CURRENT CONCEPTS REVIEW

Current Concept of Bioactive Glass-loaded 3D-Printed Alginate-based Scaffolds for Bone Tissue Engineering Applications

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Received: 20 December 2025 *Accepted: 29 April 2026*

Abstract

Bone is a mineralized connective tissue composed of osteoblasts, osteocytes, and osteoclasts, and its integrity is essential for structural and physiological function. Defects arising from trauma, tumors, or developmental abnormalities often require surgical reconstruction to restore normal performance. Autografts and allografts have long served as standard treatments for bone repair, however, their usefulness is restricted by limited availability, donor-site complications, and the potential transmission of underlying diseases. These challenges have accelerated interest in bone tissue engineering (BTE) as an alternative strategy capable of enhancing regeneration while reducing postoperative risks. Advances in three-dimensional (3D) printing have introduced powerful technique for fabrication of scaffolds with precisely controlled architectures and tunable mechanical and biological characteristics. This technology enables the creation of porous constructs that mimic the structural complexity of native bone, supporting cell infiltration, nutrient transport, and vascularization. Effective scaffolds for BTE must demonstrate biocompatibility, biodegradability, appropriate strength and stiffness, and the ability to promote osteogenesis and angiogenesis. Among natural polymers, alginate (Alg) has become a prominent candidate due to its inherent biocompatibility, degradability, abundance, low cost, and non-immunogenic nature. Its versatility makes it suitable for developing customized 3D-printed scaffolds. Additionally, bioactive glasses (BGs) are widely incorporated into composite scaffolds because their composition closely resembles the mineral phase of bone. BGs significantly enhance osteoconductivity, support mineral deposition, and can improve the mechanical resilience of polymer-based constructs. This review highlights recent progress in 3D-printed Alg-based scaffolds for BTE, emphasizing how advanced fabrication techniques and BGs incorporation contribute to improved biological performance and structural reinforcement.

Level of evidence: III

Keywords: 3D-printed, Alginate, Bioactive glass, Bone tissue engineering, Scaffolds

Introduction

Bone diseases such as osteoporosis, osteosarcoma, fractures, and post-surgical defects frequently require clinical intervention to restore skeletal integrity.[1] Conventional treatments predominantly rely on autografts, allografts, and xenografts.[2] Despite their historical utility, these grafting techniques are constrained by significant limitations, such as donor site morbidity, restricted availability, potential for disease transmission, and high rates of graft failure.[3] Consequently, these clinical shortcomings have shifted the therapeutic focus toward bone tissue engineering (BTE).[4,5] BTE employs a multidisciplinary approach integrating nanotechnology and advanced biomaterials to regenerate damaged tissue. By enhancing osteogenic cell activity and providing

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mechanically robust scaffolds, BTE strategies aim to address the limitations of traditional grafts.[6,7] Despite advancements, achieving rapid and sustained vascularization post-implantation remains a critical challenge in clinical practice.[8] In this context, the development of three-dimensional (3D) biomimetic scaffolds, which synergistically combine organic and inorganic components to emulate the structural and mechanical properties of the native bone matrix, is essential for the successful reconstruction of critical-sized bone defects.[9,10]

3D printing technique has emerged as an innovative strategy for fabricating scaffolds with optimized structural, mechanical, and biological properties for BTE.[11] This technique enables the production of constructs that closely resemble native bone in both mechanical behavior and biological function. In addition, 3D printing allows precise control over scaffold porosity and internal architecture, which is essential for nutrient transport, cell infiltration, and tissue regeneration.[12] BTE aims to repair critical-sized bone defects and ultimately promote de novo bone formation. Achieving this goal requires the design of scaffolds that integrate cells with bioactive components to support osteogenesis. Although numerous natural and synthetic polymers have been developed for bone regeneration, many are limited by poor biomineralization potential, inadequate mechanical performance, and insufficient adaptability.[13-15]

To biomimice native bone composition, primarily composed of the natural polymer collagen and calcium phosphate. Among natural polymers, alginate (Alg) is frequently utilized in tissue engineering due to its appropriate physical characteristics, biocompatibility, and biodegradability.[16] Its high water absorbency capacity is particularly beneficial for cell behavior. However, alginate also presents limitations, notably its low mechanical strength. To enhance the mechanical and osteoconductive properties of Alg, it is often combined with other materials, such as ceramic-based nanoparticles like bioglass, for specific applications in bone regeneration.[17,18] The bioactive potential of bioglass concerning bone formation has been extensively studied since the pioneering work of Larry Hench. Bioglass exhibits excellent bioactivity, mechanical properties, osteoconductivity, and biodegradability, making it a valuable component in bone repair materials.[19] Its unique ability to form bonds with both hard and soft tissues, alongside its capacity to promote gene expression in osteoblasts and angiogenic cells, has led to its clinical application. [20,21] This review focuses on the development of 3D-printed Alg-based scaffolds, optimized for mechanical properties, structural characteristics, and osteoconductivity through the incorporation of bioglass.

