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Biomaterials, Bioinks, and Cellular Approaches in 3D Bioprinting for Periodontal Tissue Regeneration

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Abstract
Three-dimensional bioprinting is a promising approach for periodontal regeneration, allowing precise fabrication of patient specific constructs that replicate the complex architecture of periodontal tissues. Using biocompatible materials such as living cells, hydrogels like growth factors and bioactive scaffolds, this technology enables simultaneous regeneration of gingiva, periodontal ligament, and alveolar bone. Advanced scaffold designs such as monophasic to triphasic and optimized printing parameters enhance structural integrity and cell viability. Despite significant progress, challenges remain in bioink rheology, cell incorporation, and clinical translation. Continued innovation is essential for advancing personalized, biologically integrated periodontal therapies.

Keywords: 3D bioprinting; periodontal regeneration, scaffold, tissue engineering, hydrogel

Introduction

Periodontal disease is a common chronic inflammatory condition that gradually destroys the periodontium, including alveolar bone, periodontal ligament (PDL), cementum, and gingiva, eventually resulting in tooth loss if untreated.[1] Current periodontal regenerative therapies, including guided tissue regeneration (GTR), bone grafts, and the use of growth factors, confront substantial constraints in repairing the intricate architecture and functional integration of multi-tissue systems. [1,2,3] Given these obstacles, tissue engineering technologies have emerged as viable ways to restore the periodontium in a more biomimetic manner.[1,2,4] Among these, 3D bioprinting provides a transformative approach by allowing the creation of finely organized, cell-laden constructions that can imitate natural periodontal architecture.[1] 3D bioprinting, which combines living cells, biomaterials (in the form of "bioinks"), and growth factors, provides for spatial control over cell placement, mechanical property gradients, and microstructure — all of which are necessary for reproducing the hierarchical structure of periodontal tissues.[3] Recent advances in bioprinting processes, bioink formulations, and biomaterial design have increased the possibility for clinical translation of bioprinted periodontal structures.[3,5] Recent advances in bioprinting processes, bioink formulations, and biomaterial design have hastened the clinical translation of bioprinted periodontal structures.[3] This review article gives a detailed overview of recent achievements in 3D bioprinting for periodontal tissue regeneration, addresses existing obstacles, and identifies potential avenues for clinical use.

Periodontal Tissue Complexity

The gingiva, periodontal ligament (PDL), cementum, and alveolar bone are the four main tissues that form the periodontium, a complex multi-tissue organ. [7] Together, these tissues form a gomphosis, a specialized fibrous joint that firmly anchors the tooth.[6] For effective load transmission, functional regeneration requires not only cell repopulation but also correct orientation of PDL fibres with Sharpey-like insertion into cementum and bone.[8] The periodontal interface has strong gradients in stiffness, composition, and biological signals that must be reproduced to prevent non-functional scar tissue or ankylosis.[9] The native PDL contains diverse cell populations, including fibroblasts, PDLSCs, vascular, and neural cells, along with extracellular matrix markers that influence cell fate.[10] Therefore, successful periodontal engineering requires multiphasic structures with controlled mechanical properties, porosity, and signaling to guide site-specific tissue differentiation.[5]

Principles of 3D Bioprinting

3D bioprinting is an advanced technique of rapid prototyping and additive manufacturing in which stem cells, bioactive molecules, and biomaterials are directly printed and arranged layer by layer using an automated system.[3] It is mainly composed of three steps: (as mentioned in Figure 1)

The stage of Pre-printing - In 3D bioprinting, the process usually starts with developing a detailed design using computer-aided design (CAD) software, which acts as the basic blueprint for creating the complex structure.[11] Next, a specialized 3D bioprinter is used to precisely place layers made of living cells, bioactive molecules, and biomaterial scaffolds—together known as bioinks—onto a prepared substrate or tissue culture dish.[3] This layering process is carried out with high precision and control, ensuring that the final structure closely replicates the natural organization of periodontal tissues.[12]

