Biomaterials Translational

Advances in bone defect repair using bio-3D printing technology: Innovations and challenges in mechanically assisted post-bioprinting strategies

Lingbin Che, Juhan Li, and Dianwen Song*

Department of Orthopedics, Shanghai General Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

***Corresponding author:**
Dianwen Song,
dwsong@sjtu.edu.cn

How to cite this article:
Che L, Li J, Song D. Advances in bone defect repair using bio-3D printing technology: Innovations and challenges in mechanically assisted post-bioprinting strategies. *Biomater Transl.* 2026, 7(1), 170-173.

doi: 10.12336/bmt.25.00012

The repair of bone defects remains a core challenge in tissue engineering and regenerative medicine, particularly for large segmental and osteoporotic defects. These conditions exhibit limited self-healing capacity, and conventional treatments, such as autologous bone grafting, are often hindered by donor site scarcity and associated complications, thereby necessitating innovative solutions.[1] In this context, bio-three-dimensional (3D) printing technology, leveraging its ability to precisely fabricate complex 3D structures, is regarded as a highly promising strategy for bone defect repair.[2] It demonstrates unique advantages, especially in manufacturing personalized scaffolds that mimic the structure of native bone tissue.[3] However, despite the significant attention garnered by bio-3D printing for its capability to accurately construct cell-laden 3D structures, its application in complex bone repair is limited by several factors, including low cell viability during the printing process, insufficient nutrient supply to deeper tissue regions within the scaffold, and inadequate mechanical properties of the construct.[4] Traditional scaffold designs often rely on passive cell migration or stimulation by exogenous growth factors, making it difficult to achieve efficient and uniform cell distribution. While emerging printing strategies offer improvements, achieving a balance between maintaining cell viability and ensuring adequate scaffold functionality remains a significant challenge.

The mechanistic challenges in bone regeneration therapy primarily revolve around the synergistic optimization of maintaining cell viability, simulating the tissue microenvironment, and providing adequate mechanical support.[5] First, bone repair relies on the proliferation and differentiation of osteoblasts and mesenchymal stem cells (MSCs). However, within traditional scaffolds, cells often undergo apoptosis due to hypoxia or nutrient deficiency, particularly in large-scale defects, where inefficient substance exchange in deeper tissue regions limits regenerative efficacy. Second, native bone tissue possesses a complex vascular network and a microenvironment characterized by multi-cellular synergy.[6] Present technologies struggle to replicate this dynamic equilibrium within 3D scaffolds, thereby restricting neovascularization and trabecular bone remodeling. Furthermore, the mechanical environment at the site of the bone defect is crucial for regulating cell behavior.[7] Yet, many bioprinted scaffolds, while providing sufficient mechanical support, often compromise flexibility or biocompatibility, making them ill-suited for adapting to the dynamic stress conditions found in pathological states such as diabetes mellitus.[8] Consequently, the future goal for 3D printing in bone repair is to construct bioactive scaffolds capable of mimicking the complex structure and function of native bone to achieve complete functional regeneration.[9] Nevertheless, this endeavor still faces significant challenges, including how to accurately replicate the *in vivo* microenvironment, promote rapid vascularization, and optimize the coordination between mechanical properties and biodegradation rates.

A study published in *Nature Communications* by Yang *et al.*[10] introduces an innovative mechanical-assisted post-bioprinting strategy. This approach utilizes hollow hydrogel scaffolds (HHSs) inspired by cardiac design to achieve highly efficient cell loading within a mere 4 s through mechanical response. This method not only significantly increases the quantity of loaded cells – a 13-fold enhancement compared to static conditions – but also facilitates the precise zonal loading of multiple cell types. Its potential for repairing complex bone defects has been validated through *in vivo* experiments (**Figure 1**). The research employed a hybrid ink, combining gelatin methacryloyl (GelMA), nanoclay (Laponite), and N-acryloyl glycinamide

