metal, is gaining increasing attention, with a growing body of research dedicated to its use. Tantalum offers several advantages over many existing materials due to its structural continuity, high strength, low stiffness, and high porosity. These properties are crucial for constructing porous scaffolds with complex configurations and unique shapes [112, 113]. Unlike many metals, which suffer from inertness detrimental to implant integration, tantalum exhibits excellent biological activity. This is attributed to its ability to form a self-passivating surface oxide layer that promotes the formation of a bone-to-bone interface [114].

The elastic modulus is a critical parameter for assessing the mechanical properties of porous tantalum bone scaffolds, indicating their capacity to resist elastic deformation and recover after stress application. When subjected to tensile or bending tests, the elastic modulus of porous tantalum scaffolds typically ranges from about 2 GPa to 8 GPa. Such resistance to compression and deformation is advantageous in metal materials and is highly beneficial for bone regeneration [112].

Zhiyi Zhang et al. fabricated porous tantalum scaffolds using the selective laser melting method and created unique micro-gradient nanostructures on the surface. This bionic hierarchical structure enhances the surface hydrophilicity of the scaffolds. Additionally, these porous tantalum scaffolds demonstrated enhanced early bone integration in a rabbit femur implantation model [115].

Polymers

Polymers are widely used in the biomedical field, with increasing applications in orthopedics. However, biopolymers such as collagen and cellulose can illicit immune responses. Natural biopolymers contain various proteins, such as collagen, gelatin, albumin, [85, 116, 117] and polysaccharides, such as cellulose, hyaluronic acid, chitosan, and alginate [118, 119]. These are derived from natural cellular components. Their composition is highly consistent with the natural ECM, and the body readily absorbs them. This compatibility fosters cellular integration without typically inducing immune reactions. Collagen, primarily sourced from animal skin, bones, and other connective tissues, predominantly consists of type I collagen [120], whereas type II collagen is primarily derived from cartilage tissue [121].

The production of collagen involves various specialized methods, which crucially influence its physical and biological properties. A significant aspect of collagen production is maintaining its native, undenatured form, which retains resistance to proteases. Avoiding high temperatures and denaturing agents during production is essential to preserve the fiber-modified structure on the collagen surface, thereby enhancing its immune resistance [122, 123]. Additionally, these natural materials feature specific amino acid sequences that promote cell adhesion, proliferation, and differentiation [83, 124].

Among the natural polymers utilized in 3D printing, collagen is arguably the most prevalent [125]. Given its significant presence in the ECM proteins of bone, collagen is a vital component of physiological bone tissue, noted for its exceptional biocompatibility and abundant sources. As a scaffold material, collagen is preferred due to its minimal

side effects. Type I collagen, in particular, is the most widely used [85]. Despite the excellent biological properties of pure collagen scaffolds, their mechanical properties are lacking, rendering them unsuitable for use alone in bone tissues that require mechanical support. The mechanical properties of collagen can be enhanced through intermolecular crosslinking using physicochemical methods. While such strategies can improve the structural integrity of collagen scaffolds, they may adversely impact cellular responses in vivo [126].

The limitations of single-component systems are often addressed by employing a blend of polymers. Natural polymers are extensively utilized in tissue engineering, mirroring the properties of natural extracellular matrices [124]. Notably, most materials for cranial defect regeneration are either biologically inert or non-biodegradable. Addressing this, Li et al. developed a high-strength mineralized collagen bone scaffold for large-scale calvarial defects in sheep, featuring a biomimetic composition and microstructure. In their process, calcium and phosphate ions were introduced into a type I collagen solution to form a precipitate, which was then combined with PCL to create a mineralized collagen complex. This dense scaffold, characterized by a small pore size, compensates for the mechanical deficiencies of collagen pores. The exceptional performance of this composite material shows the critical role of material composites in scaffold applications [126].

