From concepts to clinical reality: 3D printing and biomimetic innovation in periodontal regeneration (Review)

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Abstract. Periodontal regeneration remains a challenge due to the intricate structure and functional requirements of the periodontium. Conventional techniques, such as guided tissue regeneration and bone regeneration fail to yield consistent regeneration. Recent advancements in 3D printing and biomimetics have allowed for the manufacturing of multilayered scaffolds with precise spatial organization. The present review discusses the various 3D printing methods employed in periodontal regeneration including electrospinning, stereolithography and selective laser sintering. The key scaffold materials include bioceramics and synthetic polymers, and the incorporation of biofunctional components and layering designs. Despite the promising results, the optimization of the resorption rate of the scaffold and bioink formulation remains a challenge. However, further research on the convergence of 3D printing and biomimetics is warranted as this may pave the way for a revolutionary change in periodontal regeneration.

Contents

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1. Introduction

Periodontitis is a prevalent inflammatory condition involving the supporting structures of the teeth, gingiva, periodontal ligament, cementum and alveolar bone. It occurs primarily due to the accumulation of dental plaque and bacterial biofilm that trigger the host mediated inflammatory reactions, thereby causing periodontal destruction. This process eventually results in tooth mobility and eventual tooth loss if left untreated (1,2).

Several methods have been employed over a period of time to accomplish periodontal regeneration. Using barrier membranes to prevent the rapid migration of epithelial and connective tissue cells into the defect area, guided tissue regeneration (GTR) and guided bone regeneration (GBR) are two well-established clinical modalities (1) that enable slower-growing periodontal ligament cells, cementoblasts and osteoblasts to repopulate the site and promote regeneration (3). Conventional GTR/GBR methods frequently produce only partial and unpredictable regeneration, despite their success in improving clinical outcomes. The coronal regions are often populated by a long junctional epithelium or non-functional connective tissue, and regeneration is often restricted to the apical portion of the defect (4).

The majority of regenerative materials available today are unable to actively direct or instruct cell behavior in a manner that replicates the intricate structure of the native periodontium. True regeneration is therefore still difficult to achieve in standard clinical practice (5,6).

In recent years, 3D printing and biomimetics have emerged as promising approaches for periodontal regeneration (7). The combination of biomimetic principles and additive manufacturing signifies a paradigm shift toward a more potent, biologically relevant treatment, as traditional regenerative methods struggle with predictability and integration. With a focus on their revolutionary role in next-generation regenerative dentistry, the present review attempts to summarize and discuss the present uses, underlying mechanisms and future prospects of 3D printing and biomimetics in implant and periodontal therapy (4).

2. Convergence of biomimetics and 3D printing

Biomimetics aims to replicate the natural healing and developmental processes of tissues. It refers to the design and development of materials and systems that mimic biological structures and functions. With the use of bioactive compounds, stem cell-based treatments and intelligent scaffolds that direct tissue-specific regeneration, biomimetic approaches in periodontics seek to replicate the intricate architecture of the periodontium (8). These methods draw inspiration from biological concepts, such as the collagen fiber orientation of the periodontal ligament (PDL), the slow mineralization of cementum, and the coordinated cellular and vascular networks necessary for functional regeneration (9,10).

3D printing or additive manufacturing complements biomimetic approaches by making it possible to precisely fabricate patient-specific scaffolds with customized geometries, porosities and compositions on the basis of digital imaging modalities such as cone-beam computed tomography. Unlike traditional scaffold fabrication techniques, 3D printing enables the layer-by-layer spatial arrangement of various materials and cell types, closely resembling the hierarchical and heterogeneous structure of the periodontium (4).

Thus, the combination of biomimetic principles and 3D printing technologies offers not only biological and structural fidelity to natural tissues, but also personalized, functional regeneration that overcomes the drawbacks of conventional treatment modalities, including limited tissue specificity and incomplete integration. It also provides promising periodontal therapies that are more clinically relevant, predictable and effective (4).

3. 3D printing techniques in dentistry

3D printing includes several different techniques, all of which are appropriate for use in dentistry (Fig. 1). Electrospinning, which uses an electric field to pull a charged polymer solution into ultrafine fibers, is one of the most promising methods. At the needle tip, a Taylor cone is formed, and fibers are then sent in the direction of a collector plate. Applications, such as antibiotic-eluting nanofiber scaffolds for regenerative endodontics can benefit from the ability of electrospinning to precisely control fiber diameter, porosity and drug loading (5).