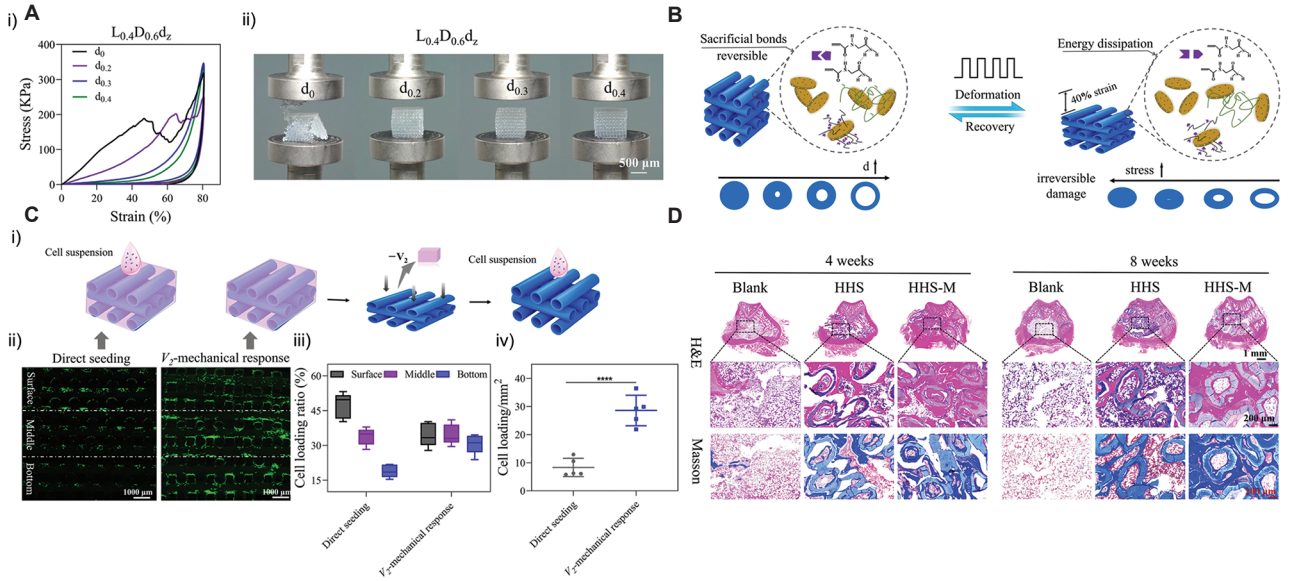

Figure 1. Material properties and biological evaluation of hollow hydrogel scaffolds (HHSs). (A) Compression test of HHSs: (i) Compression-recovery curve with 80% strain of HHSs; (ii) Photograph of HHSs after removal of compression at 80% strain. (B) Illustration of the mechanism of HHS' resistance to fatigue. (C) Cell seeding, distribution, and histological analysis of bio-3D printed scaffolds. (i) Schematic diagram, (ii) fluorescence images, (iii) quantitative analysis of cell distribution, and (iv) cell numbers by direct seeding and V2-mechanical response, respectively. $n = 5$, ****$p<0.0001$. (D) Hematoxylin and eosin staining, as well as Masson's trichrome staining at weeks 4 and 8. Each experiment was repeated four times independently with similar results. Magnified images are in the dotted boxes. Reprinted from Yang *et al.*[10] Copyright © 2024 Authors.

(NAGA), fabricated through a one-step coaxial printing technique to produce HHSs with excellent mechanical properties. This offers an efficient and broadly applicable solution for bone tissue engineering. The introduction of this strategy not only transcends the limitations of traditional bioprinting but also paves the way for new possibilities in cell-mediated regenerative therapies, meriting further exploration of its technical specifics and application potential.

The research team employed coaxial printing technology to combine GelMA, Laponite, and NAGA into a photocurable hybrid ink, thereby fabricating scaffolds with hollow lumens and porous wall structures. By integrating the high shear-thinning properties of Laponite with the tunable biocompatibility of GelMA, the HHSs formed a 3D structure that balances flexibility with mechanical support. This design enables dynamic loading, where periodic external mechanical compression and release, leveraging the scaffold's elasticity and porous architecture, drive the rapid flow and uniform distribution of cell suspensions within the scaffold, mimicking the rhythm of cardiac pulsation. Furthermore, by adjusting the mechanical rhythm and the zonal design of the scaffold, the study achieved precise spatial distribution of multiple cell types, laying the foundation for mimicking the complex microenvironment of bone tissue. *In vivo* experiments further validated the efficacy of this strategy. In a rat segmental bone defect model, the bone regeneration volume of HHSs loaded with stem cells reached 2.5 times that of the control group after 8 weeks, with significantly improved bone density. The success of this technology relies on the synergistic effects of material selection, such as the shear-thinning properties provided by Laponite and the enhanced mechanical toughness from NAGA, ensuring that the scaffold remains both stable and flexible under dynamic loading conditions.

