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Advancements in Periodontal Tissue Engineering: A Review of 3D Bioprinting in Periodontics

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Abstract

Various technologies and materials have been developed with the goal of repairing and reconstructing tissue loss in patients with periodontitis. Periodontal guided bone regeneration (GBR) and guided tissue regeneration (GTR) involve the utilization of a membrane to prevent epithelial cell migration, thereby maintaining space and creating a protected environment conducive to tissue regeneration. Over time, the manufacturing procedures of these barrier membranes have undergone significant improvements.Three-dimensional (3D) printing technology has resulted in significant advancements in periodontal regeneration techniques. The process of three-dimensional (3D) printing involves constructing 3D objects through additive manufacturing techniques. While its application spans various dental specialties such as endodontics, maxillofacial surgery, prosthodontics, orthodontics, and restorative dentistry, our review article focuses specifically on its use in periodontology. A comprehensive literature search was conducted on PubMed/Medline and Google Scholar using diverse key terms. The majority of selected studies were either in vitro, preclinical, case reports, retrospective, or prospective studies, with a limited number of clinical trials also being conducted. Periodontal applications of 3D printing encompassed educational models, scaffolds, socket preservation, sinus and bone augmentation, and guided implant placement. The findings revealed several advantages, including improved alveolar ridge preservation, enhanced regenerative capabilities, significant reduction in pocket depth and bony fill, simplified implant placement in complex cases with greater precision and efficiency, reduced procedure time, and improved outcomes.

Introduction

Periodontitis, is an infectious inflammatory disease caused by the bacteria of the dental plaque, resulting in the progressive destruction of the tooth supporting structures, i.e. the gingiva, the periodontal ligament, cementum, and the alveolar bone.[1,2] Periodontal disease is characterized by periods of exacerbation interspersed with periods of remission and presents a local microbial burden that initiates local inflammation and local tissue destruction.[3]Severe alveolar bone resorption caused by periodontitis is one of the leading causes of tooth loss in adults.[4] The aim of periodontitis treatment is not only to control inflammation via mechanical removal of plaque, but also to regenerate the periodontium. The traditional treatment of periodontitis can only achieve healing with long junctional epithelium attachment. It cannot acquire a complete periodontal regeneration.[5]

Tissue engineering emerges as a prominent area of interest within medical research, integrating biological principles with engineering concepts to facilitate the restoration and functionality of injured tissues or organs through a triad of essential components: seed cells, biocompatible scaffolds, and bioactive factors.[6] Within oral tissue engineering, periodontal regeneration has long been a focal point. Guided tissue regeneration (GTR) stands as a prevalent surgical approach in periodontology, with numerous reviews affirming its efficacy in achieving stable recovery of periodontal alveolar bone.[7-9] Extensive investigation into stem cells derived from the oral cavity has underscored their potential for periodontal tissue regeneration.[7, 8, 10–12] The microenvironment of periodontal defects significantly influences the success of GTR, highlighting the importance of biocompatible scaffolds in providing a conducive healing milieu for periodontal tissue recovery. Thus, the development of suitable scaffolds assumes paramount importance.

3D printing refers to the additive manufacturing method, wherein materials are constructed layer by layer.[13] This process utilizes data from CAD software, which analyzes thousands of cross-sections to create precise replicas of each product. [13] Within dentistry, 3D printing finds application in producing stone models, custom impression trays, and dental prostheses. [13]Moreover, it is under investigation for its potential in providing tissue scaffolding during bone grafting procedures.[14] Bioprinting stands out as the primary application of additive manufacturing.[15] Its benefits include thorough preoperative planning, enhanced accuracy in prosthesis fitting, and reduced procedure duration.[16] However, the primary drawback lies in the time and cost involved, making the justified utilization of this technology feasible only in complex cases. [16]