Main body

3D-printed pure Alginate scaffolds

3D printing technique is a novel sterategy that allows the automated and reproducible fabrication of functional, scalable and customized artificial structures for personalized medicine.[22] Generally, this additive manufacturing technique employs a layer-by-layer deposition of biocompatible materials to achieve stable 3D constructs.[9] Alg, a polysaccharide derived from brown seaweed, can be readily processed into hydrogels. These highly hydrated networks effectively mimic the extracellular matrix (ECM) of numerous native tissues.[23] This biopolymer has garnered significant attention as a promising component for bioinks due to its inherent biocompatibility, low cytotoxicity, and high water content, which closely resembles natural ECM.[8] . The shear-thinning properties of biomaterials like Alg are advantageous for extrusion-based 3D printing. Upon application of shear stress, the viscosity of the material is reduced, facilitating extrusion. Once deposited onto the substrate, the viscosity increases with decreasing shear rate. This self-supporting characteristic prevents excessive flow, allowing the hydrogel to maintain its precise shape on the surface.[10,24] Consequently, Alg-based 3D-printed scaffolds exhibit suitable rheological properties. However, the application of pure Alg scaffolds in BTE is significantly limited by their inherently poor mechanical properties.[25,26] Strategies to enhance the properties of pure Alg scaffolds primarily involve cross-linking, which can be broadly categorized into physical and chemical methods. Physical cross-linking relies on non-covalent interactions, most commonly the ionic interaction between the anionic carboxylate groups of Alg and positively charged divalent cations. Common divalent cations utilized for this gel synthesis include Ca^{2+}, Mg^{2+}, Br^{2+} or Sr^{2+}.[11] The choice of cation and its concentration critically influence the degree of cross-linking and, consequently, the mechanical properties and degradation rate of the scaffolds. Chemical cross-linking, conversely, involves the formation of stable covalent bonds between Alg chains and other molecules. This approach generally yields scaffolds with superior mechanical strength, enhanced stability, and more controlled degradation profiles compared to physical cross-linking. A common and effective chemical cross-linker is glutaraldehyde, which forms covalent bonds through Schiff base formation. However, its potential cytotoxicity necessitates careful control of concentration and post-processing to ensure cell viability. Other chemical cross-linking strategies include the use of genipin or click chemistry approaches, which offer high specificity and efficiency under mild conditions. The selection of the chemical cross-linker and optimization of its density are critical determinants of the final mechanical properties of the alginate scaffolds. Beyond cross-linking, fabricating composite scaffolds represents another significant method for improving Alg-based scaffolds for BTE. These composites typically consist of Alg combined with other natural or synthetic polymers and inorganic reinforcing agents, such as ceramic or metallic nanoparticles.[27] These added components are often chosen for their inherent mechanical robustness and ability to promote specific biological responses relevant to bone regeneration. Furthermore, the inherent bioinert properties of Alg, while beneficial for biocompatibility, limits its intrinsic bioactivity for bone regeneration. Therefore, numerous studies have explored the incorporation of various reinforcing materials, particularly bioceramics like hydroxyapatite (HA), BGs, and tricalcium phosphate (TCP), into Akg-based scaffolds.[28] These bioceramic additions not only act as mechanical reinforcing agents, significantly enhancing the scaffold's compressive strength and stiffness, but also promote osteoconductivity and osteoinductivity by mimicking the mineral component of native bone and providing a favorable environment for osteoblast adhesion, proliferation, and differentiation.[29]