In the study, the team evaluated the performance of HHSs in an osteoporotic rat model. The results demonstrated that scaffolds loaded with MSCs significantly enhanced new bone formation over a 12-week period. Micro-computed tomography (CT) analysis revealed that the trabecular thickness and bone volume/total volume ratio increased by approximately 40% and 35%, respectively, significantly surpassing the control group without cell loading. The results from hematoxylin and eosin and Masson's trichrome staining showed that HHS-M groups exhibited the most new bone formation at weeks 4 and 8, consistent with the micro-CT findings. This effect can be partially attributed to the vascular-like network mimicked by the hollow lumens within the scaffold, which not only accelerated nutrient supply and metabolic waste removal for the cells but also promoted angiogenesis through the compartmentalized loading of endothelial cells (ECs). This characteristic was evidenced by a marked increase in a cluster of differentiation 31-positive areas observed in immunofluorescence staining. The vascularization of HHSs offers multiple advantages and significantly promotes bone regeneration. First, the hollow structure of HHSs can effectively facilitate the transport of nutrients and oxygen, thereby supporting cell survival and proliferation. Second, HHSs provide a favorable microenvironment for the growth of MSCs and ECs, enhancing cell migration and proliferation and thereby accelerating osteogenesis. Moreover, *in vivo* experiments have demonstrated that HHSs loaded with cells demonstrate excellent vascularization capacity, markedly improving the rate of new bone formation, reducing

inflammatory responses, and enhancing biocompatibility. Finally, HHSs possess superior mechanical properties, enabling them to withstand loading and maintain structural stability, offering essential support for bone healing. Therefore, the vascularization of HHSs not only improves the efficiency of bone tissue regeneration but also provides a novel solution for the treatment of large and osteoporotic bone defects. Meanwhile, dynamic mechanical loading significantly influences osteogenic differentiation through multiple mechanisms. First, dynamic mechanical loading promotes the migration and proliferation of cells, such as MSCs, enabling their uniform distribution and rapid seeding within the scaffold. Second, mechanical loading activates intracellular signaling pathways, thereby enhancing the expression of osteogenesis-related genes, such as alkaline phosphatase and collagen, type I, alpha 1, and consequently promoting osteoblast differentiation. Furthermore, mechanical stimulation improves the pericellular microenvironment, facilitating vascularization and the transport of nutrients, both of which are critical for bone regeneration. Studies have shown that mechanically stimulated cells exhibit superior proliferation and osteogenic activity, and that cell–cell interactions – such as those between osteogenic and ECs – are enhanced, thereby accelerating the healing of bone defects. Collectively, these findings indicate that dynamic mechanical loading significantly promotes osteogenic differentiation and bone regeneration by facilitating cell migration, activating signaling pathways, improving the microenvironment, and strengthening intercellular interactions.

A mechanically assisted post-bioprinting strategy, through the innovative design of HHSs, provides an inspiring example for the repair of complex bone defects. Its significance lies not only in the technical breakthrough but also in its implications for the future direction of bone tissue engineering. By combining heart-inspired dynamic loading with coaxial printing technology, the study successfully addressed challenges such as uneven cell distribution and insufficient nutrient supply in deep tissues, which are common in traditional bioprinting. However, its limitations and potential risks also warrant attention. First, the preparation of HHSs relies on a complex ink system composed of GelMA, Laponite, and NAGA. Although this combination endows the scaffold with excellent biocompatibility, detailed toxicological data on the degradation products of these materials are lacking, especially in pathological environments such as osteoporosis or immune hyperactivity, where Laponite nanoparticles may trigger unpredictable inflammatory responses. Second, while the mechanical loading process is highly efficient, it heavily depends on the precise control of external equipment. Finally, although the repair efficacy of HHSs for segmental bone defects and osteoporotic bone defects has been validated in mouse and rat models, the bone metabolism rates and mechanical environments in these models differ significantly from those in humans. Particularly in elderly patients or those with systemic diseases, the complexity of bone regeneration may further amplify the uncertainties surrounding this technology.

Compared to sacrificial bioprinting and electrospinning hybridization, the dynamic mechanical loading strategy offers unique advantages in enhancing cell seeding efficiency and promoting osteogenic differentiation, making it particularly suitable for bone tissue engineering. However, sacrificial bioprinting excels in the precise spatial control of cell distribution and architectural organization, while electrospinning hybridization provides a high specific surface area and tunable pore structure. The selection of an appropriate bioprinting method should therefore be determined by the specific application requirements, cell types, and characteristics of the target tissue. Future studies may focus on integrating the strengths of these approaches to develop more efficient and biocompatible strategies for tissue engineering.