The first 3D printing method was created in 1984 and was termed stereolithography (SLA). Layer by layer, the liquid photopolymer resin is cured using a laser. High resolution and rapid speeds render modern SLA printers perfect for detailed prosthetics and surgical guides (11,12).

Thermoplastic filaments are heated and then extruded layer by layer through a nozzle in fused deposition modelling, also known as fused filament fabrication. Despite being widely used and reasonably priced, it has trouble with unsupported overhangs and frequently requires dual-nozzle printers and dissolvable support structures (13).

Using a powder bed fusion process known as selective laser sintering, a laser is used to sinter powdered material into solid layers. There is no need for extra support as the structure is supported by the powder bed itself during printing. Complex, load-bearing components can benefit from this technique (11).

Finally, inkjet printing creates structures by ejecting small material droplets onto a substrate. Fast printing and material versatility, including bioprinting applications, are made possible by this technique's multi-nozzle heads (13).

A key limitation in current periodontal tissue engineering is the inability to reproduce the intricate hierarchical architecture of the periodontium. Conventional layer-by-layer fabrication techniques generally produce isotropic scaffolds that fail to replicate the anisotropic orientation of fibers and mineral phases required for physiological load transfer. Magnetic-assisted 3D printing has emerged as a promising strategy to address this challenge. In this approach, an external magnetic field is applied during direct ink writing to precisely regulate the spatial orientation of magnetically responsive particles, such as hydroxyapatite (HAp) nanorods, incorporated within the bioink. The magnetic field induces the directional alignment of these nanorods, enabling the fabrication of anisotropic microstructures that resemble the organized mineral arrangement observed in natural dental tissues. Such controlled alignment has been explored to replicate hierarchical dental interfaces, particularly the enamel-dentin junction, where anisotropic mineral orientation contributes to a gradual mechanical gradient between tissues. This biomimetic architecture can improve stress distribution and enhance crack-deflection and fracture-resistance properties, thereby better mimicking the functional performance of natural dental interfaces (14).

4. Scaffold biomaterials used in periodontal regeneration

The success of periodontal regeneration largely depends on the selection of suitable scaffold materials to provide suitable environment for cell differentiation. Various scaffold materials available for periodontal regeneration (Fig. 2).

Synthetic polymers. Second-generation degradable membranes, replace the non-resorbable membrane (PTFE) and are primarily comprised of synthetic polymers. They are frequently utilized as scaffold materials due to their adjustable mechanical strength, degradation profiles and manufacturing reproducibility. Among these, the most widely used materials are poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA) and Polycaprolactone (PCL) (15).

PGA offers high mechanical stability and biocompatibility. It has demonstrated promising results in both *in vitro* and *in vivo* models for tissue regeneration, and promotes the growth and production of the extracellular matrix by periodontal ligament stem cells (16).

Compared with PGA, PLA is more hydrophobic and breaks down into lactic acid. Its efficacy as a scaffold is increased when it is combined with natural polymers, such as chitosan, to enhance cell attachment and degradation behavior (15).

The benefits of PLA and PGA are combined in PLGA, which provides properties that can be adjusted by changing the copolymer ratio. PLGA scaffolds have demonstrated success in promoting cell adhesion, controlled drug delivery, and periodontal tissue regeneration, particularly when functionalized with proteins, such as fibronectin or when combined with hydrogels (16).

