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REVIEW ARTICLE

Emerging bioprinting strategies for osteoporosis research and bone regeneration

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Abstract

Bioprinting has emerged as a promising technology for osteoporosis research and bone tissue engineering, enabling the fabrication of personalized scaffolds that mimic key features of native bone microarchitecture. Through 3D biofabrication, this technology facilitates the development of accurate osteoporotic bone models for in vitro and in vivo studies, drug screening, and the evaluation of therapeutic strategies. Bioprinted animal models and cell culture systems provide controlled platforms for investigating disease progression and testing candidate therapies, thereby addressing several limitations of conventional research approaches. In addition, bioprinting has advanced the design of bone substitutes by enabling precise control over scaffold properties, including mechanical strength, porosity, and biodegradability, all of which are critical for bone regeneration. Nevertheless, several challenges remain, including the trade-off between printing resolution and speed, limitations in current bioink formulations, difficulties in scaffold functionalization, and barriers to large-scale manufacturing. The clinical translation of bioprinted constructs is further complicated by ethical and regulatory challenges, particularly regarding stem cell applications and product approval pathways. Despite these challenges, bioprinting continues to demonstrate considerable potential in osteoporosis research and bone regeneration, with ongoing efforts focused on improving printing precision, developing smart bioinks, and advancing personalized therapeutic strategies. Continued interdisciplinary collaboration, together with improvements in scalability, cost-effectiveness, and regulatory standardization, will be essential to integrating bioprinting into clinical practice and advancing regenerative strategies for osteoporotic bone repair.

Keywords: Osteoporosis; Bioprinting; Bone regeneration; Scaffolds; Stem cells; Personalized medicine

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1. Introduction

1.1. Osteoporosis: A persistent unmet clinical need

Osteoporosis is a progressive, systemic skeletal disorder characterized by compromised

bone strength resulting from deterioration of bone mineral density and microarchitectural integrity, culminating in a dramatically elevated fracture risk.[1] The global burden of osteoporosis is substantial, affecting hundreds of millions of individuals, with postmenopausal women and the elderly being particularly vulnerable.[2] Fractures associated with osteoporosis, especially those of the hip and vertebrae, contribute significantly to morbidity, mortality, and healthcare costs.[3] Epidemiological studies indicate that the lifetime risk of osteoporotic fractures for women aged 50 is approximately 53%, while for men, it is around 21%, highlighting the clinical and societal importance of this condition.[4]

Despite substantial advances in osteoporosis management, current therapeutic strategies are primarily focused on reducing fracture risk and slowing disease progression, with limited capacity to regenerate lost bone tissue or restore native bone microarchitecture.[5-8] Consequently, impaired bone regeneration and progressive deterioration of bone quality remain major clinical challenges. These limitations have stimulated growing interest in regenerative medicine approaches capable of reconstructing physiologically relevant bone microenvironments and promoting functional bone repair. In this context, bioprinting has emerged as a promising strategy for both disease modeling and bone tissue engineering.

1.2. Bioprinting: A promising technology for regenerative medicine

Bioprinting, an emerging technology that integrates additive manufacturing with biological principles, has garnered significant attention in regenerative medicine and tissue engineering.[9,10] Unlike traditional manufacturing techniques, bioprinting enables the precise layer-by-layer deposition of bioinks comprising living cells, biomaterials, and growth factors to construct three-dimensional (3D) structures that mimic native tissues.[11,12] This technology holds immense potential for fabricating complex, functionally tailored tissue constructs for specific medical needs. Over the past decade, bioprinting has evolved from the fabrication of simple scaffolds to the generation of biologically active tissue constructs incorporating living cells and bioactive molecules, thereby enabling more physiologically relevant tissue models.[13]

Advances in extrusion-based, inkjet-based, and laser-assisted bioprinting have significantly improved resolution, printing speed, and cell viability, enabling the creation of increasingly sophisticated structures.[14] In regenerative medicine, bioprinting has demonstrated promise in applications ranging from skin grafts and cartilage implants to vascularized tissues and early-stage organ prototypes.[15-19] By leveraging patient-specific data, such as anatomical information derived from imaging technologies, bioprinting offers the potential to develop personalized medical solutions.[20]

In the context of bone tissue engineering, bioprinting has emerged as a promising technology for constructing biomimetic bone models and engineered scaffolds. Traditional bone grafting techniques, such as autografts and allografts, are often limited by donor-site morbidity, immune rejection, and material scarcity. In contrast, bioprinting enables the precise fabrication of engineered scaffolds incorporating bioactive factors to promote bone regeneration.[21] Furthermore, the integration of vascular networks into bioprinted constructs addresses a critical challenge in tissue engineering, as vascularization is essential for the survival and integration of engineered bone tissue.[22]

These capabilities make bioprinting particularly attractive for osteoporosis research, where accurate reconstruction of bone microarchitecture and the development of patient-specific regenerative strategies are urgently needed.

1.3. Bioprinting in osteoporosis research: Opportunities and challenges

The application of bioprinting in osteoporosis research provides a promising platform for improving our understanding of disease mechanisms and developing potential regenerative strategies. Traditional research models, including animal models and two-dimensional (2D) cell cultures, are limited in their ability to recapitulate the complex physiology and pathophysiology of human bone. As osteoporosis involves dynamic interactions among bone cells, extracellular matrix, vascular networks, and mechanical cues, conventional models often fail to reproduce the native bone microenvironment. Bioprinting provides a unique opportunity to overcome these limitations by creating 3D in vitro models that accurately mimic the anatomical and cellular complexities of osteoporotic bone.[23] These models serve as physiologically relevant platforms for studying disease mechanisms, testing pharmacological interventions, and investigating bone remodeling dynamics.

In drug development, bioprinted bone models can accelerate the discovery of novel therapies by providing high-throughput, cost-effective platforms for evaluating drug efficacy and toxicity.[24] Additionally, the incorporation of patient-derived cells into bioprinted constructs facilitates the development of personalized medicine, enabling the testing of tailored treatments based on an individual's genetic and phenotypic profile.[25]

Another promising future direction of bioprinting in osteoporosis research is the development of advanced bone scaffolds for therapeutic purposes[26,27]. These scaffolds can be designed to replicate the hierarchical structure of bone, with porosity and mechanical properties closely resembling those of native tissue.[28] Moreover, the functionalization of scaffolds with bioactive molecules, such as bone morphogenetic proteins (BMPs), can enhance osteogenesis and angiogenesis.[29] By leveraging patient-specific data, bioprinting enables the customization of scaffold designs to optimize compatibility and functionality, thereby improving the efficacy of regenerative treatments.[30]

Despite these opportunities, several scientific and engineering challenges remain before bioprinting can be translated into osteoporosis research and clinical practice, including limitations in biomaterial design, scaffold fabrication, tissue vascularization, and manufacturing scalability, particularly under osteoporotic microenvironment conditions characterized by impaired bone remodeling and reduced regenerative capacity.

1.4. Objective of this review

This review aims to systematically summarize the latest advancements in bioprinting technology for osteoporosis research and preclinical bone regeneration applications; critically analyze the challenges related to materials, techniques, and translational barriers; and explore potential future research directions. By providing a comprehensive overview of the current state of the field, this review seeks to offer a theoretical foundation and practical insights that will facilitate the realistic translation of bioprinting technologies.

2. Overview of 3D bioprinting technologies

Bioprinting technology, which enables the precise layer-by-layer deposition of biomaterials, cells, and bioactive factors, has emerged as a valuable tool in tissue engineering and regenerative medicine. In the context of bone tissue engineering, bioprinting provides precise control over scaffold design and fabrication, allowing researchers to recapitulate key mechanical properties and biological functions of native bone tissue. Bioprinting platforms differ in their printing mechanisms, material compatibility, and achievable structural complexity. Understanding these characteristics is essential for selecting appropriate technologies for osteoporosis-related applications. This section summarizes the fundamental principles and major classifications of bioprinting technologies.