Compared to natural polymers, synthetic polymers offer broader sources, higher strength, diverse functionality, slower degradation rates, and strong structural plasticity [127, 128]. Bone tissue engineering necessitates the specific modification and processing of polymer materials to meet unique requirements, a challenging task with natural polymers due to their limited malleability. In contrast, synthetic polymers are highly adaptable, allowing the design of polymer functional groups to exhibit various structures and properties. This adaptability renders synthetic polymers extremely valuable in managing complex clinical conditions [74]. The most frequently used synthetic polymers in producing tissue engineering polymers are aliphatic polyesters, including PCL, PLA, and PLGA [129–132].

As a semi-crystalline aliphatic polyester, PCL is recognized for its excellent toughness and biocompatibility, with a non-toxic degradation profile. However, its slow degradation rate and insufficient mechanical properties are considered limitations in the bone tissue regeneration process, as this synthetic polymer alone does not possess the mechanical properties required to adequately replace certain bone tissues [133, 134]. PCL, which exhibits a semi-crystalline state in vivo due to its melting temperature being higher than body temperature, is chemically quite hydrophobic and lacks specific cell recognition sites, resulting in insufficient cell-scaffold interaction. This limitation affects the ability of cells to adhere, survive, and proliferate, making surface modification of PCL a widely adopted method for material enhancement [135, 136]. By integrating apatite materials, known for their excellent compatibility, with PCL to introduce carboxylic acid groups, dense hydroxyapatite deposition can be promoted on the material's surface [137]. Senem Buyuksungur et al. enhanced the characteristics of PCL scaffolds by 3D printing them with methacrylate gelatin (GelMA)-loaded dental pulp stem cells (DPSCS), creating a hybrid scaffold that leverages the hydrophilicity, high biocompatibility, and adequate pore size coefficient of GelMA to improve the PCL framework. This approach ensures

mechanical strength while enhancing cell activity, osteogenic differentiation, and mineralization levels [88]. Techniques such as laser treatment and bioceramics such as calcium phosphate have also proven effective for modifying PCL surfaces [136, 138]. The application of PCL in composite materials is remarkably extensive, exhibiting excellent synergistic capabilities when combined with metals or other polymers. Hou et al. developed a PCL-PEG-PCL composite scaffold that was noted for its good biocompatibility and biodegradability. They incorporated the metal nanomineral zinc oxide (n-BD) into the PCL polymer to enhance biological activity and osteogenic capacity, resulting in an n-BPC bioactive scaffold with interconnected large pores. The addition of PEG, known for its superior mechanical properties and amphiphilicity, significantly enhances the water absorption, degradation rate, and mechanical strength of the bone scaffold. This improvement promotes cell proliferation and differentiation [139]. Integrating materials with higher mechanical strength has broadened the applicability of PCL materials, making them suitable for repairing bone defects that require robust mechanical support.

One of the primary challenges in clinical practice remains the repair of extended bone defects, which necessitates using bone grafts, growth factors, and mechanical stability. A novel approach involves a 3D-printed polycaprolactone (PCL)/β-tricalcium phosphate (β-TCP) scaffold coated with polydopamine (PDA) and alginate microspheres (AM) for the sustained delivery of bone morphogenetic protein-2 (BMP-2). Polydopamine (PDA), inspired by mussel adhesives, exhibits strong adherence to various material surfaces, including superhydrophobic ones, whereas alginate can encapsulate bioactive molecules through cross-linking reactions. This configuration in the rabbit femoral segmental bone defect model facilitated improved cortical bone connectivity and induction [140].

While traditional materials such as PCL have advantages, their performance alone is relatively limited, preventing their sole use in clinical applications. The current trend focuses on encapsulating osteogenic-inductive molecular substances within slow-release materials to offset the inherent limitations, such as the strength deficiencies of natural materials. Composite scaffolds that balance these properties may more likely achieve clinical translation, presenting a balanced solution for complex medical challenges.