Various 3D printing techniques have been documented in the literature, each with its own set of advantages and disadvantages. These techniques include stereolithography, photopolymer jetting, selective laser sintering, fused deposition modeling, and powder binder printers. Stereolithography involves the use of a laser beam to construct objects layer by layer from light-curable, polymerizable resin. It tends to be expensive and poses challenges in post-processing. Photopolymer jetting entails the jetting and curing of light-curable polymer onto a platform in a layer-by-layer fashion. It supports the use of different materials such as resin, waxes, and silicon-based materials but can be costly and may trigger skin allergies. [17] Selective laser sintering employs a heated chamber to soften powder material, utilizing a laser to fuse the heated fine powdered material to build structures layer by layer. While it offers versatility in material selection, it requires a well-developed infrastructure. [17] Fused deposition modeling utilizes thermoplastic material extruded through a nozzle onto the build platform.[17] Powder binder printers utilize colored water drops from an inkjet printer, causing the cement or plaster to set in a layer-by-layer manner on an incrementally descending platform. [17]

3D printing holds significant potential in numerous domains of dentistry, including the fields of endodontics, prosthodontics, orthodontics, oral and maxillofacial surgery, and restorative dentistry. However, the primary objective of the current literature review was to comprehensively document all English-language literature concerning the applications of 3D printing specifically in periodontology following a comprehensive and meticulous literature search.

Methodology:

A comprehensive literature search was conducted on PubMed/Medline and Google Scholar to identify articles documenting the utilization of 3D printing in endodontics and periodontology. Key terms employed in the search included: "3D printing," "rapid prototyping," "additive manufacturing," "Dental education," "Stereolithography," "3D-printed scaffold," "periodontal repair," "periodontal regeneration," "bioprinting," "dental materials," "periodontal ligament (PDL)," "selective laser sintering," "tissue engineering," "CAD," "Guided Tissue Regeneration," "Alveolar Ridge Augmentation," "Bioprinting," and "Sinus Floor Augmentation." Only studies published in English were included in the review, encompassing both human and animal studies. Publications focusing on non-dental applications of 3D printing were excluded from consideration.

Table 1: A timeline depicting the evolution of the three-dimensional (3D) printing technologies of importance for the medical field[18]

Year	Key Developments
1984	The invention of stereolithography (SLA) 3D printing credited to Charles Hull
1986	The invention of the selective laser sintering (SLS) process attributed to Carl Deckard and Joseph Beaman.
1988	Bioprinting involves the 2D micro-positioning of cells, while the first commercial SLA 3D printer is credited to Charles Hull.
1989	The patenting of fused deposition modeling (FDM) is attributed to Lisa and Scott Crump.
1999	The first 3D-printed organ, a bladder, was utilized for transplantation by the Wake Forest Institute for Regenerative Medicine.
2000	EnvisionTEC introduced the first commercial extrusion-based bioprinter, known as the 3D-Bioplotter.
2002	The first early-stage kidney prototype was bioprinted via microextrusion by the Wake Forest Institute for Regenerative Medicine.
2003	The first inkjet bioprinter was developed using a modified HP standard inkjet printer.
2005	The founding of RepRap, an open-source initiative aimed at constructing a 3D printer capable of printing most of its own components.
2007	Selective laser sintering printers become available for 3D parts fabrication from fused metal/plastic.
2008	The first 3D-printed prosthetic leg
2009	The first 3D-printed blood vessels were developed by Organovo.
2012	The first 3D-printed jaw
2014	The first 3D-printed human liver tissue was achieved by Organovo, and the first desktop bioprinter was developed by Allevi
2015	The first implanted 3D-printed bioresorbable scaffold for periodontal repair was pioneered by the University of Michigan
2018	The first commercial 3D-printed full human tissue (skin) model, Poieskin, was developed by Poietis
2019	The first 3D-printed heart that contracts, with blood vessels, was developed by the University of Tel Aviv, and the 3D-printed lung air sac with surrounding blood

	vessels was achieved by Volumetric.
2020	3D-printed lung air sac with surrounding blood vessels, developed by Volumetric.

Three dimensional printing technologies

Various mechanisms exist for 3D printing technologies to function. The specific 3D printing mechanism employed results in distinct features tailored to the intended use of the product.