2.1. Fundamental principles of bioprinting

Three-dimensional bioprinting is an advanced manufacturing approach that constructs complex structures through the precise deposition of bioinks composed of biomaterials, cells, and bioactive factors.[31] This technology leverages high precision, customization capabilities, and rapid prototyping to create scaffolds that mimic the structural and functional properties of native tissues.[32] In bone tissue engineering, bioprinting integrates biomedical imaging technologies, such as computed tomography (CT) and magnetic resonance imaging, with computer-aided design software to generate scaffold models tailored to specific defects. By controlling parameters such as shape, porosity, pore-size distribution, and spatial structure, bioprinting enables the fabrication of scaffolds that approximate the mechanical and biological characteristics of native bone.[33]

Unlike conventional 3D printing, which primarily focuses on fabricating inert structures, bioprinting enables the layer-by-layer deposition of bioinks with or without cells, thereby providing superior control over material distribution. This capability is crucial for promoting tissue regeneration and vascularization.[34] The most commonly used bioprinting methods include inkjet printing, extrusion printing, and laser printing, each possessing distinct operating principles and application scenarios in tissue engineering (Figure 1).[35-38]

2.1.1. Inkjet printing technology

Inkjet printing is a widely used bioprinting method that employs piezoelectric or thermal pressure technologies to precisely deposit bioinks.[39] This technique involves bioink preparation, nozzle control, droplet deposition, and layer-by-layer construction. Inkjet bioprinters utilize noncontact nozzles to dispense nanoliter- or microliter-sized droplets of cells, enabling the creation of small, uniform cell arrays.[40] The advantages of inkjet printing include simplicity, high resolution, efficiency, and low cost.[36,41-44]

However, inkjet printing has several limitations. The technique is constrained by the viscosity of bioinks, which must be low to prevent nozzle clogging. This requirement limits the range of materials that can be used, often resulting in scaffolds with poor mechanical properties. Additionally, the resolution of inkjet printing is highly dependent on nozzle diameter, with smaller nozzles offering higher resolution but being more prone to clogging. These limitations may make inkjet printing more suitable for simpler tissue-engineering applications, such as the fabrication of thin tissue layers or small-scale models, rather than complex, load-bearing bone scaffolds (Table 1).

2.1.2. Extrusion printing technology

Extrusion printing is one of the most widely used

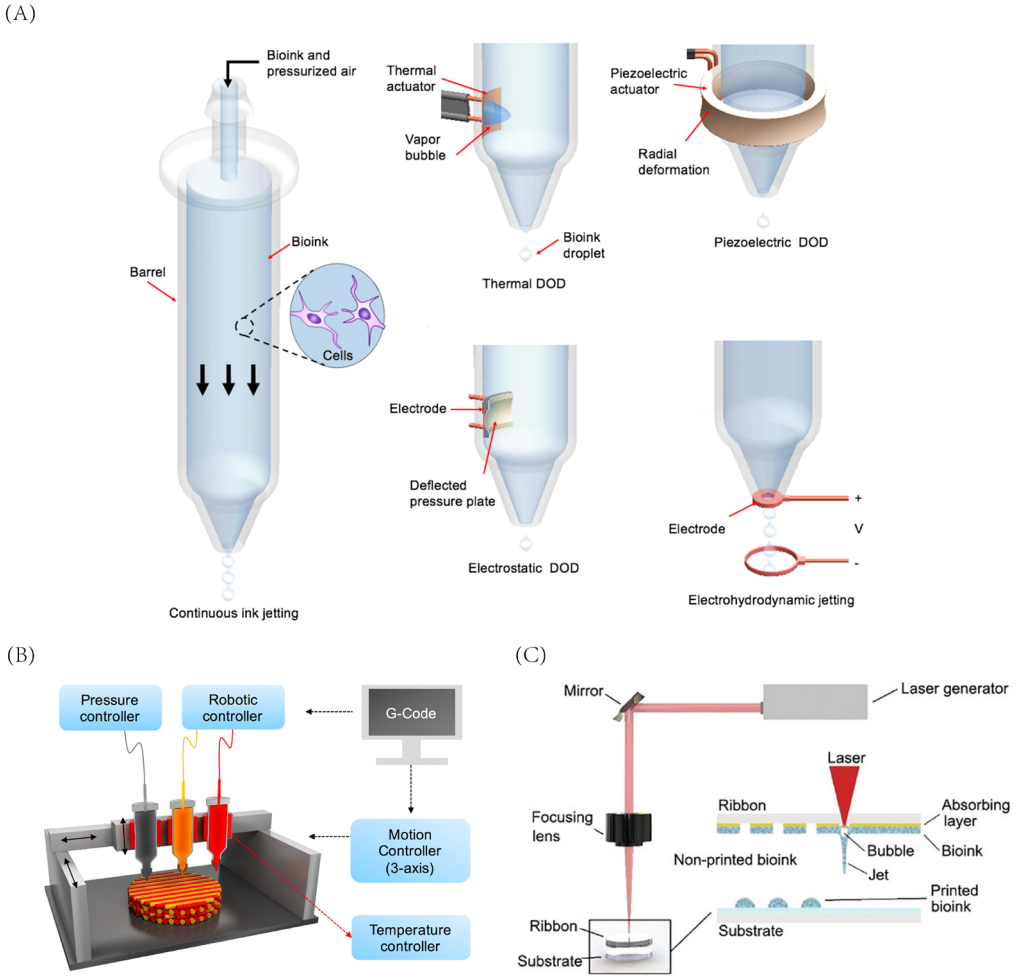

Figure 1. Schematic illustration of commonly used bioprinting techniques. (A) Inkjet-based printing. Reprinted with permission from Gudapati *et al.*[36] Copyright © 2016 Elsevier. (B) Extrusion-based printing. Reprinted with permission from Jang *et al.*[37] Copyright © 2017 Elsevier. (C) Laser-assisted printing. Reprinted with permission from Dou *et al.*[38] Copyright © 2021 Wiley. Each approach offers distinct advantages and limitations in terms of resolution, material compatibility, and cell viability.
Abbreviation: DOD: Drop-on-demand.

bioprinting techniques in bone tissue engineering. This method employs pressure or mechanical force to continuously extrude fluid-like biomaterials from a nozzle onto a work surface at a preset speed and volume.[36,39] Compared to inkjet printing, extrusion-based bioprinting can process bioinks containing natural polymers, synthetic polymers, and stem cells, due to its ability to generate higher pressures.[45,46] This versatility makes extrusion printing suitable for fabricating large, porous scaffolds and reconstructing complex anatomical structures, such as bone tissue.[47]

Despite its advantages, extrusion printing has notable drawbacks. The mechanical forces generated during the extrusion process can cause shear stress damage to embedded cells, potentially compromising cell viability and survival.[48] Furthermore, extrusion printing typically has a lower resolution (200–1,000 μm), limiting its ability to achieve fine microstructural details (Table 1).[49,50] These challenges highlight the need for further optimization of extrusion-printing parameters, such as nozzle design and printing speed, to minimize cell damage and improve resolution.

2.1.3. Laser printing technology

Laser printing is an advanced bioprinting technique that uses laser power and photopolymerization principles to create 3D structures. This method employs technologies such as laser direct writing and laser-induced direct

transfer to achieve precise cell placement.[39,51] Unlike inkjet and extrusion printing, laser printing does not require a nozzle, resulting in higher resolution and printing precision. Additionally, laser printing helps preserve the bioactivity of cells and molecules and can fabricate intricate structures with high fidelity, making it particularly suited for applications requiring high-resolution cell deposition, such as the construction of complex 3D tissue models and vascular networks.[52-54]

However, laser printing is associated with high costs and is limited to specialized biomaterials, restricting its widespread adoption (Table 1).[55] The complexity of the printing process and the need for specialized equipment further limit its scalability for large-scale applications. These challenges underscore the importance of developing cost-effective and versatile laser printing technologies to expand their applicability in bone tissue engineering.

2.2. Bioprinted bone tissue scaffolds

The design of bone scaffolds is central to bone tissue engineering. These scaffolds must support the growth and differentiation of bone cells while replicating the structure and function of native bone tissue.[56,57] Bone is a complex, multifunctional tissue that provides mechanical support, organ protection, and metabolic regulation. To fulfill these functions, bone scaffolds must achieve an optimal balance of shape, pore size, porosity, degradability, biocompatibility, mechanical properties, and cellular response.[58]

Traditional scaffold fabrication methods, such as molten salt templating, electrospinning, and solution casting, are limited by their reliance on templates or molds, making it difficult to precisely control geometric shape and pore structure.[59] Additionally, these techniques typically rely on post-fabrication cell seeding, resulting in limited control over cell distribution.[60]

In contrast, 3D bioprinting overcomes these limitations by enabling the layer-by-layer fabrication of highly complex and spatially heterogeneous structures. By simultaneously depositing biomaterials and cells during the printing process, bioprinting allows for precise control over scaffold geometry, porosity, and material distribution.[61] This capability is particularly valuable for replicating the hierarchical structure of bone, where cortical bone provides mechanical strength and trabecular bone facilitates vascularization and cellular infiltration. Furthermore, bioprinting enables the deposition of multiple materials within a single scaffold, addressing both mechanical and biological requirements. Kang *et al.*[62] employed advanced bioprinting techniques to reconstruct bone tissue at various anatomical sites, such as the mandible and calvaria (Figure 2).