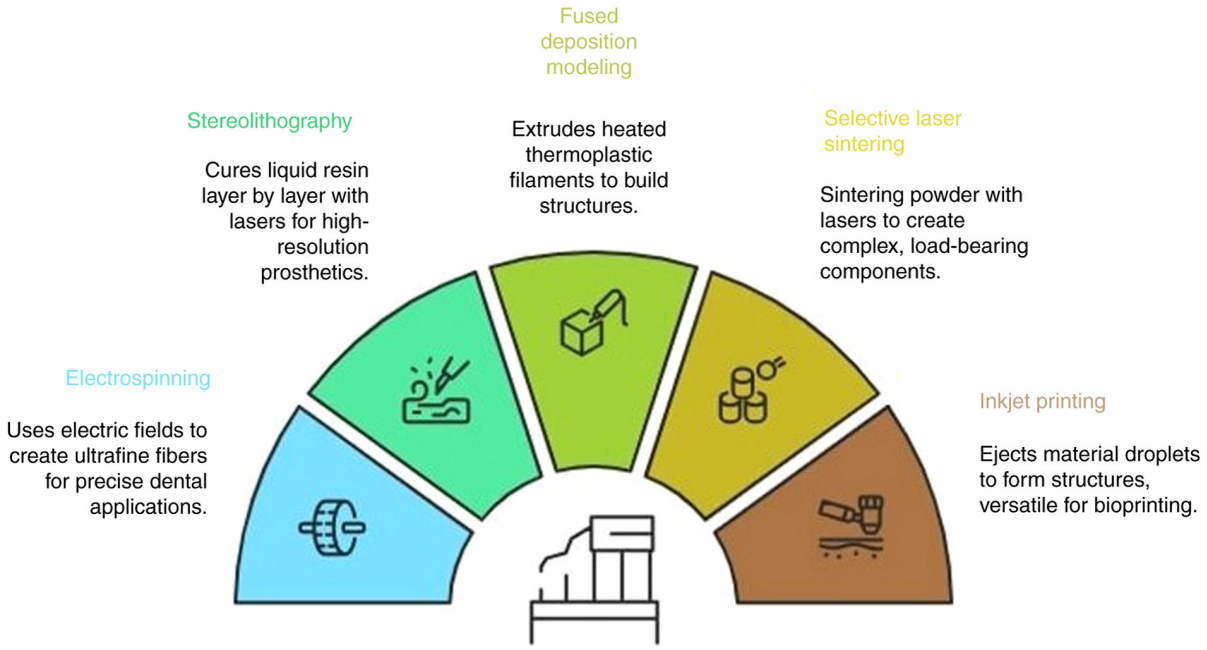

Figure 1. Illustration of the various 3D printing techniques employed in dentistry.

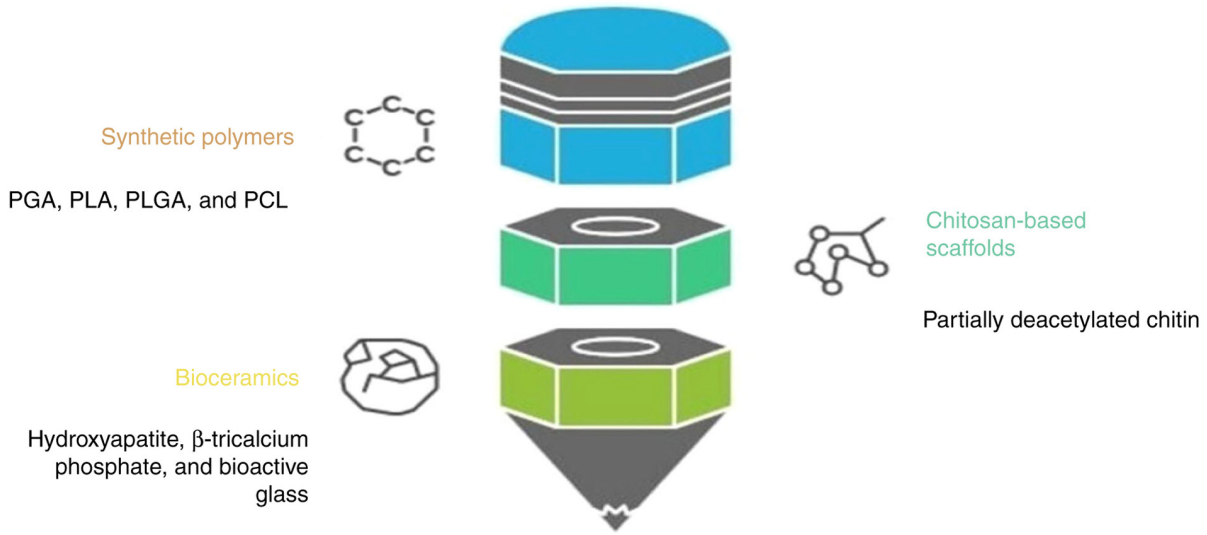

Figure 2. Illustration of biomaterials used in periodontal regeneration.