1. **Stereolithography**: Stereolithography (SLA) has emerged as a 3D printing technology boasting numerous applications, notable speed, and remarkable accuracy. SLA operates by employing photochemical processes to cure liquid resins layer by layer, resulting in intricately detailed designs.[19] While the beam-curing process of SLA technology may be time-consuming, it yields final products that are highly precise and exceptionally smooth.[19] The capacity of this technology to fabricate bespoke, patient-specific designs has garnered considerable interest within the dental community. As indicated in Table 1, SLA consistently produces designs of exceptional accuracy and finds extensive use in dentistry for tasks such as temporary and permanent crown and fixed partial denture fabrication, creation of surgical guides and templates, as well as production of diagnostic casts and models.[20] However, one notable drawback of SLA is the time-consuming nature of the process, particularly for small-scale designs, owing to the meticulous follow-up of the laser beam during material curing.[19] Nevertheless, SLA technology has significantly streamlined and expedited dental care practices, offering a more efficient approach to dental treatments.
2. **Digital Light Processing**: (DLP) Digital Light Processing (DLP) printing has emerged as an immensely valuable 3D printing technology, addressing the issues of lengthy fabrication durations.[22] DLP utilizes a light source to cure photopolymer resins layer by layer, resulting in highly precise and intricate designs.[23] This light-curing technology resolves the slower speeds seen in SLA printing, as DLP can cure an entire layer with one flash of light. However, a significant disadvantage of this technology lies in the size of each voxel. A voxel is akin to what a "pixel" represents in resolution, but within a 3D context.Consequently, a larger voxel size would result in lower resolutions, characterized by blockier and more squared-off designs., while smaller voxels would lead to higher resolutions (smoother designs).[24]Despite this drawback, DLP printing currently produces clinically acceptable temporary and

permanent restorations of crowns, fixed partial dentures, and removable prosthetic devices.[21] Overall, DLP printing offers clinicians innovative time-saving solutions for more predictable treatment outcomes.

3. **Fused Deposition Modeling (FDM):** Fused Deposition Modeling (FDM) is a valuable printing modality with applications in many areas of healthcare.[25] FDM utilizes thermoplastic filaments that are extruded when heated in a partially solid state and deposited layer by layer. [25] These layers harden when cooled but form a molecular bond with the heated filament as they are deposited onto the previous layer. While this technology provides excellent bonding of material layers, it is limited to use with thermoplastic materials. Currently, FDM has been employed to produce occlusal appliances and has also found applications in pharmaceutical settings, such as controlled-release drug delivery systems. However, its utilization in dental applications is somewhat restricted.
4. **Selective Laser Sintering (SLS):** Selective Laser Sintering (SLS) has proven to be a highly time-saving 3D printing modality within the realm of prosthodontics. SLS utilizes a high-temperature laser to selectively fuse powdered materials.[26] These materials range from ceramics to metals and even polymers. This versatility is advantageous as it allows for the production of high-density materials for dental applications.[26] However, a significant disadvantage of this technology is that it requires a large infrastructure for proper printing. SLS has demonstrated significant uses in dentistry, particularly in the fabrication of removable partial denture frameworks, which significantly reduces human error compared to traditional techniques. Selective laser sintering offers a safer and more predictable outcome in comparison to the conventional casting of metal in dental applications. An alternative to SLS printing is selective laser melting (SLM). SLM printing is comparable to SLS printing in terms of materials and processes, with the major difference being that in SLM, the material will be fully melted rather than sintered. [27]
5. **Photopolymer jetting:**Photopolymer jetting, commonly referred to as PolyJet 3D printing, offers a unique advantage to dentistry, particularly the ability to print in multiple colours. PolyJet employs inkjet printheads to dispense droplets of a fusing agent onto multiple voxels of a powder bed.[28] This process results in the melting and subsequent curing of the polymer powder.[28] The technology's ability to create multi-material and multicolour components provides significant advantages over other printing modalities. However, one major disadvantage revolves around the necessity of maintenance of the print heads, as they can clog easily. Currently, PolyJet printing

finds uses in the fabrication of dental models as well as temporary crowns. However, the material does not currently provide great mechanical properties, limiting its advantages in the oral environment. Photopolymer jetting printing holds tremendous promise for revolutionizing the dental industry by providing multiple colour options during printing, which is highly valued in esthetic dentistry.