Table 1. Comparison of different 3D bioprinting techniques in bone tissue scaffolds

Bioprinter types	Technical principles	Applicable biomaterials	Application areas
Inkjet-based[36,39,41,43,44]	Thermal/piezo-driven microdroplet injection	(i) Low viscosity hydrogels: Agarose, sodium alginate (ii) Microsphere encapsulation system: PLGA microspheres loaded with BMP-2, cell-laden microgels	Integrated scaffolds for bone repair and drug delivery, osteoporosis modeling, bone regeneration microenvironment regulation
Extrusion-based[39,50]	Layer-by-layer stacking of mechanically extruded material	(i) Natural polymers: Collagen/Gelatin, sodium alginate, hyaluronic acid (ii) Synthetic polymers: PLA/PCL/PLGA (iii) Composites: Hydroxyapatite (HA)-reinforced PLA/PCL, nanoclay composite hydrogel	Craniomaxillofacial bone defect repair, temporary scaffolds for load-bearing bone, joint repair
Laser-based[39,53,54]	Laser-induced material transfer	(i) Cell suspensions: Mesenchymal stem cells, osteoblasts (ii) Bioinks: Fibrinogen/collagen, low-concentration GelMA	Periosteal bionic structures with directional cell arrangement, bone tumor model, growth factor gradient release scaffolds

Abbreviations: BMP-2: Bone morphogenetic protein-2; GelMA: Gelatin methacryloyl; PCL: Polycaprolactone; PLA: Polylactic acid; PLGA: Poly (lactic-co-glycolic acid).

Despite these advancements, challenges remain in optimizing scaffold design for specific clinical applications. For example, achieving a balance between mechanical strength and porosity is critical to ensure that scaffolds can withstand physiological loads while promoting cell infiltration and nutrient exchange.[63] Additionally, the long-term stability and integration of bioprinted scaffolds in vivo require further investigation.

2.3. Bioinks

The selection of bioinks is a critical factor in the success of bone bioprinting. Bioinks, which typically consist of

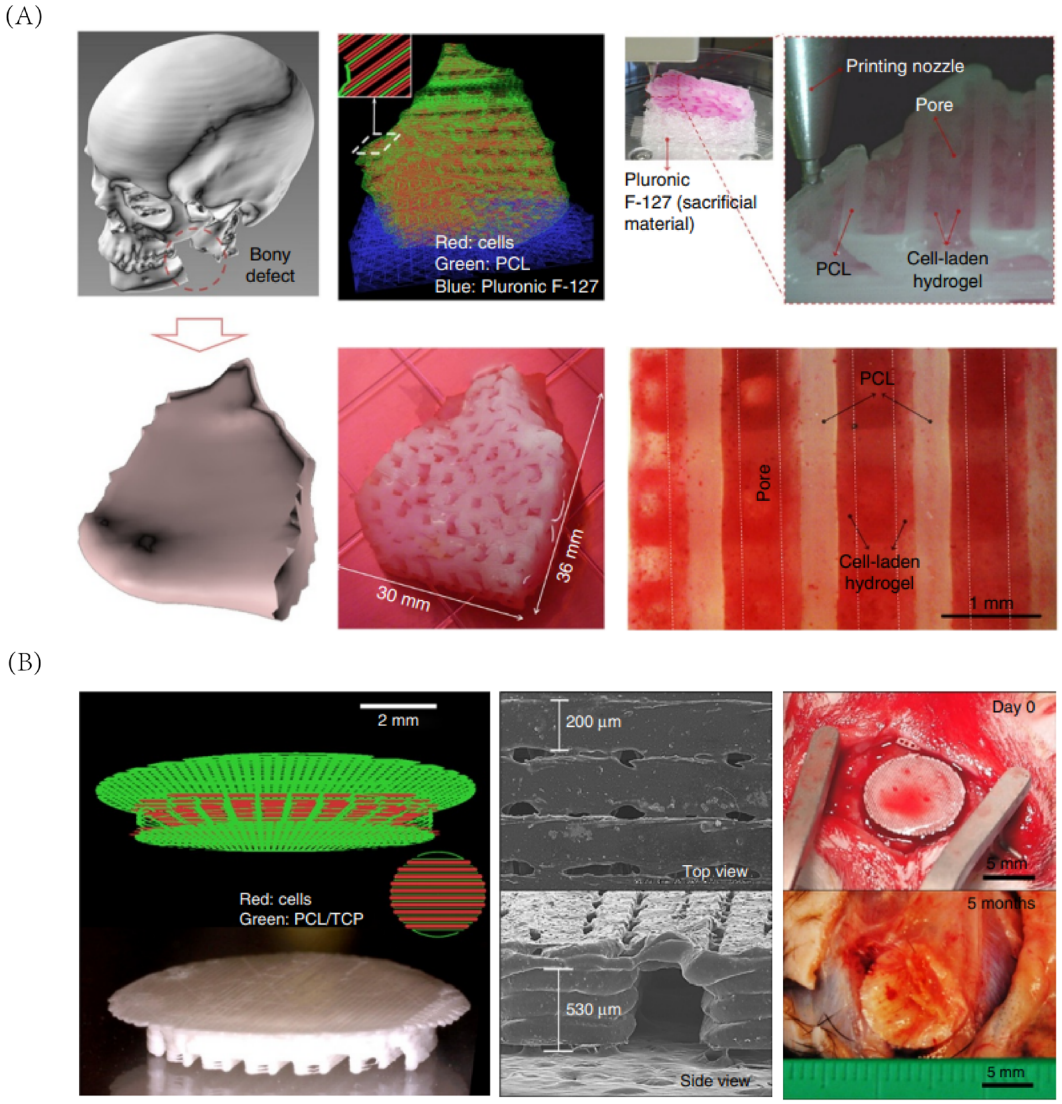

Figure 2. 3D bioprinting for bone reconstruction. (A) Mandibular bone reconstruction: A 3D computer-aided design model derived from computed tomography imaging was used to design a construct composed of polycaprolactone (PCL), Pluronic F-127, and human amniotic fluid stem cell (hAFSC)-laden hydrogel. After 28 days of osteogenic induction, Alizarin Red S staining confirmed calcium deposition. (B) Calvarial bone reconstruction: Bioprinted constructs consisting of PCL/beta-tricalcium phosphate (β-TCP) and hAFSCs showed new bone formation and vascularization after 5 months of implantation. Reprinted with permission from Kang *et al.*[62] Copyright © 2016 Springer Nature.

natural polymers, synthetic materials, or stem cells, directly influence the mechanical properties, biocompatibility, and regenerative potential of the scaffold.[12] Ideal bioinks should exhibit good biocompatibility, appropriate mechanical strength, degradability, and efficient crosslinking mechanisms to support scaffold construction and function.

The printability of bioinks depends on their rheological properties and crosslinking mechanisms. Key parameters, such as viscosity, viscoelasticity, surface tension, and flow rate, must be carefully optimized to ensure high shape fidelity and cell viability during the printing process.[61] For example, bioinks with low viscosity are easier to print but may lack the mechanical strength required for load-bearing applications, while high-viscosity bioinks can compromise cell viability due to shear stress.

Despite significant progress in bioink development, challenges remain in achieving a balance between printability, mechanical properties, and biological functionality. Future research should focus on the development of advanced bioinks that mimic the complex

microenvironment of bone tissue while maintaining high cell viability and functionality.

3. Applications of bioprinting in osteoporosis research

Bioprinting has emerged as an important platform for osteoporosis research, enabling more physiologically relevant investigation of the structural, cellular, and mechanical characteristics of osteoporotic bone. By constructing accurate 3D models, bioprinting provides innovative platforms for investigating the pathophysiology of osteoporosis, evaluating therapeutic strategies, and developing novel treatments. However, while the potential of bioprinting in this field is significant, several challenges remain, including the need for improved model fidelity, scalability, and clinical translation.

3.1. In vivo and in vitro studies

Bioprinting has revolutionized the development of in vivo and in vitro models for osteoporosis research. Traditional methods, such as animal models and 2D cell cultures, are limited in their ability to replicate the complex physiology of human bone, particularly the coupled processes of bone resorption and formation under osteoporotic microenvironmental conditions such as increased oxidative stress and impaired remodeling balance. In contrast, bioprinting enables the creation of 3D models that more accurately mimic the structural, cellular, and mechanical properties of osteoporotic bone, providing a more physiologically relevant platform for research.[23,26,27,64-70]

3.1.1. Animal models

Bioprinting has enhanced the development of animal models for osteoporosis research by enabling the fabrication of small-scale scaffolds or implants that replicate the damaged structures of osteoporotic bone. These bioprinted constructs can be implanted into animals to study disease progression, bone resorption, remodeling, and fracture healing.

Furthermore, Wang *et al.*[68] evaluated the effects of a 3D-printed bilayer scaffold loaded with human gingival fibroblasts (hGF) in an osteoporotic animal model. The study demonstrated that the scaffold significantly promoted new bone formation, particularly in the core region, compared to scaffolds without hGF (Figure 3A, B). The enhanced regenerative outcome may be associated with increased osteogenic and angiogenic activity within the defect area, suggesting that the bioprinted construct may provide a favorable microenvironment for bone repair under osteoporotic conditions. These findings highlight the utility of bioprinted constructs for evaluating the regenerative performance of biomaterials in osteoporotic animal models and support their potential application in osteoporosis-related bone repair.