The stage of 3D bioprinting - By reproducing the complex structure of these tissues, the 3D bioprinted construct can integrate smoothly with the surrounding tissues and support the healing process.[3,5] The living cells involved are commonly enclosed within a biodegradable scaffold material.[3,13] This scaffold serves as an essential structural framework and also directs tissue growth, ensuring that development occurs in a regulated and well-organized way.[5,13] In addition, bioactive molecules are included in the structure, where they play a key role in promoting and guiding tissue regeneration, thereby improving the overall effectiveness of the bioprinting process.[3]

The stage of post-printing- After successful fabrication, the 3D bioprinted construct is cultured in a laboratory environment to allow the cells to proliferate, differentiate, and form new tissues. This cultivation phase is essential for proper maturation, ensuring the construct is suitable for implantation.[14,15,16,17] During this period, the construct may undergo spinning and microscopic evaluation, followed by placement in an incubator or bioreactor to support further growth and maturation.[18] Depending on the intended application, the final product is maintained under in vitro or in vivo conditions.[18] Once the construct reaches the appropriate stage of development, it is surgically implanted into the patient's oral cavity, where its seamless integration with surrounding tissues and the regenerative effects of embedded bioactive molecules contribute to a successful clinical outcome.[14,15,16,17]

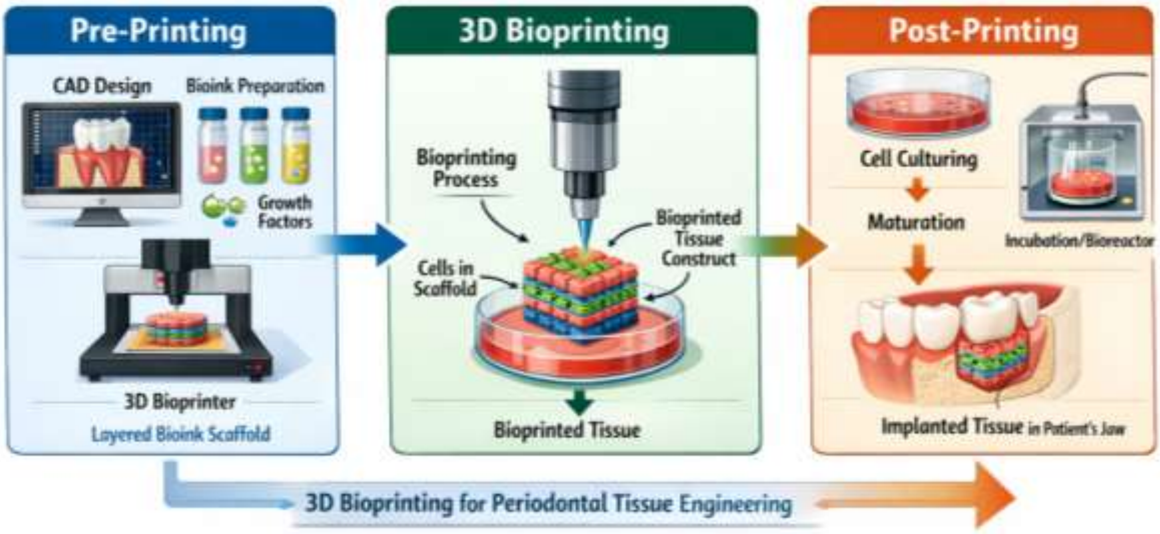

Figure 1: Principles of 3D Bioprinting.