Different types of 3D-printed Alginate-based polymeric scaffolds

To address the insufficient mechanical strength and structural stability of pure Alg scaffolds, which have limited their application in BTE, composite strategies are frequently employed. These approaches leverage the precise, layer-by-layer fabrication capabilities of 3D printing to construct complex scaffolds with tailored characteristics by combining Alg with other biomaterials. The aim is to achieve enhanced mechanical robustness and a suitable degradation rate, thereby improving both the mechanical and biological performance for BTE.[24] One strategy involves creating Alg composites with other polymers. For instance, Alg/Carboxymethyl Cellulose (CMC) composites are advantageous because CMC is highly hydrophilic, capable of retaining significant water within its cross-linked network.[7] Pioneering work by Li et al. demonstrated the 3D printing of an Alg/methyl cellulose composite using trisodium citrate for layer bonding and calcium chloride for cross-linking.[12] Compared to pure Alg's rapid degradation and poor mechanical strength, CMC offers a slower degradation profile and greater mechanical rigidity, alongside favorable biological properties such as supporting protein adsorption, cell aggregation, and differentiation, even exhibiting shear-alignment and shape memory characteristics suitable for bioink formulations.[16] Similarly, Alg/Chitosan composites are highly promising for bone regeneration due to chitosan's inherent biocompatibility, hydrophilicity, biodegradability, low immunological response, and favorable mechanical properties.[17] Chitosan acts as an excellent substrate for osteoblast adhesion, proliferation, and the subsequent matrix formation and mineralization critical for bone repair.[13] Investigations into Alg/Gelatin composites by Smith et al. specifically highlighted that material composition significantly dictates mechanical properties, with higher gelatin content generally enhancing scaffold flexibility.[20] They emphasized that the precise composition and the chosen cross-linking method profoundly influence the structural integrity and mechanical performance of these 3D-printed constructs . A comprehensive overview of various 3D-printed Alg-based scaffolds investigated for BTE, detailing these diverse compositions and their properties, is presented in [Table 1]. Beyond polymer blending, the bioinert nature of Alg often requires further enhancement for osteogenic purposes. Thus, the incorporation of bioactive and mechanical reinforcing agents is a critical approach. These bioceramic particles not only bolster compressive strength and stiffness, but also actively promote osteoconductivity and osteoinductivity by mimicking the mineral phase of native bone, thereby creating an optimal microenvironment for osteoblast activity.

Table 1. 3D-Printed Alginate-Based Scaffolds for Tissue Engineering Applications

Composition	Fabrication Method	Types of cells/growth factor	Applications	Result
Alg -Gelatin	Extrusion-based printing	-	Cartilage tissue engineering	The bioink's printing performance was improved by mimicking the hierarchical structure of articular cartilage, while adjustments to the treatment process successfully increased the hydrogel's mechanical strength.
Alg-Nano cellulose-HA	Extrusion-based printing	Mesenchymal stem cells (MSCs)	Cartilage tissue engineering	Scaffolds incorporating HA demonstrated superior mechanical properties, biocompatibility, and cell viability compared to those composed of sodium alginate and nanocrystalline cellulose (SA/NC).
Alg-Polycaprolactone (PCL)	Extrusion-based printing	Bone marrow-derived mesenchymal stem cells (BMSCs)	Cartilage tissue engineering	The implementation of printed gradient architectures proved superior to monolayer structures for promoting cell adhesion, proliferation, and chondrocyte differentiation.
Alg-Gelatin -BGs	Extrusion-based printing	-	BTE	The incorporation of BGs significantly improved the mechanical properties of the scaffolds and effectively modulated their degradation and swelling behavior. Furthermore, in vitro assessments demonstrated excellent cell viability.
Alg-PLA	Extrusion-based printing	-	Cartilage tissue engineering	The scaffold showed notable cellular activity, while Young's modulus increased from 6.9 ± 1.7 kPa to 25.1 ± 3.8 kPa, corresponding to a threefold enhancement.
Alg-HA	Fused Deposition Modeling (FDM)	-	cartilage tissue engineering	The addition of HA significantly enhanced the printability of the bioink and positively influenced cellular activity.
Alg-Gelatin	Extrusion-based printing	BMSCs	Tissue engineering	The Gelatin/Alg composite hydrogel demonstrated excellent biocompatibility and promoted osteogenesis in BMSCs. Histological analysis further indicated that these composite hydrogels effectively accelerate in vivo bone repair.
SA-Chitosan	Extrusion-based printing	Osteoblast sarcoma cells	BTE	The concentration of chitosan within the SA-chitosan scaffold network significantly influenced its properties. Higher chitosan content resulted in reduced swelling and degradation, thereby enhancing structural stability.

Table 1.Continued

Alg-Gelatin-Poly Lactic-co-Glycolic Acid (PLGA)	Extrusion-based printing	Vascular endothelial growth factor (VEGF)	BTE	The VEGF-incorporated scaffolds displayed favorable structural properties, characterized by high porosity (73.42 ± 8.4%) and a high Young's modulus (98.31 ± 10.21 MPa).
Alg-BGs	Extrusion-based printing	Human bone mesenchymal stem cells (hBMSCs)	BTE	This biomimetic scaffold, characterized by 78% porosity and a compressive strength of 4.8 MPa, has the potential to enhance the adhesion, proliferation, and osteogenic differentiation of hBMSCs.
Alg-Agarose	Selective laser sintering (SLS)	-	BTE	The scaffold exhibited favorable cell survival and high resolution, with a vertical spatial resolution of approximately 250 μm.
Alg- Polyvinyl alcohol (PVA)	Extrusion-based printing	Bone morphogenetic protein-2 (BMP-2)	BTE	The incorporation of PVA into Alg scaffolds resulted in significantly higher porosity, promoting the rapid release of bovine serum albumin (BSA) due to the substantial presence of micropores.