Similarly, Koo *et al.*[26] conducted an in vivo evaluation of a highly porous collagen/hydroxyapatite (HA) scaffold loaded with human adipose-derived mesenchymal stromal cells (hASCs) and endothelial cells (ECs) in an osteoporotic mouse model. The scaffold was fabricated using a foam-based biofabrication strategy, generating an interconnected porous architecture with approximately 70% porosity and a mean pore size of about 112 μm. Following implantation into ovariectomized mice, micro-computed tomography (μCT), histological staining, and immunofluorescence analyses demonstrated significantly enhanced spinal fusion and bone regeneration in the hASC/EC-laden scaffold group compared with acellular or single-cell controls. Quantitative μCT analysis further confirmed increased bone volume and improved trabecular parameters in the hASC/EC-laden foam structure (CFS-2) group. In addition, immunofluorescence staining revealed elevated expression of osteogenic marker osteopontin and angiogenic markers CD-31 and α-smooth muscle actin (α-SMA), indicating enhanced bone formation and vascularization in vivo (Figure 3C–F). These findings showed that the highly porous collagen/HA scaffold loaded with hASCs and ECs significantly improved bone regeneration in an osteoporotic animal model.

However, while bioprinted animal models offer significant advantages, they also face limitations. For example, replicating the human bone microenvironment in animal models remains a challenge. Additionally, the long-term stability and integration of bioprinted constructs in vivo require further investigation (Table 2). Future research should focus on optimizing scaffold design and material properties to improve the clinical relevance of these models.

3.1.2. In vitro models

Three-dimensional bioprinting has also advanced the development of in vitro models for osteoporosis research. These models can more accurately replicate the microenvironment of osteoporotic bone, including matrix stiffness, cell–cell interactions, and biochemical signaling, making them valuable tools for drug screening and toxicity testing.

For example, Wang *et al.*[68] developed a collagen-based bioprinting ink that exhibited no cytotoxicity to hGF cells and promoted cell proliferation. The collagen-based hydrogel provided a favorable 3D microenvironment for cell encapsulation and growth. In vitro analyses further demonstrated that hGF-laden bilayer scaffolds exhibited

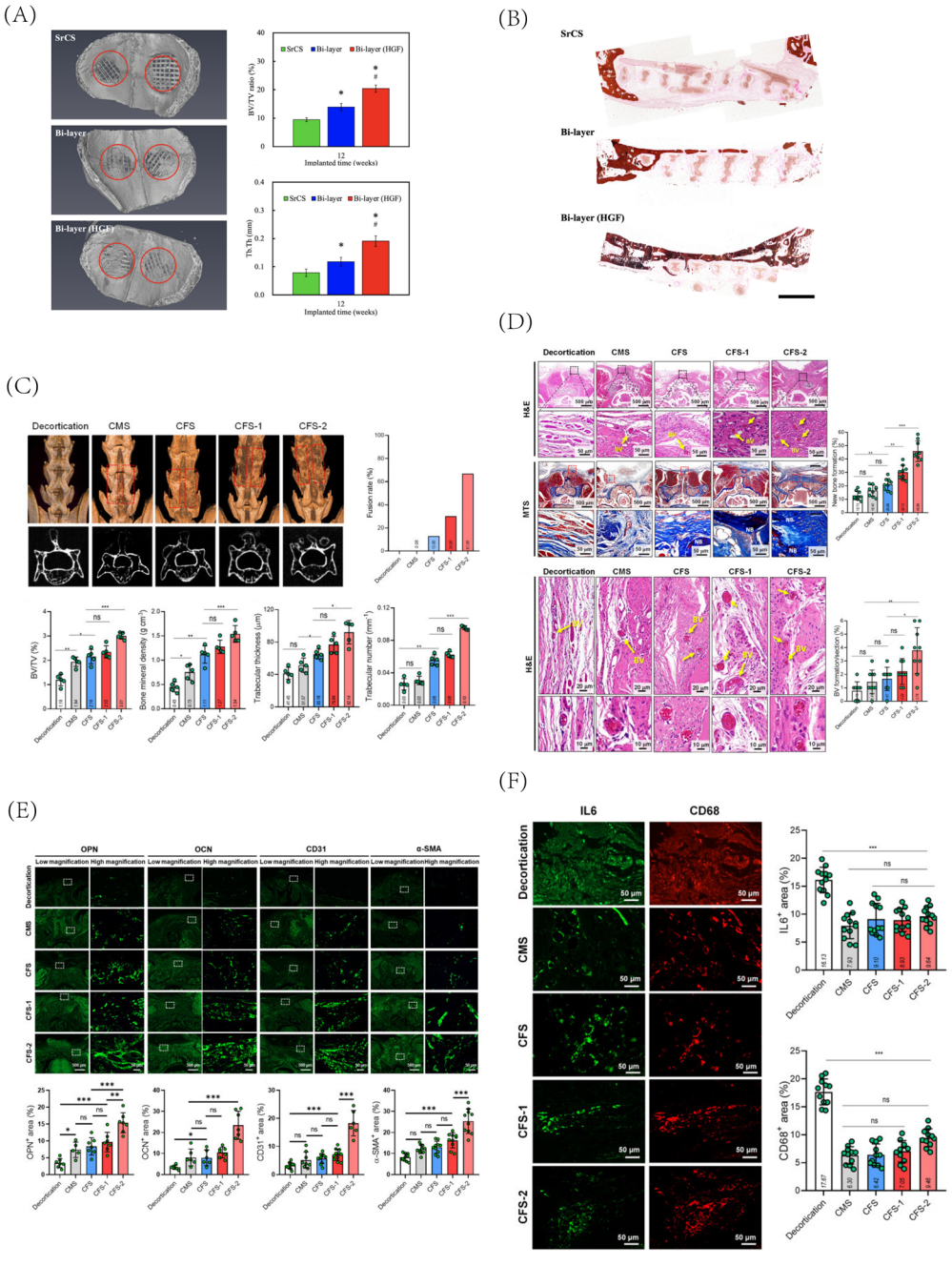

Figure 3. Bioprinted scaffold-based osteoporotic animal models demonstrating enhanced bone regeneration. (A) Representative micro-computed tomography (CT) and quantitative analyses showing enhanced new bone formation in bi-layer human gingival fibroblasts (HGF) scaffolds compared with strontium-doped calcium silicate (SrCS) and bi-layer groups after 12 weeks of implantation. (B) Von Kossa histological staining demonstrating greater mineralized bone regeneration and tissue integration in the bi-layer (HGF) group. Reprinted from Wang *et al.*[68] (C) Micro-CT and quantitative analyses six weeks post-implantation showing that adipose-derived mesenchymal stromal cell/endothelial cell (ASC/EC)-laden collagen/hydroxyapatite (HA) scaffolds significantly enhanced bone volume fraction (BV/TV) and trabecular thickness (Tb.Th) compared with decortication and other control groups. (D) Histological staining (hematoxylin and eosin and Masson's trichrome) after six weeks of implantation, demonstrating increased new bone formation and vascular infiltration within ASC/EC-laden scaffolds. (E) Immunofluorescence analysis performed six weeks post-implantation, revealing upregulated expression of osteogenic markers (osteopontin, osteocalcin) and endothelial markers (CD31, α-smooth muscle actin [α-SMA]), confirming concurrent osteogenesis and angiogenesis. (F) Immunofluorescence images stained with anti-interleukin (IL)-6 (green) and anti-CD68 (red) six weeks post-implantation, showing a reduced inflammatory response in ASC/EC-laden scaffolds; quantitative analysis demonstrated significantly lower IL-6 and CD68 immunoreactivity compared with controls. Reprinted with permission from Koo *et al.*[26] Copyright © 2022 Elsevier.

significantly increased secretion of growth factors, including fibroblast growth factor 2 (FGF-2), BMP-2, and vascular endothelial growth factor (VEGF), compared with single-layer constructs. These findings suggest that the bioprinted microenvironment may enhance the paracrine activity of hGF cells, thereby contributing to osteogenic and angiogenic processes relevant to bone regeneration.

Pragnere *et al.*[23] created a bioprinted in vitro model that accurately captured the differentiation of primary human osteoblasts into osteocytes. Rather than focusing solely on hydrogel stiffness, they systematically tuned the elastic modulus and viscoelastic relaxation behavior of gelatin/alginate/fibrinogen-based bioinks through different transglutaminase and calcium crosslinking strategies. Mechanistically, the study demonstrated that a viscoelastic hydrogel with a relatively low elastic modulus (~8 kPa) and increased microporosity provided a permissive microenvironment for osteoblast-to-osteocyte transition. The stress-relaxing matrix enabled cell-mediated remodeling, construct contraction, and enhanced cell–matrix interactions, which promoted dendrite formation, collagen I deposition, and expression of the osteocyte-specific marker phosphate-regulating endopeptidase homolog X-linked (PHEX). In contrast, stiffer and more elastic matrices restricted matrix reorganization and delayed cellular maturation. They further suggested that the combined effects of viscoelasticity, degradability, and microporosity improved nutrient diffusion and facilitated osteogenic differentiation, highlighting that matrix dynamic properties may be more critical than stiffness alone in regulating osteocyte maturation. This model provides a valuable platform for studying bone remodeling dynamics and testing pharmacological interventions relevant to osteoporosis and other bone pathologies (Figure 4).