In summary, this study proposes a mechanically assisted post-bioprinting strategy that utilizes heart-inspired HHSs to achieve efficient and uniform cell implantation through dynamic loading, significantly improving the repair of large segmental bone defects and osteoporotic bone defects. The highlight of this work lies in the integration of coaxial printing and mechanoresponsive technologies, which overcomes the limitations of uneven cell distribution and insufficient nutrient supply in deep tissues, commonly encountered in traditional bioprinting. Compared to other studies, its unique contribution is the construction of a regenerative platform that more closely mimics the natural bone microenvironment by simulating vascular networks and compartmentalized loading of multiple cell types. In addition, the synergistic optimization of the material system endows the scaffold with excellent mechanical properties and biocompatibility, providing an innovative paradigm for bone tissue engineering.

Acknowledgement
None.
Financial support
This work was financially supported by the National Natural Science Foundation of China (82202675).
Conflicts of interest statement
The authors declare no competing financial interest.
Author contributions
Conceptualization: LC; *Writing – original draft*: JL; *Writing – review & editing*: DS and LC. All authors have approved the final version of the manuscript.
Ethics approval and consent to participate
Not applicable.
Consent for publication
Not applicable.
Availability of data
Not applicable.

References

1. Szczodra A, Houaoui A, Agniel R, *et al.* Boron substitution in silicate bioactive glass scaffolds to enhance bone differentiation and regeneration. *Acta Biomater.* 2024;186:489-506. doi: 10.1016/j.actbio.2024.07.053
2. Shi J, Liu Z, Ren X, *et al.* Bioinspired adhesive polydopamine-metal-organic framework functionalized 3D customized scaffolds with enhanced angiogenesis, immunomodulation, and osteogenesis for orbital bone reconstruction. *Int J Biol Macromol.* 2025;284:137968. doi: 10.1016/j.ijbiomac.2024.137968

3. Ren X, Wang J, Wu Y, *et al.* One-pot synthesis of hydroxyapatite hybrid bioinks for digital light processing 3D printing in bone regeneration. *J Mater Sci Technol.* 2024;188:84-97.
doi: 10.1016/j.jmst.2024.01.001
4. Feng B, Zhang M, Qin C, *et al.* 3D printing of conch-like scaffolds for guiding cell migration and directional bone growth. *Bioact Mater.* 2023;22:127-140.
doi: 10.1016/j.bioactmat.2022.09.014
5. Hu Y, Wang H, Wang D, *et al. In situ* preparation of nano cone-like structures on 3D printed titanium alloy implants via one-step femtosecond laser manufacturing for better osseointegration, anti-corrosion, and anti-fatigue. *J Mater Sci Technol.* 2025;206:88-99.
doi: 10.1016/j.jmst.2024.03.070
6. Zhou X, Qian Y, Chen L, *et al.* Flowerbed-inspired biomimetic scaffold with rapid internal tissue infiltration and vascularization capacity for bone repair. *ACS Nano.* 2023;17(5):5140-5156.
doi: 10.1021/acsnano.3c00598
7. Zhou T, Cavalcante RC, Ge C, Franceschi RT, Ma PX. Synthetic helical peptides on nanofibers to activate cell-surface receptors and synergistically enhance critical-sized bone defect regeneration. *Bioact Mater.* 2025;43:98-113.
doi: 10.1016/j.bioactmat.2024.08.017
8. Xu Z, Qi X, Bao M, *et al.* Biomineralization inspired 3D printed bioactive glass nanocomposite scaffolds orchestrate diabetic bone regeneration by remodeling micromilieu. *Bioact Mater.* 2023;25:239-255.
doi: 10.1016/j.bioactmat.2023.01.024
9. Mirkhalaf M, Men Y, Wang R, No Y, Zreiqat H. Personalized 3D printed bone scaffolds: A review. *Acta Biomater.* 2023;156:110-124.
doi: 10.1016/j.actbio.2022.04.014
10. Yang J, Chen Z, Gao C, *et al.* A mechanical-assisted post-bioprinting strategy for challenging bone defects repair. *Nat Commun.* 2024;15(1):3565.
doi: 10.1038/s41467-024-48023-8

Received: March 29, 2025
Revised: April 16, 2025
Accepted: April 27, 2025
Available Online: May 20, 2025