6. **Powder binder jetting:** Powder binder jetting, also known as binder jetting, is a useful modality for maxillofacial prostheses involving medical-grade silicones and biocompatible elastomers.[29] Binder jetting often employs a water-based binder to selectively bond layers of starch-based powder, which is then infiltrated with silicone polymers. [29] The resulting material then undergoes post-processing to harden it into acceptable properties. The technology's capability to produce patient-specific and colour-matched maxillofacial designs is unmatched. However, these materials often have weaker mechanical properties and are delicate. Powder binder jetting provides an early and revolutionary solution to patient-specific maxillofacial applications and holds great promise in advancing dental manufacturing processes involving a less invasive production process for this unique patient population.
7. **Laser bioprinting (LAB):** Three-dimensional laser bioprinting (LAB) has emerged as a groundbreaking fusion of additive manufacturing and biotechnology, introducing notable advancements in dental regenerative therapies. This technology employs precise laser-based techniques to facilitate the meticulous layer-by-layer deposition of bioinks, encompassing living cells and a variety of biomaterials.[30] LAB printing has revolutionized the production of tissue-engineered constructs for periodontal regeneration, bone augmentation, and oral mucosal reconstruction.[30] In essence, 3D laser bioprinting presents a promising avenue for transforming dental treatments, equipping clinicians with innovative tools to craft personalized regenerative solutions tailored to individual patients. This holds the potential to significantly improve patient well-being and quality of life by addressing complex oral and maxillofacial challenges.

Table 2: Advantages and disadvantages of various 3D print technologies.

Following table summarizes the advantages and disadvantages of various 3D print technologies.

3D Technology	Advantages	Disadvantages
Stereolithography (SLA)	• Quick production speed; • Precise and highly accurate; • Can accommodate complex designs; • Numerous material options.	• Production can be slower compared to other printers; • High post-processing requirements.
Digital light processing (DLP)	• High speed; • Precise and highly accurate; • Can accommodate complex designs; • Numerous material options.	• Arguably lower quality than other printers; • Limited by voxel size.
Fused deposition modeling (FDM)	• Cheaper technology; • Great layer bonding.	• Only thermoplastic materials.
Selective laser sintering (SLS) and selective laser melting (SLM)	• Can print polymers or metals; • Batch production; • No supports needed.	• Requires high printing infrastructure; • Use of fine powders can he hazardous.
Photopolymer jetting	• Extremely high resolution; • Can print with multiple colors on one single print.	• Low mechanical properties; • Limited heat resistance; • Costly maintenance of printer heads.
Powder binder printing	• Wide range of unique materials; • High speed printing.	• Low mechanical properties; • Low resolution; • High waste of material.
3D laser bioprinting	• Only option to print	• Costly;

(LAB)		living cells and other biomaterials; • Completely unique.	• Very specific conditions to produce viable biomaterials.
Photocuring-based bioprinting		• high speed • high printing resolution • good structural integrity and • mechanical property • excellent cell viability	• hard to operate • required photosensitive material • with certain viscosity
Cell-Electrospinning		• good cellular activities • similar to the structure of • extracellular matrix • homogeneous cell density in structure	• poor mechanical strength • hard to develop to 3D structure • poor accuracy of fiber deposition
Cell-Electrospinning		• good cellular activities similar to the structure of extracellular matrix • homogeneous cell density in structure	• poor mechanical strength • hard to develop to 3D structure • poor accuracy of fiber deposition
Extrusion		• sufficient mechanical • Multi-choices of biomaterials able to print high concentration cell fluid	• low cell viability caused byinevitable shear force • limited printing accuracy • Bio-ink with certain curing and shear thinning properties
Droplet-jet bioprinting	Inkjet	• simple to operate • fairly affordable • excellent resolution and precision • fast speed	• narrow range of bio-active materials • potential mechanical or thermal damage to cells • low cellular concentration • lack of structural strength
	laser assisted	• high speed • up to single cell accuracy	• costly • long preparing stage

	bioprinting	• able to print different materials • to regenerate native structure • Non-contacting and nozzle-free	• limited choice in bio-ink • possibility in containing metalresidue