Bioceramics

Bioceramics dominate the market for bone tissue engineering scaffold materials, primarily due to their high strength, excellent biocompatibility, significant bioactivity, and robust bone induction and conductivity. These materials can also load stem cells, growth factors, and drugs [141, 142]. However, their application is limited by insufficient degradability and mechanical strength. Additionally, bioceramics are highly brittle as they are produced by sintering inefficiently filled powders [143, 144], which contributes to their fragility. Bioceramics can be classified based on their interaction with bone tissue into three types: resorbable calcium phosphates, which include hydroxyapatite (HA), tricalcium phosphate (TCP) and their combination in biphasic calcium phosphate (BCP), bioactive types, such as bioactive glass, and near-inert types such as zirconia [145–148]. These materials are clinically useful as surgery implants and as drug delivery carriers [149, 150].

Given that the core component of natural bone is hydroxyapatite (HA) nanocrystals, HA is frequently used with natural polymers in bone tissue scaffolds, particularly for repairing bone defects [151, 152]. HA and TCP have shown promise in regenerating alveolar bone, initially demonstrating potential in dental applications [153]. These materials are highly biocompatible and non-toxic and excel in osteoconductivity and osteoinductivity. Their bone-like porous structure facilitates vascular growth and osseointegration, enhancing their efficacy in medical applications [154]. Although HA is a principal component of bone tissue, its application in bone tissue engineering is somewhat limited due to its slow degradation rate in implants, which hampers new bone formation. Additionally, HA's mechanical properties are relatively weak, making it unsuitable as a load-bearing material for bone defects. These challenges necessitate the development of advanced composite materials that enhance its strength while capitalizing on its excellent biocompatibility. Composite materials incorporating hydroxyapatite can significantly improve the adhesion, migration, and differentiation of osteoblasts on the scaffold. K. Zafeiris et al. created a composite by mixing chitosan, L-arginine, and hydroxyapatite nanocrystals, further enhancing scaffold strength with genipin, given that hydroxyapatite provides the essential calcium and phosphorus elements for bone growth [155].

Bioactive glass, a type of ceramic material, has been a staple in materials engineering for centuries and underwent a transformational shift in 1969, revolutionizing implant materials by providing a viable alternative to inert substances. Its composition—rich in calcium, phosphorus, and silicon—renders it highly compatible with the human body. A notable attribute of bioactive glass is its ability to foster bone regeneration. Upon implantation, bioactive glass activates osteoblast proliferation, which is essential for bone formation, facilitating the growth of new bone tissue and repairing bone defects or fractures. Moreover, bioactive glass's superior biocompatibility ensures minimal adverse effects on surrounding tissues, making it an ideal material for bone tissue engineering and orthopedic surgeries. Furthermore, its antibacterial properties are advantageous for preventing infections at the implantation site. The release of silicon ions from bioactive glass boosts its antibacterial effectiveness and modifies cellular behaviors. This alteration enhances the fluidity of cell membranes, influencing cellular responses to the implant and exerting a broader bioactive effect.

Bioactive glass (BG) stands out in bone engineering applications due to its strong adherence to bone tissue, excellent biocompatibility, and robust antibacterial properties. These attributes enhance its capacity to promote bone regeneration and positively influence cell behavior, broadening its versatility and future potential in the field [156, 157]. The antibacterial properties of bioactive glass are particularly noteworthy, leading to extensive research in this area. Innovations have included the incorporation of silver, known for its bactericidal efficacy against various bacteria while being benign to human cells. Rodrigo L. M. S. Oliveira et al. developed bioactive glass scaffolds with well-defined pore structures using a sponge replication technique. These scaffolds have two pore size ranges: one from 1 mm to 1.5 mm and another from 170 μm to 700 μm. Silver nanoparticles were coated onto the scaffolds, resulting in a layer of silica gel on the microcrystalline surface that promotes adhesion between the nanoparticles and the scaffold. This silver coating effectively inhibits bacterial growth, such as

Staphylococcus aureus and *Pseudomonas aeruginosa*, addressing infection risks in clinical bone transplantation and suggesting a pathway for further development through manufacturing best practices and clinical trials [158].