Koo *et al.*[26] investigated the in vitro cellular responses of a highly porous collagen/HA-based foam scaffold seeded with hASCs and ECs. The scaffold exhibited a highly interconnected porous architecture, providing a microenvironment that supported enhanced cell

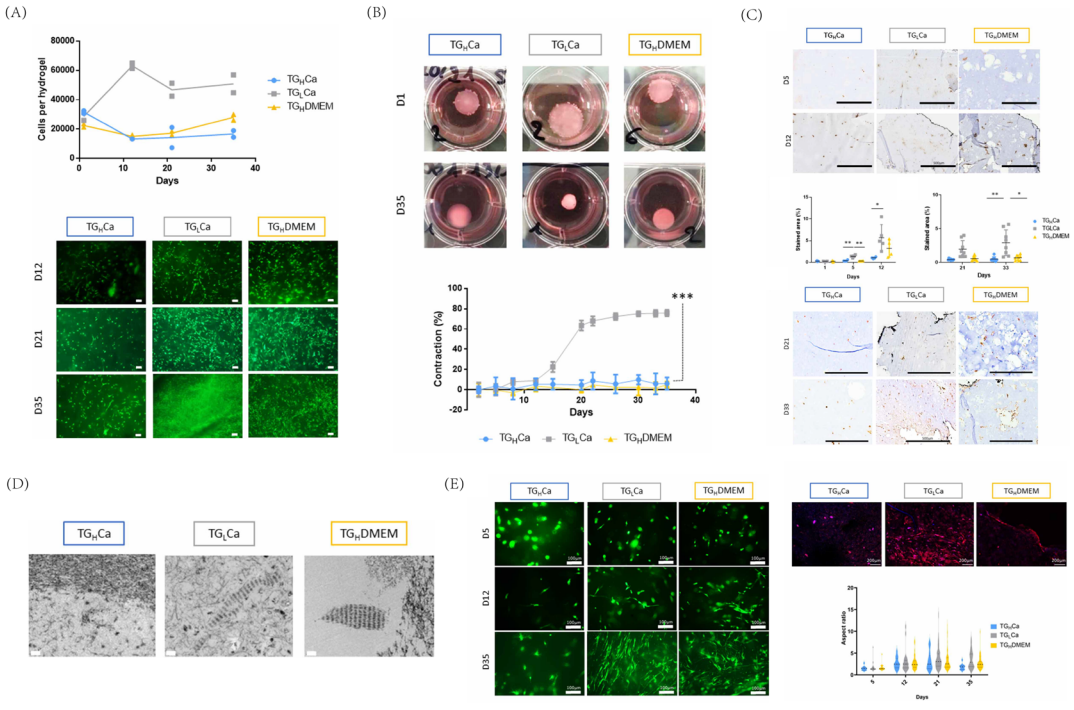

Figure 4. Bioprinted in vitro model promoting osteoblast-to-osteocyte differentiation and extracellular matrix maturation. (A) Cell proliferation kinetics and fluorescence imaging demonstrating high viability and sustained proliferation of primary osteoblasts cultured within TG_HCa hydrogels for 35 days. (B) Macroscopic and quantitative analyses showing enhanced tissue contraction and compaction in TG_HCa constructs compared with TG_LCa and TG_HDMEM groups. (C) Immunohistochemical staining illustrating time-dependent secretion of fibronectin and collagen I, indicating active extracellular matrix remodeling and enhanced biosynthetic activity in TG_LCa constructs. (D) Transmission electron microscopy (TEM) images after 35 days showing organized collagen fibrils and early mineralization in TG_HCa hydrogels. (E) Fluorescence and confocal microscopy demonstrating morphological evolution and cytoskeletal alignment of osteoblasts, reflecting progressive differentiation toward osteocytes. Reprinted with permission from Pragnere *et al.*[23]

proliferation and cell–cell interactions compared with conventional constructs. In vitro results demonstrated that the hASC/EC-laden foam scaffold promoted higher expression of osteogenic markers, including alkaline phosphatase (ALP), runt-related transcription factor 2 (RUNX2), osteocalcin, and osteopontin, as well as angiogenic markers such as von Willebrand factor (VWF), platelet endothelial cell adhesion molecule-1 (PECAM1/CD31), and α-SMA, compared with acellular scaffolds. Gene expression analyses further indicated the involvement of WNT/β-catenin and phosphoinositide 3-kinase (PI3K) signaling pathway-related genes in the observed cellular responses under co-culture conditions. In addition, increased expression of paracrine factors, including VEGF, FGF-2, transforming growth factor-beta 1 (TGF-β1), and BMP-2, was observed in the hASC/EC co-culture system. Overall, these in vitro findings suggest that the highly porous collagen/HA scaffold is associated with enhanced osteogenic and angiogenic-related cellular activity, and that co-culture of hASCs and ECs is associated with improved cellular responses within a 3D porous microenvironment.

Despite these advancements, challenges remain in replicating the full complexity of human bone physiology in vitro. For example, the dynamic interplay between osteoblasts, osteoclasts, and other cell types in the bone microenvironment is difficult to fully capture in bioprinted models. Future research should focus on developing more sophisticated models that incorporate multiple cell types and mechanical stimuli to better mimic in vivo conditions (Table 2).

3.2. Bone substitutes

Bone substitutes, particularly bioprinted scaffolds, have been extensively investigated for bone regeneration and skeletal defect repair. Bioprinting offers unprecedented precision and customization in scaffold design, overcoming the limitations of traditional fabrication methods, which often struggle to achieve precise control over pore architecture, mechanical compatibility, and biocompatibility. Although these features make bioprinted scaffolds attractive candidates for osteoporotic bone repair, most current studies have been conducted in critical-sized defect models rather than in osteoporosis-specific clinical settings. Therefore, caution is warranted when extrapolating outcomes from conventional bone defect models to osteoporotic bone, as osteoporosis is characterized by impaired osteogenesis, excessive bone resorption, altered immune responses, and compromised vascularization, all of which may substantially affect scaffold performance and tissue integration.

3.2.1. Scaffold design

The design of bioprinted scaffolds is critical for their success in bone regeneration. Scaffolds must replicate the structural features of natural bone, including porosity, pore size, and mechanical properties, to support cell infiltration, nutrient exchange, and new bone formation.[71] For example, pores larger than 300 μm are typically preferred to facilitate angiogenesis, while pores ranging from 200–500 μm offer optimal conditions for tissue infiltration and vascularization.[59,72,73] Meanwhile, Woodard *et al.*[74] investigated HA bone scaffolds with multiscale porosity, focusing on their surface morphology and osteoconductivity, providing experimental evidence for optimizing pore design (Figure 5).

Biodegradability is another key consideration in scaffold design. Scaffolds should degrade at a rate that matches the pace of new bone formation to provide continuous mechanical support without triggering immune responses or inflammation.[75] Future research should focus on developing scaffolds with tunable degradation rates and improved mechanical properties.

3.2.2. Material selection

The selection of materials for bioprinted scaffolds is crucial for their performance in bone regeneration. Natural polymers, such as collagen and chitosan, offer excellent biocompatibility and osteoconductivity but often lack the mechanical strength required for load-bearing applications. Synthetic polymers, such as polylactic acid and polyglycolic acid, provide predictable mechanical properties and degradation rates but may exhibit lower biocompatibility.[76]

Ceramic materials, such as HA and tricalcium phosphate (TCP), are widely used in bone tissue engineering due to their osteoconductivity and high compressive strength.[77] However, their inherent brittleness limits their application in load-bearing defects. To address this, researchers have explored composite materials that combine the advantages of ceramics with the flexibility of polymers. For example, doping β-TCP scaffolds with ZnO and SiO_2 has been shown to improve mechanical performance.[78]

Metal alloys, such as titanium and magnesium, are also used in bone scaffolds due to their excellent strength and biocompatibility.[79] However, their high cost and potential for corrosion limit their widespread use. Future research should focus on developing cost-effective and biocompatible composite materials that meet the mechanical and biological requirements for bone regeneration.