PCL is characterized by high flexibility and a slow rate of degradation. To improve tissue regeneration and control inflammation, it has been utilized as a delivery system for antimicrobial and anti-inflammatory drugs, such as tetracyclines, ibuprofen and resveratrol. The biological performance and structural mimicry of composite scaffolds containing PCL and osteoconductive materials, such as gelatin or calcium phosphate are enhanced (17).

Chitosan-based scaffolds in periodontal regeneration. As a naturally occurring biopolymer produced by partially deacetylating chitin, chitosan has demonstrated immense promise in periodontal regenerative treatments. It is particularly well-suited for use in periodontal scaffolding due to its intrinsic qualities, which include biocompatibility, biodegradability, antimicrobial activity and mucoadhesiveness. To replicate the structure of periodontal tissues, recent developments have investigated layered and composite scaffolds that incorporate chitosan (18).

Owing to the high cell viability of osteoblasts, fibroblasts and PDL cells, a tri-layered scaffold comprise of crosslinked chitosan and genipin has been shown to support the simultaneous regeneration of bone, gingiva and periodontal ligament. Similarly, the addition of bioactive glass nanoparticles to chitosan matrices enhances their mechanical flexibility and cellular metabolic activity, particularly when they are wet, suggesting that they may have *in vivo* functionality (18,19).

The function of chitosan extends beyond structural repair. It reduces key clinical indicators of periodontitis, including plaque buildup, gingival inflammation and attachment loss,