Despite its advantages, traditional bioactive glass's brittleness and limited degradation capacity are less ideal for load-bearing bone growth. In a study on rat cranial bone defects, Angela Maria Paiva Magri et al. enhanced these properties by combining PLGA, a porous material, with bioactive glass. This combination accelerated material degradation and bone healing in the cranial defect model. Additionally, bioactive glass degradation produces alkaline substances, which are unfavorable for bone tissue regeneration, whereas the acidic nature of PLGA, composed of polylactic acid and glycolic acid, neutralizes this effect, thus improving the bone regeneration environment [159, 160].

Further advancements in nanomedicine include the study of iron oxide nanoparticles (IONPs), particularly in applications such as magnetic particle bone cement. Traditional Fe_3O_4 magnetic particle bone cement has demonstrated efficacy in eliminating *Staphylococcus aureus* under an alternating magnetic field. However, its non-degradability necessitates subsequent surgical interventions. To overcome this, Ying Jin and colleagues developed a borosilicate bioactive glass (BSG) scaffold combined with iron tetroxide (Fe_3O_4), enhancing both antibacterial efficacy and bone repair capabilities. This scaffold increases the expression of osteogenic factors. Flow cytometry revealed the polarization of M2 cells towards RUNX 2, ALP, and OCN, demonstrating superior antibacterial effects at the implantation site and effectively controlling SAC and *Staphylococcus aureus*. The scaffold promoted ideal new bone formation around the original infection site [161]. This study demonstrates a processing approach similar to previous materials, employing a novel antibacterial material in combination with traditional borosilicate bioactive glass. It simultaneously achieves antibacterial and bone regeneration effects, making the prospect of osteogenesis alongside antibacterial activity more promising.

Special processing method of materials

Many materials are limited in clinical applications due to insufficient specific functions. To improve material characteristics, researchers have devised a modification method that enhances the biomimetic ability of materials. This method uses surface-modified coatings to modify materials with certain functional deficiencies, such as typical metallic materials [37]. Due to high-stress shielding and low tissue compatibility, typical metallic materials cannot achieve good bone integration after implantation [36]. Therefore, the mechanical properties of metallic materials can be utilized by designing well-modified surface coatings. However, their incompatibility with regenerating bone can also be avoided, allowing for normal automatic repair of the defect structure after implantation [27]. Thus, first, we need to completely understand bone tissue regeneration. In addition, surface modification can also be expected to improve problems such as poor integration of bone grafts with host bone tissue, infection, and inflammatory reactions [162]. Although coating treatment of the material can greatly improve certain aspects of the scaffold, different coating treatments are required due to the varied characteristics of the

materials. At present, achieving a unified coating method to solve all material problems is impossible.

Hydroxyapatite, renowned for its exceptional biocompatibility and osteoconductive properties, is increasingly utilized in metal coatings to enhance metal–bone integration. It effectively reduces the corrosion of metallic implants and the toxicity caused by metal ions, thereby promoting more substantial bone growth and deeper penetration depth while facilitating more direct contact with tissue surfaces [163]. In a study focused on material selection for cranioplasty, Armaghan Naderi et al. employed the sol–gel method to coat hydroxyapatite onto a metal mesh, resulting in a 3D composite implant. This modification aligned the material's elastic modulus closely with that of the human skull and demonstrated superior compatibility. The presence of adipose-derived stem cells (ASC) thriving in the open mesh areas of the coating indicated that the hydroxyapatite coating promotes cellular activity within the composite matrix. Additionally, the electrochemical behavior of the scaffold was shown to reduce metal electrode corrosion, enhancing the corrosion resistance of the metal. These findings illustrate that hydroxyapatite coatings can significantly improve the biocompatibility and corrosion resistance of metal implants while maintaining the metal's strength, making it suitable for applications such as cranioplasty [164].