Table 2. Applications of bioprinting in osteoporosis-related research

Bioprinting model	Bioprinting technology	Model construction methods	Key findings
Heart-inspired hollow hydrogel-based scaffolds (HHSs)[64]	Extrusion bioprinting with mechanical assistance	Ovariectomy-induced model in SD rats	(i) HHSs mechanically responded to cell loading within 4 s, yielding a 13-fold increase in cell number compared with static conditions. (ii) Cell-laden HHSs showed enhanced regenerative capacity in repairing critical-sized segmental and osteoporotic bone defects in vivo.
Hybrid suture anchor (HSA) with wing mechanism[65]	Titanium 3D Printing (laser powder bed fusion [LPBF])	(i) Artificial bone models simulating severe osteoporotic bone conditions (ii) Shoulders of the Yorkshire pig	(i) Winged HSA outperformed CSA in osteoporotic bone strength. (ii) Both had comparable bone ingrowth.
Oblique lumbar interbody fusion (OLIF) cage with embedded fixation screws[66]	Titanium 3D printing (selective laser melting [SLM])	Finite element modeling based on computed tomography (CT) statistical images	(i) The OLIF cage demonstrated superior stability, reduced endplate stress, and exceeded FDA fatigue standards. (ii) Anatomical morphology and porous structure design enhanced bone ingrowth and reduced stress shielding effects.
Nanocellulose–alginate (NC–Alg) scaffolds reinforced with hydroxyapatite (HAP) and graphene oxide (GO)[67]	Extrusion-based 3D bioprinting	Mouse D1 mesenchymal stem cells	(i) Both HAP- and GO-containing scaffolds showed good biocompatibility. (ii) GO significantly promoted osteogenic gene expression. (iii) GO scaffolds performed better in terms of mechanical properties, osteogenic differentiation, and cellular function and were suitable candidates for osteoporosis-related bone defect repair.
Biodegradable Mg alloy scaffolds with ceramic coating[27]	3D printing (SLM)	(i) Ovariectomy-induced model in SD rats (ii) rBMSCs and BMMs	(i) ZA-coated Mg scaffolds slowed degradation, boosted osteogenesis, and inhibited osteoclast activity. (ii) The Mg/Sc/ZA scaffold group promoted bone repair in vivo 9 weeks after implantation.
Highly porous collagen/hydroxyapatite (HA) scaffolds with hASCs and HUVECs[26]	3D bioprinting using whipped bioink and polycaprolactone (PCL) mold	Ovariectomized mouse model	Highly porous scaffolds enhanced osteogenic/angiogenic activity via cell–cell crosstalk, with ovariectomized mice showing improved spinal fusion.
Bi-layer scaffold model: Cell-laden collagen/Strontium-doped calcium silicate ($SrC^{S)}$[68]	3D printing	Ovariectomy combined with methylprednisolone injection in New Zealand White rabbits	(i) SrCS surface induced mineralization (14 days) and sustained ion release (6 months), elevating growth factors and osteogenic activity. (ii) Histology showed new bone growth in the core area of the bilayer scaffold.
PLA–HA nanocomposite femur bone scaffold with varying ceramic nanoparticle concentrations[69]	3D printing (fused deposition modeling [FDM])	Adjustment of the mechanical properties of materials to simulate the properties of osteoporotic bone combined with finite element analysis	(i) The scaffold exhibited stable mechanical behavior under static loading, with a peak stress of 56–58 MPa at 100 N. (ii) 80–85% porous PLA–HA (25% HA) scaffolds showed potential for femoral bone applications with improved mechanical properties.

(*Cont'd...*)

Table 2. (*Continued*)

Bioprinting model	Bioprinting technology	Model construction methods	Key findings
Posterior lumbar interbody fusion cage with anatomical curved surface and internal lattice design for osteoporosis patients[70]	3D printing (metal 3D printing)	Construction of a finite element model conforming to osteoporotic endplate morphology based on lumbar spine CT images	(i) Metal-printed CS-type fusion device using titanium alloy (Ti6Al4V) with an internal lattice structure that promotes bone ingrowth. (ii) CS-type cage (gyroid-lattice structure, 0.25 mm) reduced endplate stress and met ISO 23089 standards.
3D hydrogel environment[23]	Micro-extrusion bioprinting using gelatin, alginate, and fibrinogen	In vitro bone model	Hydrogel with an elastic modulus of 8 kPa and viscoelastic properties promoted osteoblast-to-osteocyte differentiation.

Abbreviations: BMM: Bone marrow-derived macrophage; CS: Curved surface; CSA: Commercial solid anchor; FDA: Food and Drug Administration; hASC: Human adipose-derived mesenchymal stromal cell; HUVEC: Human umbilical vein endothelial cell; rBMSC: Rat bone marrow mesenchymal stem cell; ZA: Zoledronic acid.

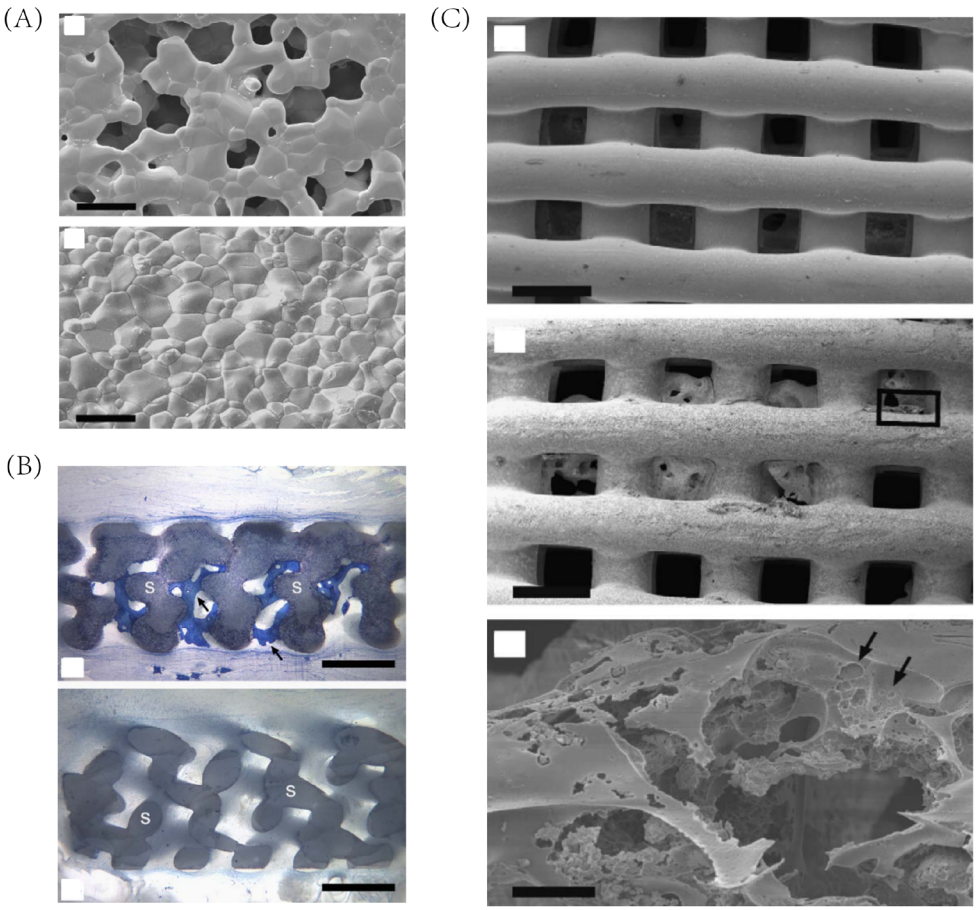

Figure 5. Surface morphology and osteoconductivity of hydroxyapatite scaffolds with multiscale porosity. (A) Scanning electron microscopy (SEM) micrographs showing the surface of microporous (MP) and non-microporous (NMP) scaffolds. Micropores ranged from 2 to 8 μm in diameter. (B) Toluidine blue-stained sections of poly(methyl methacrylate) (PMMA)-embedded scaffolds. MP scaffolds display royal blue-stained bone (arrows) within macropores, whereas NMP scaffolds show no bone formation. (C) SEM images of implanted scaffolds after pyrolysis at 427 °C to remove soft tissue. The upper image shows that NMP scaffolds did not contain any bone within the macropores. The middle and lower images demonstrate that bone formed within MP scaffolds exhibits pores of 10–30 μm in diameter and surface pits of 2–8 μm (arrows), suggesting active bone ingrowth and remodeling. Reprinted with permission from Woodard *et al.*[74] Copyright © 2007 Elsevier.

3.2.3. Functionalization

Functionalized scaffolds that incorporate bioactive molecules, cells, or growth factors represent a promising direction in bone substitute design. For example, the incorporation of growth factors such as BMP-2 and VEGF can enhance cell signaling, promote angiogenesis, and accelerate bone healing.[78,80] However, the use of growth factors may be associated with adverse effects, such as ectopic ossification, underscoring the need for more precise delivery systems.[81]

The bioprinting of mesenchymal stem cells (MSCs) and osteoprogenitor cells into scaffolds has also shown promise for accelerating bone regeneration.[82] MSCs, in particular, are a valuable cell source due to their strong osteogenic differentiation potential and immunomodulatory properties.[76,83] However, challenges remain in maintaining cell viability and functionality during the printing process.