Studies on modifying periodontal scaffolds are conducted with a focus on three key aspects:

- Identifying appropriate seed cells while considering ethical and bio-safety concerns.
- Innovating scaffold fabrication by exploring new biocompatible materials and their potential clinical applications.
- Discovering more effective bioactive factors to facilitate complete periodontium regeneration.

In this review, we aim to provide a comprehensive summary of 3D bioprinting technology's applications in periodontal regeneration, covering three main areas: oral seed cells, biocompatible scaffolds, and bioactive factors.

1. **Seed/Stem cells:** These cells possess the unique ability for multi-differentiation and self-renewal, making them valuable seed cells in tissue engineering. They can generate new stem cells and transform into specialized functional cells like osteocytes and more.[10]

   Due to their versatile differentiation and self-renewal capabilities, stem cells hold significant promise for regenerating damaged tissues and restoring their original functions. However, achieving this requires the assistance of bioactive factors or biocompatible scaffolds to facilitate stem cell proliferation and differentiation.[7,10]

   In the human body, stem cells are broadly categorized into embryonic stem cells and adult stem cells. Embryonic stem cells, originating from embryos, have the potential to differentiate into any cell type. On the other hand, adult stem cells are typically found in various tissues and play crucial roles in tissue self-renewal and repair. Recent research underscores the widespread utilization of adult stem cells in oral tissue engineering, owing to the abundant sources of stem cells within the oral cavity.

   Mesenchymal stem cells are particularly noteworthy due to their versatile application potential. While they are primarily sourced from bone marrow and adipose tissue, they can also be derived from other tissues such as placenta, liver, skin, muscle, and the oral cavity itself. Stem cells obtained from oral and facial tissues exhibit properties similar to mesenchymal stem cells in laboratory settings, earning them the designation of pluripotent stromal stem cells. These cells can differentiate into various cell types including chondrocytes, osteoblasts, muscle cells, and adipocytes.

Adult stem cells sourced from oral tissues, specifically pertinent to periodontal regeneration, can be categorized into non-dental and dental groups.[10, 31-34]

Table 3: Seed cells of non-dental origin:[35-45]

Cells	Sources	Differentiation and Functions
Mesenchymal Stem Cells Derived from Alveolar Bone	Alveolar bone	Osteoblasts Adipocytes Chondrocytes Immunomodulation
Gingival Mesenchymal Stem Cells	Gingiva	Adipocytes Osteoblasts Chondrocytes
Adipose Derived Stem Cells	Adipose tissue	Osteoblasts Periodontal ligament-like tissue Immunomodulation

Table 4: Seed cells of dental origin:

Cells	Sources	Differentiation and Functions
Tooth Germ Progenitor Cells	Tooth germ	Adipocytes Hepatocytes Osteoblasts Neurogenic tissues
Dental Follicle Stem Cells	Dental follicle	Osteoblasts Odontoblasts Periodontal ligament tissue Adipocytes Chondrocytes
Stem Cells from Apical Papilla	Apical papilla	Odontoblasts Nerve cells Hepatocyte-like cells

		Periodontal tissue
Periodontal Ligament Stem Cells	Periodontal ligament	Osteoblasts Adipocytes Chondrocytes Immunomodulation Periodontal regeneration
Stem Cells from Human Exfoliated Deciduous Teeth	Pulp of the human exfoliated deciduous teeth	Adipocytes Osteoblasts Odontoblasts Nerve cells Hepatocytes Endothelial cells