In many cases, the application of a composite scaffold alone may not be sufficient to produce a good healing effect in bone defect models due to the need for special factors to stimulate bone tissue repair [165]. Many bone-related growth factors can promote bone tissue healing by enhancing bone induction and integration. Adding these growth factors to biologically active scaffolds helps improve the functional characteristics of the scaffolds and is a novel modification method. Bone morphogenetic protein is the most widely used, and many other cell factors can also be used to encapsulate tissue material. Table 4 presents the common application of various bone regeneration-related growth factors and bone scaffold materials, providing important insights for improving material functionality.

Bioprinting

Firstly, in bone engineering, the printing method significantly impacts the properties of scaffolds, making it crucial to understand the various techniques involved in scaffold manufacturing. The evolution of bioprinting technologies and the development of compatible "ink" materials have been central to advancing 3D scaffolds for bone defect repair. Among the bioprinting methods developed so far are inkjet-based, extrusion-based, and laser-based bioprinting, each with unique characteristics and applications [166, 167].

Inkjet-based bioprinting utilizes a non-contact, droplet-based system, allowing for high-resolution deposition of biomaterials. Binding jetting is a special type of inkjet printing; it typically uses two materials, namely metal/ceramic-based materials for manufacturing components and adhesive materials, to lay and deposit a layer of adhesive on a powder metal/ceramic layer. Using computer-aided design (CAD) models, a layer of adhesive is deposited on the metal layer, and fine water jets are accurately printed layer by layer onto the metal powder bed. The metal/ceramic powder material is layered and bonded, and then the printed metal parts are sintered in a furnace to achieve the

Table 4 Features of growth factors related to bone tissue engineering and materials

Growth factor	Material carrier	Animal model	Functions/ advantages	Limitations	References
BMP-2	Chitosan coatings on Ti	Tibial defect in rabbits	Promotes cell adherence, proliferation, differentiation and calcium mineralization	Short half-life easily degradable	[207]
BMP-7	PLA/PCL nano-HA/ polyamide PLGA	Mandibular defect osteochondral defect of rabbit knees	Low dose required	Cell differentiation rather than proliferation	[208, 209]
PDGF-BB	Brushite–chitosan Bioglass/silk fibrin	Osteoporotic critical-sized femur defect of rat	Recruits mesenchymal progenitor cells inducing bone tissue regeneration promotes angiogenesis	Inhibit BMP-2 induced bone healing inhibit osteogenesis of mesenchymal stem cells	[210, 211]
FGF	PLGA/β-TCP	Rat cranial bone defect	Promotes rapid tissue in growth in the scaffold		[212]
VEGF	PLGA SiHA HG-HA-TCP	Rat cranial bone defect bone defect of sheep limbs	Promotes angiogenesis, osteoinductive increases ALP activity increases the permeability of the vessels	Limited osteogenic inductive effect	[213–215]

required mechanical strength [168]. The main advantages of this printing method are low equipment cost and a thermally controlled sintering process, making the manufacturing process fast. However, its manufacturing accuracy is relatively low, making it suitable for printing requirements with lower precision [169]. Selective laser melting (SLM) is a technology that uses advanced high-energy fiber lasers to melt powders and rapidly laser shape materials in a vacuum higher laser energy density and finer focusing can produce materials with higher dimensional accuracy and better performance. Powder materials can be single or multi-component substances; the raw materials do not need to be specially prepared. SLM can provide the advantage of design freedom, which gives a wide range of material choices. Complex-shaped scaffolds can also be prepared to meet the needs of many delicate organ tissues in clinical practice [170]. However, laser-assisted bioprinting also has limitations, including high complexity, high cost, and slow manufacturing speed. Moreover, the potential damage of laser to cells and the toxicity of photoinitiators also limit its clinical application [171]. Extrusion bioprinting is currently widely used in scaffolds. Fused deposition modeling (FDM) is a typical extrusion type based on a continuous extrusion process where pressure is applied to a syringe to extrude the bioink through a micro-nozzle. This extrusion method has many unique advantages. It has a high sedimentation and printing speed, which can promote scalability in a short time. This technology does not require heating, is fast to manufacture, and is beneficial for cell loading. In addition, this method provides various bio-ink options to manufacture more specialized scaffolds as needed [172]. However, a major limitation of FDM is that the technology can only produce biological scaffolds

with limited shapes and relatively regular structures; with insufficient precision, only limited printing resolution can be achieved. Therefore, to produce scaffolds for clinical use, these issues must be improved [173].