Requirements for Periodontal Bioprinting

3D bioprinting is a promising technology for periodontal regeneration because it enables precise layer-by-layer placement of cells, biomaterials, and bioactive molecules, allowing constructs to mimic the native anatomy of periodontal tissues.[1] A primary requirement of periodontal bioprinting is the use of biomimetic scaffolds that can support the complex structure of gingiva, periodontal ligament (PDL), cementum, and alveolar bone in one construct.[5] (as mentioned in Figure 2). Hydrogel-based bioinks are widely preferred in periodontal bioprinting because they mimic the hydrated extracellular matrix environment necessary for PDL and gingival cell survival.[5] These scaffolds must be biocompatible, meaning they should not cause toxicity or immune rejection and should support cell attachment and survival.[5] Collagen and decellularized extracellular matrix (dECM)-based hydrogels have demonstrated excellent biocompatibility and enhanced periodontal cell adhesion and differentiation .[22] Scaffolds also need controlled biodegradability, so that they gradually degrade while new tissue forms, avoiding interference with healing.[5] Hyaluronic acid and gelatin-based hydrogels allow tunable degradation rates through chemical modification and crosslinking, enabling synchronization with periodontal tissue formation.[21] Designs should incorporate interconnected porosity, which allows nutrient/waste exchange and vascular infiltration, essential for long-term cell survival and function.[3] Porous hydrogel constructs fabricated through extrusion bioprinting enhance nutrient diffusion and vascular integration in periodontal defects.[18] The printing process must retain high cell viability, as harsh printing conditions (e.g., excessive pressure or heat) can damage cells before implantation.[5] Shear-thinning hydrogel bioinks improve print fidelity and maintain high post-printing viability of dental and periodontal stem cells.[11] Patient-specific customization using imaging (e.g., CT or MRI) and computer-aided design (CAD) ensures constructs fit the unique defect shape and anatomy of each patient.[1] Recent advances demonstrate multiphasic hydrogel-based constructs capable of spatially organizing bone, ligament, and cementum compartments for functional periodontal regeneration.[3] Composite hydrogel bioinks reinforced with bioactive ceramics further enhance osteogenic differentiation and mechanical stability for alveolar bone regeneration.[19]

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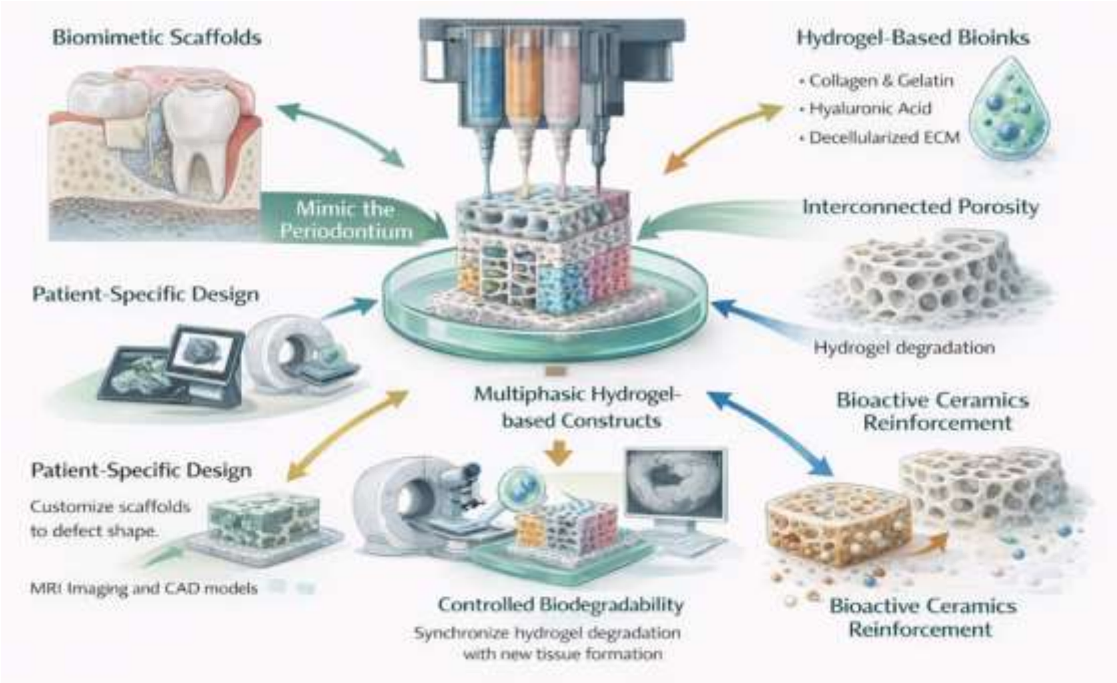