2. Seed/Stem cells:

A. Natural polymers:

Collagen, a natural polymer found abundantly in various tissues from lower vertebrates to mammals, including cartilage, skin, and bones, has demonstrated significant efficacy in clinical settings for promoting tissue repair, regeneration, and reconstruction.[46] Collagen bioink is widely used in tissue engineering due to its compatibility with human tissues, particularly Type I collagen, which constitutes over 90% of the total collagen mass in the human body.[47] However, collagen is temperature-sensitive and prone to degradation during sterilization processes, necessitating cross-linking or combination with other materials.[48] Despite its excellent biocompatibility, collagen faces challenges in forming cell-carrying bioinks with suitable viscosity, resulting in scaffolds with low strength and sensitivity to metalloproteinases. The exploration of composite bioinks with collagen as the core is ongoing to overcome these limitations.

Gelatin, derived from collagen through partial hydrolysis, shares collagen's biocompatibility and belongs to denatured collagen.[49]Gelatin exhibits strong maneuverability similar to some synthetic polymers, making it preferable in certain experimental studies.[50] However, like collagen, gelatin requires treatment with acid or alkali before use. Functionalized forms such as gelatin methacrylate are compatible with various crosslinking chemistries and polymerization systems for long-term cell encapsulation.[51] While both collagen and gelatin promote extracellular matrix deposition in vitro, concerns remain regarding potential immune responses in the human body, especially to externally sourced collagen or gelatin. Glutaraldehyde crosslinking improves the shape fixation rate of gel systems, but compromises scaffold biocompatibility.[52] Pure gelatin is often employed as a sacrificial material in 3D bioprinting to facilitate oxygen and nutrient transmission. Modification strategies and UV cross-linking are explored to enhance gelatin's biocompatibility and mechanical strength.[53]

Alginate, a biodegradable polysaccharide, is non-immunogenic and negatively charged, making it widely used in tissue engineering. Its low toxicity and shear-thinning properties are advantageous for bioink applications. However, alginate hydrogels exhibit low bioactivity, necessitating modification to enhance bioactivity.[54,55]The use of calcium chloride solution as a chelating agent for crosslinking alginate is a common method in 3D bioprinting, maintaining scaffold biological phase integrity. However, alginate's short cell-binding domain and potential inflammation from calcium ions necessitate modification to improve cell adhesion, stretching, and proliferation on alginate scaffolds.[56]

In biological applications, the mechanical properties of hydrogels based on natural polymers depend on factors like concentration, crosslinking mechanism, and conditions. Composite materials combining multiple natural polymers can enhance mechanical properties. While single-component bioinks have been explored, composite bioinks are increasingly favored to meet diverse performance requirements in 3D bioprinting.[57]

B. Synthetic polymers:

PCL (Polycaprolactone) is a widely used polymer known for its high mechanical strength, excellent biocompatibility, degradability, and printability. It has received FDA approval for medical device applications. One of its notable characteristics is shape memory, allowing printed objects to return to their original shape under specific conditions. In medicine, PCL finds applications in printing heart models, bone scaffolds, nerve guides, and more. Despite its advantageous properties, PCL has drawbacks such as hydrophobicity and poor cell adhesion. Various methods and technologies have been proposed to address these issues, aiming to tailor PCL-based biological scaffolds to meet tissue repair and regeneration requirements.[58]

PLA (Polylactic Acid), derived from α-hydroxy propionic acid, is a thermoplastic aliphatic polyester prized for its outstanding mechanical properties, processability, transparency, dimensional stability, and biocompatibility. It is a biodegradable material sourced from renewable resources, making it environmentally friendly. PLA is the most widely produced biodegradable thermoplastic, showing an increasing trend in usage among biodegradable plastics.[59] Its biodegradability in the human body, eventual excretion as CO_2 and H_2O, and antibacterial and antifungal properties make it extensively used in medical applications.[60] Despite its numerous advantages, pure PLA suffers from poor toughness, high brittleness, and limited heat resistance. Research efforts have focused on modifying PLA to enhance its properties, with continuous updates in PLA-based 3D bioprinting materials.[61]

PLGA (Poly(lactic-co-glycolic acid)) is a biodegradable polymer certified by the FDA as a pharmaceutical excipient. Its degradation products, lactic acid, and glycolic acid, are metabolites in the human body, ensuring its biocompatibility and absence of toxic side effects.[62] PLGA exhibits good biocompatibility, minimal inflammatory response, and no rejection, making it widely used in tissue engineering.[63] PLGA microspheres are extensively studied for various drug delivery applications, particularly as carriers for proteins and enzymes. Additionally, PLGA's reliability and thermal properties enable its processing through additive manufacturing techniques like melt extrusion.