Secondly, the compatibility of bioprinting with various scaffold materials is another critical area of research in bioprinting. Bioprinting involves the precise deposition of bioinks, which are formulations containing living cells and biomaterials, to create complex tissue structures. The choice of scaffold material significantly impacts the success of bioprinting, as it must support cell viability, proliferation, and differentiation while maintaining structural integrity. Hydrogels are among the most commonly used scaffold materials in bioprinting due to their high water content and biocompatibility, which mimic the natural ECM [174]. However, hydrogels often suffer from poor mechanical properties and low printability, which can limit their application in creating robust tissue constructs. To address these issues, researchers have developed various strategies to enhance the mechanical stability and printability of hydrogel-based bioinks. For instance, dual-crosslinking methods, which involve both physical and chemical crosslinking, have been shown to improve the mechanical properties of hydrogels, making them more suitable for bioprinting applications [175]. The rheological properties of bioinks are crucial for successful bioprinting, as they determine the flow behavior and printability of the material. Bioinks must exhibit shear-thinning behavior, where viscosity decreases under shear stress, to facilitate smooth extrusion through the printer nozzle [176]. Additionally, the crosslinking strategy employed can significantly affect the final properties of the printed construct. For example, photo-crosslinkable bioinks allow for precise control over the gelation process, enabling the creation of complex structures with high fidelity [177]. Ceramic materials, on the other hand, are often used in bioprinting for applications requiring high mechanical strength, such as bone tissue engineering. The incorporation of ceramic particles into bioinks can enhance the osteoconductivity and mechanical properties of the printed scaffolds [178]. However, the high viscosity of ceramic-containing bioinks can pose challenges for extrusion-based bioprinting, necessitating the development of novel rheology modifiers and crosslinking strategies to improve printability [179]. Despite these advancements, there are still limitations in the current bioprinting technologies. The compatibility of different scaffold materials with bioprinting processes needs further exploration to optimize the properties of the final constructs. Moreover, the development of bioinks that can seamlessly integrate with various scaffold materials without compromising cell viability and function remains a significant challenge [180, 181]. In conclusion, the compatibility of bioprinting with hydrogels and ceramics is being continuously improved through innovative techniques and material combinations. These advancements are crucial for the successful application of bioprinting in tissue engineering, offering new possibilities for the creation of complex and functional tissue constructs.

Clinical applications, challenges, and prospects

Currently, 3D printing technology has been applied in orthopedic surgery. Combined with CT and other medical imaging techniques, 3D printing implants can be more specific to the target bone structure. Hu et al. designed a 3D-printed artificial vertebral body for multiple segments of the spinal resection, which is used for spinal surgery.

They found that the combination of adjuvant therapy had a good outcome, and the spine gradually recovered [182]. The 3D printing Ti6 Al4 V scaffold, a relatively mature scaffold, has been applied to various clinical scenes. Liu et al. made a porous Ti6 Al4 V scaffold through 3D printing to repair the defect of the lower extremities. The result indicates that the scaffold can rebuild the severe bone defect of the lower extremities without additional bone [183]. A tibial fracture is a common type of injury. Since the injury of the subcutaneous muscle tissue is minor, the blood of the tibia is poor, causing nonunion of a tibial fracture that failed to heal. Zhao et al. designed a porous tantalum metal bone plate with excellent mechanical and biological properties to treat tibial fractures, improving the therapeutic effects of the treatment [184]. In recent years, the clinical application has been doubled, and 3D-printed scaffolds have made substantial progress in orthopedic surgery.