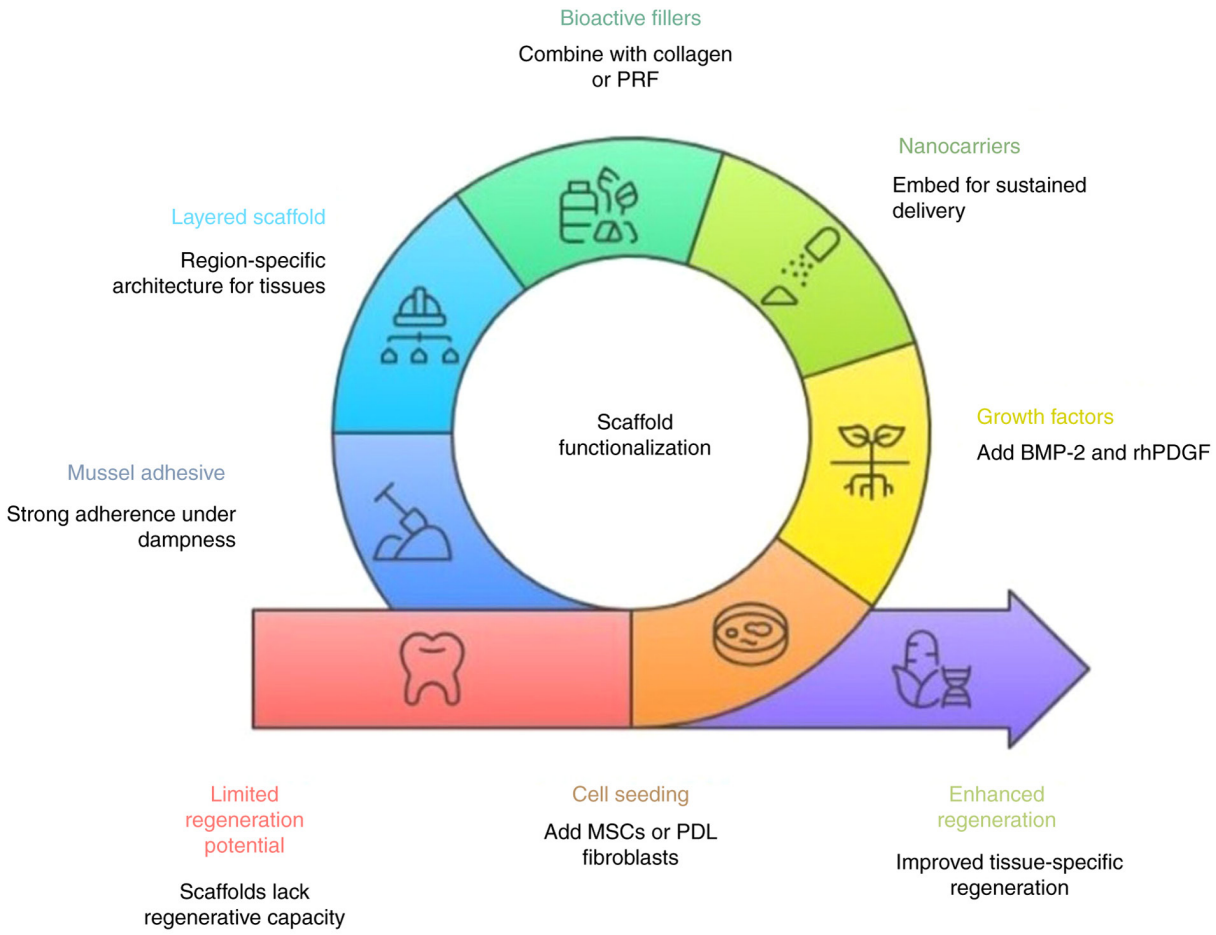

Figure 3. Illustration of the functionalization of 3D printed scaffolds.

when combined with ascorbate to create a bioadhesive gel with improved antimicrobial efficacy. The robust attachment of chitosan to root surfaces promotes tissue stability and decreases the inflammatory infiltration (20).

Bioceramic-based scaffolds. Bioceramics, such as hydroxyapatite, β-tricalcium phosphate and bioactive glass have shown immense promise in periodontal regeneration due to their superior osteoconductive and osteoinductive qualities. These materials promote alveolar bone repair in periodontal defects by providing advantageous biocompatibility, mechanical strength, and biodegradability. The clinical versatility of these materials has increased due to their availability in versatile forms, such as injectable systems, pastes and granules (15).

5. Functionalization of 3D printed scaffolds

To increase the potential of 3D printed scaffolds, they are functionalized with living cells and bioactive compounds are added to 3D-printed scaffolds to improve their capacity for regeneration (Fig. 3). To encourage tissue-specific regeneration and hasten healing, mesenchymal stem cells or PDL fibroblasts can be seeded onto these scaffolds. To promote cellular migration, differentiation and proliferation, growth factors, such as bone morphogenetic protein-2 and recombinant human platelet-derived growth factor are also added. Additionally, by embedding nanocarriers in the scaffold matrix, therapeutic agents can be delivered locally and sustainably, reducing systemic exposure and guaranteeing prolonged bioactivity. This overcomes the lack of regenerative potential of 3D printed scaffold materials (21-23).

An essential aspect to consider during 3D bioprinting is cell viability which is affected by various factors, such as shear stress, nozzle pressure and individual property of bioink. These often result in compromised the stem cells. However, the optimization of bioink can help in overcoming this obstacle. Gelatin-methacryloyl (GelMA) hydrogels have been shown to reduce the shear thinning, while also preserving the viability of cells. Therefore, the careful optimization of bioink properties can enhance the effectiveness of bioprinting in regenerative periodontics. In addition, batch standardization and quality control are essential for clinical translation. Computational modelling approaches with micro-CT porosity mapping can help ensure minimal variability in scaffold architecture across production batches (14).

Role of growth factors. Synthetic polymers are excellent options for tissue engineering applications due to their favorable mechanical strength, adjustable degradation kinetics, and adaptability in drug and gene delivery systems (15).

Bioactive substances, such as fibroblast growth factor-2 (FGF-2) have been effectively transported by PLGA. Research has demonstrated that PLGA scaffolds containing

plasmid FGF-2 (pFGF-2) release the gene continuously without causing an initial burst, and retain its bioactivity for as long as 21 days (24). In contrast to PLGA scaffolds without gene loading, this controlled delivery stimulates the growth of human periodontal ligament cells (hPDLCs), increases the expression of extracellular matrix proteins (such as collagen I and scleraxis), and facilitates the formation of more ordered PDL-like tissues *in vivo* with less root resorption (23).

Furthermore, composite scaffolds that combine synthetic scaffolds with bioactive fillers, such as collagen or platelet-rich fibrin, HAp and calcium derived from eggshells have demonstrated enhanced hPDLC cell adhesion and viability. By addressing the inherent drawbacks of 3D scaffolds, such as low cell affinity and hydrophobicity, these changes improve its biofunctionality (25).

The modification of PLGA scaffolds to achieve the ideal porosity, structural integrity and spatial distribution of genetic material or growth factors is possible. Due to these characteristics, PLGA is a very versatile and promising scaffold material for tissue engineering in the periodontal and peri-implant regions (24-26).