Bioactive glass-loaded 3D-printed Alginate-based scaffolds

Building upon strategies to enhance the mechanical and biological properties of Alg-based scaffolds, the incorporation of BGs represents a significant advancement in BTE. Pioneered by Larry Hench in 1969, BGs have garnered extensive attention for their remarkable potential in bone repair applications due to their unique ability to bond with host bone tissue. This exceptional osteoconductivity, coupled with controllable biodegradability and inherent bioactivity, facilitates the stimulation of new bone growth through promoted dissolution and ion release. This exceptional osteoconductivity, coupled with controllable biodegradability and inherent bioactivity, facilitates the stimulation of new bone growth through promoted dissolution and ion release.[19] By incorpotating BGs into an alginate matrix, composite scaffolds can be fabricated that harness the structural support of alginate with the potent osteogenic signaling of bioactive glasses.[18] Research by Guilin Luo et al. demonstrated the 3D printing of such composite scaffolds under mild conditions, where the mass ratio of BGs to Alg directly influenced the resulting scaffold architecture, including pore size, porosity, and shrinkage.[21] The study highlighted that these 3D-printed BGs/Alg scaffolds exhibited a fully interconnected porous structure and significantly improved HA-forming ability in simulated body fluid (SBF), a key indicator of osteoconductivity.[23] This process typically involves extruding a bioink composed of Alg and BGs particles, often using a printing needle of a specific diameter (406 μm), and subsequently cross-linking the Alg with Ca^{2+} ions. The composition of the BGs itself, often including SiO_2, $CaCO_3$, Na_2CO_3, K_2CO_3, $MgCO_3$ and NaH_2PO_4, indictates its dissolution kinetics and ion release profile, thereby modulating the osteogenic response.[23] Further innovations have explored the use of bioactive glass microspheres (BGMs), synthesized via sol-gel methods with a molar ratio of SiO2:CaO:P_2O_5 (80:15:5). Fujian Zhao et al. fabricated self-crosslinked composite scaffolds where methylcellulose formed the structural framework along with BGMs. These structures were then immersed in an Alg solution to facilitate cross-linking, or alternatively, cross-linking could occur via sintering and Ca^{2+} ions. The resulting 3D-printed scaffolds, possessing porosities between 57-75%, demonstrated compressive strengths comparable to human trabecular bone and a remarkable ability to facilitate in vitro apatite formation. More recently, the field has advanced to incorporate MBGs, which offer enhanced surface area and ordered mesoporous channels (2–50 nm), thereby improving drug delivery capabilities and osteoinduction compared to conventional BGs.[30] MBGs, typically composed of 80 mol% SiO, 15 mol% CaO, and 5 mol% P_2O_5, inherently possess poor mechanical properties and rheological characteristics unsuitable for direct 3D printing. To circumvent this, MBGs are combined with biopolymers like Alg to create composite bioink. For example, an Alg and MBG/sodium alginate (SA) bioink mixture can be extruded layer-by-layer, followed by cross-linking in a calcium chloride solution. The resulting 3D-printed MBG/Alg scaffolds exhibit high porosity with an interconnected macroporous structure, and their mechanical properties are significantly improved through cross-linking. The released calcium and silicon ions from the MBG are crucial for stimulating cell proliferation and differentiation, contributing to enhanced bone regeneration.[22] Rodrigo L.M.S. Oliveira et al. developed 3D-printind base on BGs S53P4/Alg sintering-free scaffolds.[31] BG S53P4 is a type of BGs that has been extensively studied for its ability to promote bone regeneration and treat bone infections. In this study, BG S53P4 powder consist of $53SiO_2$, 20CaO, $23Na_2O$ and $4PO_4$ wt.% was synthesize by using the melting-quenching method. Then BG S53P4/Alg bioink used on the 3D-printed scaffolds' fabrication. The BG S53P4/Alg bioink demonstrated excellent printability, resulting in scaffolds that closely resembled the designed model. Researchers reported that the 3D printing mesoporous BGs/Alg/gelatin scaffolds provide a potential application for BTE.[32,33] Other BG formulations, such as BG S53P4 (53% SiO_2, 20% CaO, 23% Na_2O, and 4% P_2O_5), synthesized via melt-quenching, have also been utilized in Alg-based bioinks for 3D printing, demonstrating excellent printability and adherence to designed models. Beyond osteoconductivity, BGs are also being integrated for their angiogenic properties, which are critical for tissue regeneration. The synergy between Alg and gelatin, as previously discussed for its biocompatibility, biodegradability, and cell adhesion properties, is also leveraged in BGs composites. For instance, MBG (80% SiO_2, 16% CaO, 4% P_2O_5) has been formulated into an MBG/Alg-gelatin bioink for 3D printing. After cross-linking in calcium chloride and glutaraldehyde solutions, these scaffolds achieved approximately 80% porosity, similar to human cancellous bone. The presence of inorganic ions (Si, P, Ca) from the MBG, combined with the advantageous properties of gelatin, strongly induces bone cell differentiation and proliferation, leading to enhanced osteogenesis.[34] Studies by Qing Ye et al. further confirm that combining BGs with Alg and gelatin synergistically promotes mechanical strength, biomineralization, improved cell responses, and osteogenesis, leading to increased deposition of HA on the scaffold surface. This multimodal approach combining the structural matrix of Alg, the osteogenic signaling of BGs, and the cell-interactive properties of polymers like gelatin creates highly promising scaffolds for effective BTE.[35]