Currently, the treatment of bone defects continues to rely on autologous bone transplantation, and the fabrication of ideal bone tissue scaffolds remains a significant challenge. Numerous technical issues require appropriate solutions. To enhance the clinical application potential of bone tissue engineering, several key problems and potential strategies are summarized as follows:

1. Vascularization: In cell-loaded bone tissue scaffolds, although vascular regeneration can be effectively promoted by incorporating endothelial growth factors, regeneration at the microvessel level remains scarce. Constructing hollow and densely distributed microvascular networks is difficult, and both cell survival and diffusion are still limited. Therefore, with respect to vascularization, it is proposed that incorporating artificial microvascular structures within scaffold materials or the controlled release of specific pro-angiogenic substances to facilitate vascular formation may significantly enhance the efficiency of cell diffusion [185, 186].
2. Simulating the **s**tructure of natural bone tissue**:** Natural bone tissue possesses a hierarchical architecture. If a 3D-printed scaffold can accurately replicate this structure, it may exert excellent inductive effects on bone regeneration. However, the limited resolution of current 3D printing technology prevents precise simulation of such hierarchical features. Advancements in this area necessitate the development of higher precision printers, specifically engineered with finer print nozzle diameters [187].
3. Antimicrobial characteristics: In clinical practice, managing infectious bone defects is particularly challenging due to difficulties in controlling infections. Systemic administration of high-dose antibiotics may lead to toxicity and contribute to the emergence of drug-resistant strains. Therefore, the encapsulation of antibiotics within nanomaterials for targeted and sustained release offers the potential for long-term antimicrobial efficacy while minimizing systemic side effects [188].
4. Cost: The cost of 3D printing is an important issue that limits its application, so it is necessary to consider how to reduce the cost. In terms of material costs, optimizing structural design can reduce multiple operations in material printing, thereby reducing material investment. Secondly, further research should be conducted on material selection to develop cheaper printing materials. In terms of equipment investment, the incompleteness of current 3D printing development and the

absence of large-scale manufacturing facilities are closely related to the maturity of the technology. It is anticipated that as 3D printing technology achieves significant breakthroughs in both scientific research and clinical application, related investments will substantially increase, enabling the realization of mass production.

Regarding control over printing details, if only a tiny portion of a printed component requires exceptionally high precision, reducing the overall layer height is not necessarily advantageous to enhance accuracy. Such an approach would considerably prolong production time. Instead, large tolerance compensation can be applied to areas with lower precision requirements, allowing for rougher accuracy during initial printing and post-processing to improve precision in critical regions. Mastery of such detail management strategies can lead to substantial savings in both time and material costs in 3D printing.

Along with 3D printing technology, many other bone tissue repair strategies are developing rapidly. A basic understanding of 3D printing, in conjunction with other commonly used technologies, can provide a more comprehensive perspective and contribute to the further improvement of 3D printing applications. Therefore, a simple comparison between 3D printing technology, stem cell therapy, and gene therapy is presented in Table 5.

At the forefront of development in 3D structures, some researchers have demonstrated that enhancing the dynamic responsiveness of scaffolds to external stimuli can improve their adaptability in diverse clinical scenarios, leading to the emergence of four-dimensional (4D) printing strategies [189, 190]. Various physicochemical stimuli, such as light or temperature, can induce structural transformations in scaffolds when innovative materials convert external stimuli or energy into dynamic motion. This approach demonstrates significant potential for fabricating shape-variable, tissue-like structures and represents a promising direction for next-generation core printing technologies [191, 192].

For example, Alina Kirillova et al. fabricated a hollow, self-folding hydrogel-based tube using 4D printing technology. They achieved precise dynamic control over its mechanical properties, resulting in an adjustable and responsive structure capable of accurately forming the desired geometry [193]. This innovation provides a potential comprehensive strategy for clinical decision-making in disease treatment, enabling the modulation of scaffold characteristics to meet the varying requirements of different recovery phases following scaffold implantation in bone defects.