Vascularization is another critical challenge in scaffold design, particularly for large-scale bone defects. Bioprinting offers the potential to create microvascular networks within scaffolds, improving nutrient supply and oxygen delivery to support new bone growth. The incorporation of angiogenic factors, such as VEGF, can further enhance vascularization and bone regeneration.[72,84]

3.2.4. Osteoporosis-specific functionalization strategies

Osteoporosis is characterized not only by reduced bone mass but also by a pathological microenvironment involving excessive oxidative stress, chronic low-grade inflammation, enhanced osteoclast activity, and impaired osteogenic differentiation. Therefore, scaffold design for osteoporosis should extend beyond structural support and actively modulate the local biological environment.[85,86]

Recent studies have explored antioxidant functionalization strategies, including the incorporation of cerium oxide nanoparticles, polydopamine coatings, and bioactive ions such as selenium and strontium, which can reduce reactive oxygen species accumulation and modulate cell survival and osteogenic-related activity.[87-90] In addition, osteoimmunomodulatory biomaterials capable of modulating macrophage polarization have shown considerable promise for restoring bone homeostasis and promoting bone regeneration.[91,92]

Furthermore, controlled delivery systems targeting excessive osteoclastogenesis, including receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors, anti-inflammatory cytokines, and osteogenic growth factors, may collectively regulate bone resorption and formation.[93,94] These approaches are particularly relevant in osteoporosis, where impaired bone remodeling rather than simple bone loss is the primary pathological feature.

4. Current challenges in bioprinting for osteoporosis

Despite significant advancements, bioprinting technologies continue to face several fundamental challenges in printing precision, scaffold functionalization, bioink properties, and scalability. In addition to the universal limitations of bioprinting, osteoporosis introduces disease-specific biological barriers, particularly the impaired regenerative capacity of the osteoporotic bone microenvironment, including reduced cellular activity, dysregulated bone remodeling, and compromised osseointegration. These barriers not only hinder clinical translation but also highlight limitations of current technological approaches in addressing the complex pathological features of osteoporosis. A critical analysis of these obstacles is necessary to guide future research and development in the field.

4.1. Printing precision and tissue complexity

Bone tissue possesses a highly hierarchical architecture ranging from nanoscale collagen fibrils to trabecular and cortical bone structures. Replicating these multiscale features remains a major challenge for current bioprinting technologies.

A major engineering challenge is the trade-off between printing resolution and fabrication throughput.[95,96] Technologies capable of producing microscale features, such as laser-assisted bioprinting, generally require slower processing speeds and are difficult to scale for clinically relevant constructs. Conversely, extrusion-based systems enable rapid fabrication of large scaffolds but often sacrifice microscale accuracy due to nozzle diameter limitations and material spreading after deposition. This trade-off is particularly problematic in osteoporosis applications, where both large defect reconstruction and faithful recreation of bone microarchitecture are required in a microenvironment characterized by reduced osteogenic responsiveness and impaired cellular regeneration capacity.

Another challenge arises from the heterogeneous composition of native bone. Bone contains mineralized inorganic phases, organic extracellular matrix components, vascular structures, and multiple cell populations. Consequently, successful fabrication requires coordinated deposition of materials with substantially different rheological properties, crosslinking kinetics, and degradation behaviors.[97-99] Mismatches among these parameters can lead to phase separation, poor interfacial bonding, structural instability, and uneven cellular distribution.

Importantly, in osteoporotic bone regeneration contexts, the reduced activity of osteoblasts and MSCs, together with increased osteoclast-mediated resorption, further complicates the integration of printed constructs, as the biological feedback required for tissue maturation is significantly impaired.

Future solutions may rely on hybrid and multi-material bioprinting systems that integrate high-resolution patterning with high-throughput manufacturing while enabling spatial control over multiple biomaterial phases.

4.2. Limitations of bioinks

Bioinks play a crucial role in bioprinting by providing a 3D microenvironment that supports cell attachment, proliferation, and differentiation.[100,101] However, the fabrication process itself introduces multiple physical and biochemical stresses, including high shear forces during extrusion, temperature fluctuations, and post-processing crosslinking steps, all of which can negatively affect cell viability and thereby limit the regenerative performance of printed constructs.

In osteoporosis applications, an ideal bioink is required to simultaneously achieve mechanical robustness and controlled biodegradability to match the dynamic process of bone remodeling. However, balancing these properties remains fundamentally challenging.[102] Bioinks with high mechanical strength often require increased polymer concentration or higher crosslinking density, which can compromise pore connectivity, reduce nutrient diffusion, and restrict cell spreading and migration. In contrast, formulations optimized for biological performance frequently exhibit insufficient mechanical stability and rapid structural deformation after printing, leading to poor shape fidelity and limited load-bearing capacity.

From a materials-science perspective, this limitation arises from the intrinsic coupling between bioink rheology, crosslinking network architecture, and cellular mechanotransduction. Increasing viscosity to improve printability and mechanical stability inevitably elevates extrusion pressure, thereby exposing encapsulated cells to shear stress that can impair viability and cellular function. Conversely, reducing viscosity to enhance cell survival often compromises structural integrity after deposition, highlighting a fundamental trade-off between cell viability and biological performance.

To address this issue, emerging strategies such as dynamic crosslinking systems, shear-thinning hydrogels, nanocomposite bioinks, and stimulus-responsive materials have been developed to partially decouple these competing requirements. While these approaches show promising improvements in balancing mechanics and bioactivity, their long-term stability, reproducibility, and scalability remain insufficiently validated for clinical translation.

4.3. Scaffold functionalization

Functionalized scaffolds, designed to enhance osteogenesis and accelerate bone repair, represent a promising direction in osteoporosis treatment. Through physical and chemical modifications, scaffolds can be engineered to release bioactive molecules, promote cell signaling, and enhance mechanical properties.[103] For example, the incorporation of BMP-2 and HA nanoparticles has been shown to enhance osteogenic differentiation and mineralization.[104-106] However, challenges remain in ensuring the controlled and sustained release of these bioactive agents.

Recent research has explored smart biomaterials capable of responding to external stimuli, such as mechanical forces and electrical fields, to modulate cellular behavior dynamically.[107] For example, conductive nanocomposites incorporating graphene or carbon nanotubes have demonstrated potential in enhancing osteoblast differentiation.[108,109] However, a deeper understanding of their long-term biocompatibility, degradation behavior, and potential immunogenic responses is necessary before clinical translation.

In osteoporosis, additional challenges arise from the inflammatory and oxidative microenvironment, which may further suppress osteogenic differentiation and reduce the efficacy of bioactive signaling cues delivered by functionalized scaffolds.

4.4. Challenges in large-scale production

Despite the promising capabilities of bioprinting, scalability remains a critical obstacle to its widespread translational application in bone tissue engineering and preclinical research systems. One major limitation is the reduced precision and reproducibility of bioprinting systems over extended periods of operation. The stability and consistency of bioprinting parameters, including nozzle calibration, extrusion rate, and layer fidelity, require continuous optimization to meet standardized research and quality-control requirements.

Additionally, the economic feasibility of bioprinting remains a concern.[110] The high costs associated with specialized bioprinters, customized bioinks, and cell culture systems create financial barriers to large-scale implementation. Furthermore, the lack of standardized protocols across different research groups and institutions complicates efforts to streamline production and regulatory approval processes. Future advancements must focus on cost-effective bioprinting strategies, such as modular and

automated systems, to enhance reproducibility and reduce production costs.[12]

4.5. Ethical and regulatory challenges

The ethical and regulatory landscape surrounding bioprinting remains complex, particularly in the context of stem cell-based therapies and artificial bone transplantation.[111] The use of stem cells, particularly embryonic-derived and genetically modified cells, raises ethical concerns related to donor consent, potential off-target effects, and long-term safety.[112] Additionally, the commercialization of unverified bioprinted products may pose risks to patient safety, highlighting the necessity for stringent validation procedures.

From a regulatory perspective, inconsistencies in classification frameworks across countries pose challenges for global implementation.[111] The approval process for bioprinted medical products varies significantly, with some regions requiring extensive preclinical and clinical validation, while others lack clear guidelines for assessing safety and efficacy. This regulatory ambiguity underscores the need for international standardization and collaborative efforts among researchers, policymakers, and regulatory agencies to establish comprehensive guidelines that keep pace with technological advancements.

5. Future directions for bioprinting in osteoporosis

Future research must address the existing limitations of bioprinting technology. Advancements in printing precision, scaffold functionality, disease-specific model development, and translational research will be essential for determining the future role of bioprinting in osteoporosis research and potential clinical applications.