Conclusion

Summary and Future Perspective

The regeneration of bone defects caused by trauma, congenital abnormalities, or disease remains a major clinical challenge. Bone tissue engineering (BTE) and regenerative medicine seek to restore the structure and function of damaged bone through the combined use of cells, bioactive factors, and scaffolds fabricated from engineered biomaterials. Among the various scaffold fabrication techniques, three-dimensional (3D) printing has emerged as a versatile sterategy for producing custom-designed constructs with precise control over architecture, porosity, and internal geometry. By enabling layer-by-layer deposition, 3D printing offers significant advantages for the fabrication of patient-specific scaffolds tailored to the requirements of bone regeneration. Alginate (Alg) is an attractive biomaterial for 3D printing due to its excellent biocompatibility, mild gelation conditions, and ease of crosslinking into stable hydrogel-based scaffolds. Despite its favorable properties, Alg alone lacks the osteoinductive and mechanical properties required for effective bone regeneration, which limits its clinical applicability. The incorporation of ceramic based nanoparticles like bioactive glasses (BGs) into Alg-based scaffolds offers a promising strategy to overcome these limitations. BGs are well known for their ability to stimulate bone regeneration through the controlled release of biologically relevant ions. These ions can enhance osteogenic differentiation, promote extracellular matrix (ECM) mineralization, and support the formation of hydroxyapatite (HA)-like layers on the scaffold. Overall, the combination of Alg and BGs in 3D-printed scaffolds holds significant promise for the development of next-generation bone substitutes with enhanced regenerative potential.

Abbreviations

List of abbreviations

Abbreviation	Meaning
BTE	Bone tissue engineering
3D	Three-dimensional
Alg	Alginate
BGs	Bioglass BGs
ECM	Extracellular matrix
CMC	Carboxymethyl cellulose
SBF	Simulated body fluid
BGM	Bioactive glass microspheres
MBG	Mesoporous bioactive glass
HA	Hydroxyapatite

Acknowledgement

The authors would like to appreciate the clinical Research Development Unit, Orthopedic Research Center, Bone and Joint Research Laboratory, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran for their assistance in the present manuscript.

Authors Contribution: Authors who conceived and designed the analysis: Nafiseh Jirofti, Afsaneh Jahani/ Authors who collected the data: Afsaneh Jahani/Authors who wrote the paper: Afsaneh Jahani/ Other contribution: Supervision: Mohammad Hossein Ebrahimzadeh, Ali Moradi, Fatemeh Kalalinia/Resource allocation: Mohammad Hossein Ebrahimzadeh, Nafiseh Jirofti/Project management and administration: Nafiseh Jirofti

Funding: This work is based upon research funded by Iran National Science Foundation (INSF) under project No.4037192 and Vice-Chancellor for Research of Mashhad University of Medical Sciences, Mashhad, Iran.

Declaration of Conflict of Interest: The authors do NOT have any potential conflicts of interest for this manuscript.

Declaration of Funding: This work was supported as a research project financed by the Research Council of Mashhad University of Medical Sciences.

Declaration of Ethical Approval for Study: N/A

Declaration of Informed Consent: N/A

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