During phases requiring high mechanical strength and load-bearing capacity, the material can transition to a lower porosity state, enhancing its mechanical properties

Table 5 Comparison between 3D printing and other technologies

	Advantages	Disadvantages
3D printing scaffold	Structure support vascularization	Clinical validation is not sufficient for mass application
Stem cell therapy	Quick, easy delivery	Multiple complications, low survival rate of cells
Gene therapy	No need for cell implantation	Technical problems are difficult to solve, serious complication

to meet stress demands. Conversely, during periods where increased nutrient exchange and vascularization are critical, the porosity and architecture of the scaffold can be adjusted to support angiogenesis. Additionally, shape-memory materials can facilitate a more accurate fit to the defect site for bone defects with irregular geometries, further improving therapeutic outcomes.

Conclusion

Bone defects represent a formidable challenge in orthopedic and reconstructive medicine, particularly for large critical-sized defects that defy conventional repair strategies. While autografts remain the clinical gold standard, their limitations have spurred innovative alternatives leveraging 3D printing technology. This review highlights the transformative potential of 3D-printed scaffolds, emphasizing material innovation, structural precision, and biological functionality as the pillars of next-generation bone regeneration. Advances in biomaterial composites—such as osteoconductive bioceramics, mechanically resilient titanium alloys, and bioactive polymers—have significantly enhanced scaffold performance. The ability to fine-tune porosity, stiffness, and degradation kinetics through additive manufacturing has enabled scaffolds to better mimic native bone architecture. Furthermore, biological functionalization via growth factor delivery, stem cell integration, and immunomodulatory coatings has bridged the gap between synthetic constructs and living tissue. Despite these breakthroughs, challenges persist. Ensuring rapid vascularization, preventing infection, and achieving seamless osseointegration remain critical hurdles. Future progress will depend on merging emerging technologies—such as 4D-printed dynamic scaffolds, AI-driven design optimization, and advanced bioreactor conditioning—with clinical insights. By uniting engineering precision with biological complexity, 3D-printed scaffolds are poised to redefine bone defect repair, moving beyond structural replacement to active tissue regeneration.

Abbreviations

3D	Three dimensional
PCL	Polycaprolactone
β-TCP	β-tricalcium phosphate
SrCSH	Strontium-doped calcium sulfate
PLA	Polylactic acid
PLGA	Polylactic acid-co-glycolic acid
nBCP	Nanobiphasic calcium phosphate
HIF-1α	Hypoxia-induced factor-1α
VEGF	Vascular endothelial growth factor
SCF	Stem cell factor
ANGPT1	Angiopoietin 1
BMP-2	Morphogenetic protein 2
BMP-7	Morphogenetic protein 7
SiHA	Silicon-substituted hydroxyapatite
ASCs	Adipose-derived stem cells
BMSCs	Bone mesenchymal stem cell
DPSCS	Dental pulp stem cells
HUVECs	Human umbilical vein endothelial cells
iPSCs	Induced pluripotent stem cells
PDLSCs	Periodontal ligament stem cells
PEG	Poly (ethylene glycol)
n-BD	Nanobredigite
HA	Hydroxyapatite
4D	Four-dimensional
PDGF-BB	Platelet-derived growth factor BB

FGF	Fibroblast growth factor
HG-HA-TCP	Heparinized gelatine-hydroxyapatite-tricalcium phosphate
ALP	Alkaline phosphatase
FDM	Fused deposition modeling
SLM	Selective laser melting

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Author contributions
C.Y. and Y.Z. conceptualized and designed the study. J.S. and C.C. wrote the initial manuscript. J.S., C.C. and B.Z. prepared all the figures. C.Y. and Y.Z. revised the paper All authors reviewed the manuscript.

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Declarations

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