5.1. Technological advancements

The future of bioprinting in osteoporosis relies heavily on significant technological advancements. Enhancing printing precision is essential to replicating the complex microstructures of bone tissue. Current bioprinting techniques still require improvement in reproducing the nanoscale features of trabecular bone, which are essential for mimicking the mechanical and biological properties of native bone. Innovations in high-resolution printing methods, such as two-photon polymerization and advanced laser-assisted bioprinting, hold the potential to substantially increase precision, enabling the creation of more anatomically accurate bone scaffolds.[113,114]

Material selection remains a core focus for future research. Although bioinks are increasingly investigated for orthopedic applications, the incorporation of smart materials (such as stimuli-responsive bioinks) promises greater versatility in bone tissue construction.[115] These materials can dynamically adapt to the in vivo environment, incorporating growth factors or other bioactive molecules to more effectively stimulate tissue regeneration. Particularly, future studies should focus on the development of osteoporosis-specific smart bioinks capable of responding to pathological cues within the osteoporotic microenvironment, such as oxidative stress, inflammatory mediators, pH fluctuations, and mechanical loading. These bioinks could enable on-demand release of osteogenic and angiogenic factors, thereby promoting bone regeneration while simultaneously modulating excessive bone resorption. Another important priority is the integration of bioactive ions (e.g., strontium, magnesium, and silicon) and osteoimmunomodulatory molecules into bioink formulations.[116-118] Such strategies may help restore the imbalance between osteoblast and osteoclast activity, which is a hallmark of osteoporosis.

Moreover, the development of faster and more efficient printing technologies will help break existing bottlenecks. Emerging techniques such as continuous liquid interface production (CLIP) and volumetric bioprinting are expected to significantly reduce production times without compromising structural accuracy.[119,120]

Future efforts should also prioritize multi-material and multimodal bioprinting platforms capable of simultaneously fabricating mineralized matrices, vascular components, and cell-laden regions. Such systems may better reproduce the hierarchical architecture of osteoporotic bone and improve functional tissue integration. A key functional requirement of these advanced platforms is the ability to achieve effective vascularization, which remains critical for the successful regeneration of large osteoporotic bone defects. Insufficient vascularization is still one of the primary causes of graft failure following implantation. To address this challenge, strategies involving the co-printing of ECs, MSCs, and angiogenic growth factors, as well as the fabrication of prevascularized microchannel networks, may enhance nutrient transport, promote vascular network formation, improve tissue integration, and increase long-term implant survival. Such approaches are particularly important in osteoporosis, where impaired angiogenesis and compromised bone regeneration frequently limit healing outcomes.

Bioprinters may also integrate artificial intelligence (AI)-powered real-time monitoring and feedback systems to ensure consistent quality throughout the printing process.

5.2. Drug screening and personalized therapy

Bioprinting has the potential to revolutionize drug screening in osteoporosis research. By creating bioprinted bone models, disease-specific microenvironments can be replicated, allowing researchers to test the efficacy and safety of new drugs under conditions that closely mirror human physiology.[121] This approach can reduce reliance on animal models and improve the predictive accuracy of human drug responses.

In addition, future bioprinting advancements could foster the development of highly personalized osteoporosis models. Using patient-derived cells, researchers could create bioprinted bone tissues that reflect the genetic and pathological characteristics of individual patients. These models would enable the design of personalized treatment strategies, optimizing drug dosages and combinations to maximize therapeutic outcomes.

When combined with AI-assisted drug screening platforms, these patient-specific models may further accelerate the identification of novel anabolic, anti-resorptive, and osteoimmunomodulatory agents, while improving the prediction of therapeutic efficacy and potential adverse effects.

5.3. Interdisciplinary collaboration as a driver of progress

The progress of bioprinting in osteoporosis will require close collaboration across multiple disciplines. Materials science will play a crucial role in developing next-generation bioinks and scaffold materials. Researchers in this field can design materials with tunable properties, enabling better control over degradation rates, mechanical strength, and bioactivity.

Cell biology is also indispensable, as understanding the behavior of osteoblasts, osteoclasts, and other cell types in the bioprinting environment is essential for creating functional bone tissue. In-depth studies of cell signaling pathways and extracellular matrix interactions will inform the optimization of scaffold designs and bioink formulations.

Clinical medicine is vital for bridging the gap between laboratory research and patient care. Clinicians can provide invaluable insights into the practical requirements of bioprinted structures, such as ease of implantation and integration with host tissue. Collaboration with surgeons and medical device specialists will ensure that bioprinted solutions meet clinical standards.

Artificial intelligence and computational modeling will further accelerate progress. AI can optimize printing parameters, predict cellular behavior in bioprinted structures, and simulate scaffold performance under physiological conditions.

Future interdisciplinary efforts should also focus on establishing standardized evaluation systems for bioprinted osteoporosis models, including benchmarks for osteogenic activity, vascularization efficiency, scaffold integration, and long-term functional outcomes. Such standards would facilitate comparison across studies and accelerate clinical translation.

5.4. Translating bioprinting from bench to bedside

Translating bioprinting technologies from laboratory research to clinical applications offers significant potential for long-term future osteoporosis management, although current applications remain largely confined to preclinical and experimental stages. A critical area of focus will be the scaling up of bioprinting. While laboratory-scale production is currently feasible, future research must focus on developing high-throughput, high-quality, and reproducible bioprinting systems that can meet the needs of potential future clinical translation.

Equally important is the development of regulatory frameworks for bioprinted products. While existing regulatory systems continue to evolve, future research should focus on establishing clear standards for safety, efficacy, and quality control to facilitate clinical translation. Collaboration among regulatory agencies, academia, and industry will be crucial in advancing standardized protocols and testing methods.

Cost reduction is also a key focus for future research.[122] By improving manufacturing processes and developing more cost-effective materials, the costs associated with bioprinting are expected to decrease. This will help increase the accessibility of the technology within healthcare systems and facilitate its widespread application. Additionally, securing financial support for translational research is vital, and public-private partnerships and government funding programs can play a critical role in advancing these technologies toward clinical readiness in the long term.

Finally, clinical trial design and implementation will be instrumental in demonstrating the safety and efficacy of bioprinted solutions. Future research should prioritize establishing interdisciplinary bioprinting research centers to accelerate the translation of laboratory findings into patient care, ensuring the safety and clinical effectiveness of bioprinted technologies.

6. Conclusion

Bioprinting has emerged as a promising platform for osteoporosis research and bone tissue engineering, offering new possibilities for constructing advanced bone models and exploring experimental regenerative strategies. By integrating advanced biomaterials, 3D printing techniques, and stem cell-based approaches, bioprinting has the potential to address key limitations of conventional bone grafts and prosthetic implants. Specifically, the ability to fabricate patient-specific bone scaffolds with tunable mechanical properties, controlled porosity, and enhanced bioactivity may improve preclinical outcomes and enhance functional integration with host tissues under experimental conditions.

However, despite its considerable potential, bioprinting for osteoporosis treatment remains at an early stage, with substantial challenges limiting its clinical applicability. Printing precision continues to be a major hurdle, as current techniques struggle to replicate the complex hierarchical structure of natural bone. Moreover, the bioinks used in bioprinting still face critical limitations in terms of mechanical strength, degradation kinetics, and the ability to sustain cellular viability and differentiation. Functionalization of scaffolds with bioactive molecules has shown promise in enhancing osteogenic potential, yet challenges such as inefficient delivery and uncontrolled release remain unresolved.

Scalability and cost-effectiveness further hinder the transition of bioprinting from laboratory research to broader translational and preclinical applications. The high cost of specialized printing equipment, bioinks, and cell culture techniques, coupled with the time-intensive nature of fabrication, raises concerns about feasibility for large-scale or clinically relevant production. Additionally, regulatory and ethical challenges—particularly those related to the use of stem cells, the classification of bioprinted products, and the standardization of manufacturing protocols—complicate the pathway to clinical approval and commercialization.

Future research must focus on addressing these technological and translational barriers. Enhancing printing precision through advanced bioprinting techniques, optimizing bioink formulations to better mimic native bone properties, and improving scaffold functionalization strategies are critical steps toward future translational and experimental validation. The integration of AI and computational modeling could further refine bioprinting processes by enabling real-time monitoring, predictive modeling, and optimization of scaffold designs.

Interdisciplinary collaboration will be essential to advancing bioprinting for osteoporosis. Close cooperation between materials scientists, biomedical engineers, cell biologists, and clinicians is crucial to developing models and technologies relevant to osteoporosis-specific pathological environments. Furthermore, establishing standardized regulatory frameworks and improving cost-efficiency will be pivotal in facilitating the stepwise translation of bioprinting technologies toward clinical feasibility.

Ultimately, although bioprinting holds considerable promise for advancing osteoporosis research and related therapeutic strategies, its widespread adoption will depend on overcoming key scientific, technical, and regulatory barriers. Continued progress in biomaterials, biofabrication technologies, and disease-specific modeling is expected to help address these challenges while expanding their utility in both mechanistic studies of osteoporosis pathophysiology and the development of regenerative approaches for osteoporotic bone repair.

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Conflict of interest

The authors declare no conflicts of interest.

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