Figure 2: Requirements for 3D Bioprinting

Requirement for Bioink

Bioink is the core material used in bioprinting. It typically includes cells, biomaterials, and bioactive molecules that together form the living construct.[5] Bioinks must be tailored for target tissues: hard tissue bioinks for bone/cementum and soft tissue bioinks for ligament/gingiva regeneration.[5]
(as mentioned in Figure 3)

Hard Tissue Bioink

Hard tissue bioinks are designed to support regeneration of bone and cementum, requiring materials that withstand mechanical stress and promote mineralization.[3] These formulations often include bioceramics like hydroxyapatite or bioactive glass microspheres that enhance osteogenesis (bone formation).[19] The bioink must balance stiffness with cell-friendly properties, because overly rigid materials can impede cell infiltration and survival.[3] Growth factors such as bone morphogenetic proteins (BMPs) can be incorporated to enhance bone-forming activities within hard tissue bioinks.[1]

Soft Tissue Bioink

Soft tissue bioinks are formulated to regenerate periodontal ligament and gingival tissues, which require elasticity and flexibility.[5] Natural polymers like collagen, gelatin, hyaluronic acid, and alginate are commonly used because they mimic the native extracellular matrix of soft tissues.[5] Collagen and gelatin provide structural support and cell-friendly environments, with collagen especially being a key protein in periodontal ligament formation.[20] Hyaluronic acid is another promising component because of its high biocompatibility and role in tissue hydration and cell migration.[21] Soft tissue bioinks must support fiber orientation (PDL fiber alignment) for correct functional regeneration, as the ligament's orientation determines mechanical force transmission.[1]