Layered scaffolds. By allowing for a region-specific architecture that replicates the intricate structure of the periodontal apparatus, layering in 3D-printed scaffolds provides a tactical advantage for periodontal regeneration. The alveolar bone, PDL and cementum are three separate, yet functionally related tissues that comprise the periodontium. Each has specific biological and structural needs. Layered scaffolds support the different cellular behaviors required for each tissue type by enabling the incorporation of different microstructures and pore sizes within a single construct. For example, electrospun nanofibrous layers mimic the fibrous network of the PDL, whereas the larger, interconnected pores of the bone facing layer encourage vascularization and bone ingrowth. Additionally, layering facilitates the creation of a gradual interface between these areas, which is very similar to the manner in which that bone, ligament and cementum naturally transition. To prevent soft tissue invasion, an upper layer in some designs may function as a GTR barrier. Therefore, layered 3D-printed scaffolds provide a biomimetic platform for the regeneration of periodontal tissue in a spatially and functionally coordinated manner (27,28).

Mussel adhesive proteins (MAPs). MAPs provide a unique advantage in enhancing scaffold-based periodontal regeneration. Stable scaffold placement is made possible by strong adherence under damp conditions, which eliminates the need for additional fixation techniques. MAPs support the differentiation of periodontal ligament and bone-forming cells, enhance extracellular matrix secretion and improve cell attachment when added to scaffolds or applied as surface coatings. These biological effects promote improved integration with surrounding structures, and hasten tissue regeneration. When combined with biomaterials, such as titanium or calcium silicate, MAPs also improve the osteogenic potential of scaffolds, promoting more efficient bone regeneration. Their compatibility with platelet concentrates, such as PRF, further promote healing. MAPs facilitate the handling of scaffolds and membranes, and their position during surgery, increasing their usability. Overall, the inclusion of MAPs in scaffolds improves their functional results and exhibits promise for more consistent and effective periodontal regeneration (29).

6. Barriers to clinical translation

Currently the use of 3D-printed scaffolds for periodontal regeneration remains largely confined to preclinical stages, in which small-animal models (e.g., rat calvarial or fenestration defects) are utilized to demonstrate proof-of-concept regeneration of PDL, cementum, and alveolar bone. Although these models validate the ability of multiphasic scaffolds to guide tissue integration, the clinical translation to humans is limited at this stage due to the anatomical differences between the animal models and human periodontium. Challenges, such as vascularization and antimicrobial functionality for the scaffold still need to be addressed to ensure its stability in the oral cavity. To bridge this gap, early phase human trials are warranted to confirm the safety and effectiveness of bioinks and the resulting clinical efficacy of the scaffolds to make progress toward personalized defect specific therapies (30).

7. Future directions

While the field of bioprinting has evolved to provide more sophisticated scaffolds, challenges remain. The currently available biomaterials have their own limitations; thereby, the need to refine the scaffolds to resemble the complex nature of the periodontium is necessary. Future studies are required to focus on the use of nanotechnology and layered scaffolding to advance the bioprinting methods. Since vascularization is crucial for the survival of the scaffold, further studies are required to focus on the incorporation of pre-vascularized networks and to also aim to improve the cellular response to stimulate the differentiation of the mesenchymal cells. Regulatory guidelines and standardization protocols are mandatory to promote the clinical adoption of 3D printed scaffolds, thereby offering a personalized patient specific solution for periodontal regeneration.

8. Conclusion

Conventional approaches, such as GTR/GBR are currently enhanced by 3D printed scaffolds for improved tissue healing and regeneration. However, the clinical significance remains limited due to the challenges faced in the development of bioinks and maintaining the resorption rate of scaffolds. The field is still a growing arena undergoing constant development to improvise clinical outcomes in terms of the controlled release of bioactive agents and to mimic the dynamic nature of the periodontium. Although preclinical studies have yielded results, further studies are required to address the long-term clinical benefits to provide superior regenerative solution and regulatory guidelines. Standardization is also essential to translate the findings into clinical practice. 3D printing and biomimetics stand as an excellent solution for providing patient specific outcomes in periodontal regeneration.

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Authors' contributions

MM and SUN were involved in the concept and design of the study, in the acquisition, analysis and interpretation of data from the literature, and in the drafting, reviewing and editing of the manuscript. ASU and SK were involved in the concept and design of the study, and in the drafting, reviewing and editing of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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