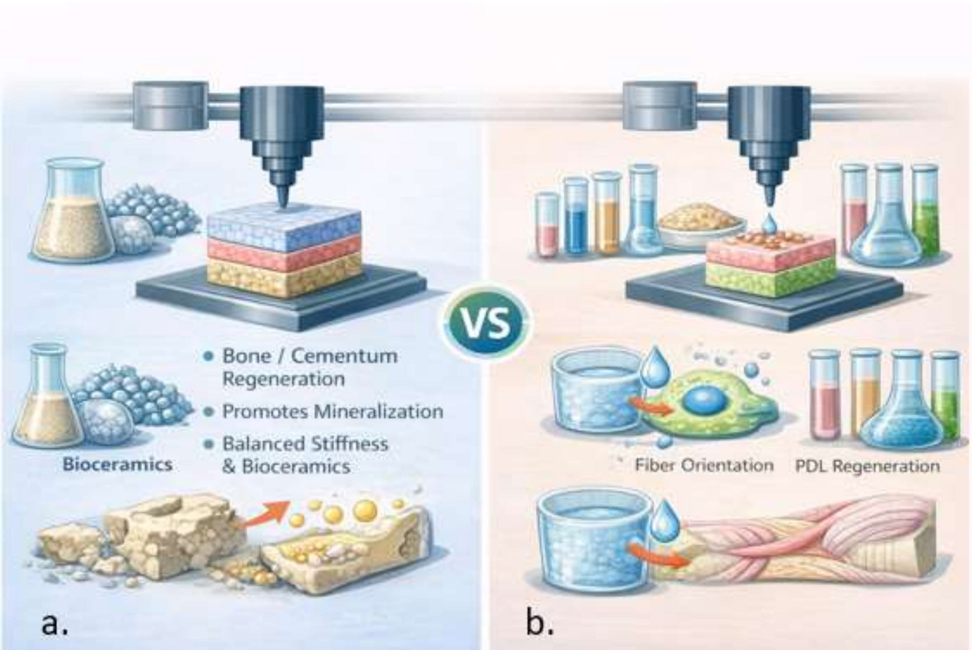

Figure 3: Requirement for Bioink a) Hard tissue bioink b) Soft tissue bioink

Advances in 3D Bioprinting for Periodontal Regeneration

Recent advances in periodontal bioprinting involve multiphasic scaffold designs, where different layers or regions of a single construct are optimized for specific tissues (e.g., bone versus ligament).[1] Emerging bioinks combine multiple natural and synthetic polymers to fine-tune mechanical, biological, and degradative properties.[3] In addition to basic hydrogels, research is exploring decellularized extracellular matrix (dECM) based bioinks, which provide native tissue cues for improved regeneration outcomes.[22] In animal models, these dECM-enhanced bioinks supported well-aligned ligament fibers and highly mineralized alveolar bone, showing promising functional regeneration.[22] 3D bioprinting enables integration of cells, such as periodontal ligament stem cells, directly within the scaffold to facilitate immediate tissue development after printing.[5] Advances in printing technologies (e.g., multi-nozzle systems) allow simultaneous deposition of varied bioinks tailored for hard and soft tissues.[1]

Innovative Technologies and Strategies

Several innovative strategies are being explored to enhance periodontal bioprinting. Multiphasic and gradient bioprinting enables constructs with smooth transitions between materials optimized for different tissue types.[3] 4D bioprinting, where printed constructs change over time in response to biological or physical cues, is a future strategy to improve integration and regeneration.[5] Microfluidic bioprinting allows precise control over cell placement and gradient formation of growth factors, enhancing complex tissue formation.[23] Integrating peptide nanostructures and other advanced fillers into bioinks enhances cell responses and might further support periodontal regeneration.[24] Artificial intelligence (AI) and computational modeling are beginning to optimize bioink formulations and print settings, improving reproducibility and outcome prediction.[5]

Preclinical and Clinical Studies

Most periodontal bioprinting research has been conducted in vitro and in animal models.[1] In Beagle dog models with critical periodontal defects, bioinks containing GelMA/dECM with human dental follicle cells significantly enhanced the regeneration of bone–ligament interfaces.[22] Results included well-aligned periodontal fibers and highly mineralized bone, essential for functional restoration.[22] Hydrogel scaffolds combining bioactive glass and growth factors also improved both soft and hard tissue regeneration in preclinical models.[19]

Research optimizing printing parameters (e.g., GelMA concentration, UV exposure) for periodontal ligament cells has improved cell viability and structural fidelity in printed constructs.[25] Clinical studies remain limited, largely due to regulatory requirements, safety concerns, and manufacturing scalability challenges, though early human pilot work is underway.[1]

Challenges and Limitations

Despite exciting progress, periodontal bioprinting faces major challenges. Achieving vascularization of large, complex constructs is difficult, yet essential to supply nutrients and oxygen to regenerating tissues.[3] Balancing mechanical properties with biological friendliness is complex, as hard materials needed for bone can negatively affect cell viability.[5] Maintaining high cell viability during the printing process is challenging due to shear stress and other physical forces.[5] Precise control over spatial distribution of multiple cell types to recreate the periodontium's complex architecture remains technically demanding.[3] Translation to clinical applications is restricted by regulatory, ethical, and manufacturing hurdles that require comprehensive safety data.[1]

Future Directions

Future research must prioritize vascularized bioprinted constructs to support long-term viability in large periodontal defects.[3] Next-generation bioinks that respond to biological cues or change properties over time (4D bioprinting) are promising for improved integration.[5] Growth factor gradients and spatiotemporal release systems may further guide tissue regeneration in situ.[5] Combining bioprinting with stem cell technologies and gene editing could enhance regenerative outcomes by driving targeted differentiation and immunomodulation.[1] Large-scale clinical trials and regulatory frameworks specifically for bioprinted regenerative products will be essential before widespread clinical use.[1]

Conclusion

3D bioprinting offers a next-generation approach for regenerating complex periodontal tissues by precisely combining bioinks, cells, and growth cues tailored to each tissue type. Advances in bioink design, printing technologies, and scaffold architectures have significantly accelerated preclinical successes. However, vascularization, multi-tissue organization, and clinical translation remain key barriers that must be addressed. With continued interdisciplinary research and improved regulatory pathways, bioprinting has the potential to revolutionize periodontal regenerative therapies and restore full periodontal function.

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