Synthetic polymers offer several advantages, including predictable mechanical and physical properties due to controlled manufacturing conditions and the ability to control impurities. Hydrogels based on synthetic polymers like PCL, PLA, and PLGA can be tailored for specific applications by adjusting functional groups, molecular weight, or polymerization chemistry.[64] However, achieving ideal structural properties for hydrated and ductile 3D hydrogel scaffolds through bioprinting remains a challenge yet to be fully realized.[65]

3. Bioactive factors:

Bioactive molecules encompass a variety of compounds with biological activity, including polysaccharides, alkaloids, peptides, nucleic acids, proteins, amino acids, and vitamins. These molecules, present in trace or small amounts, exert significant effects on life processes such as anti-inflammatory, anti-cancer, and antioxidant activities. They are widely distributed across animals, plants, marine organisms, and microorganisms. In the context of 3D bioprinting, the bioactive molecules primarily utilized are growth factors, enzymes, antibodies, antigens, plasmids, DNA, etc. These molecules are selected based on tissue type and desired functions to achieve optimal repair effects. Below are brief introductions to some commonly used bioactive molecules in 3D bioprinting and their roles in printed products.

Enzymes, highly specific and catalytically efficient proteins or RNAs, are often mixed with other polymer materials in printing processes to enhance their stability, activity, and biomedical applications.[66] For instance, a bioink composed of gelatinmethacrylamide, tyrosinase, and collagen has been utilized for in vivo skin tissue bioprinting, resulting in stable 3D living structures with high cell survival rates.

Growth factors, substances regulating cell growth and development, are essential in tissue engineering and 3D bioprinting, playing critical roles in treating various diseases. In one study,[67] muscle ink comprising gelatinmethacrylamide and VEGF-eluting Laponite particles was directly printed onto volumetric muscle loss injury sites, leading to enhanced muscle function recovery and reduced fibrosis, demonstrating potential for treating soft tissue traumas.

DNA, a fundamental biological macromolecule, is commonly used in genetic engineering but can also be applied in 3D bioprinting to prepare gene-active bioinks. When combined with bone marrow mesenchymal stem cells, DNA-based bioinks offer new avenues for bone defect regeneration.[68]

Research has shown that incorporating cells and/or bioactive molecules during 3D bioprinting enhances cell viability and regulates the microenvironment to promote tissue repair and regeneration. Meeting biological standards, ensuring cell activity and tissue function, and adhering to medical standards are essential in all 3D bioprinting processes. Extensive experimentation is necessary to identify optimal combinations of biomaterials, cells, and growth factors for each organ.

Periodontal clinical application of three- dimensional bioprinting

1. Socket preservation

After tooth extraction, there is a natural process of resorption that leads to the loss of width and height of the alveolar ridge. A systematic review has reported that, on average, there is a reduction of 3.87 mm in alveolar bone width and 1.67 mm in height following tooth extraction.[69] Recent technological advancements have introduced the use of 3D-printed scaffolds for socket preservation, aiming to maintain the dimensions of the extraction socket.

Studies have demonstrated promising outcomes with the use of 3D-printed scaffolds in socket preservation. For example, Park et al. conducted a study in beagle dogs and reported predictable results with the use of 3D-printed polycaprolactone in socket preservation. Additionally, a pilot randomized controlled clinical trial by Goh et al. showed that the use of 3D-printed bioresorbable scaffolds in socket preservation resulted in normal bone healing and significantly better alveolar ridge preservation compared to extraction sockets without scaffolds after 6 months.[70]

Further supporting evidence comes from Kijartorn et al., who reported in a prospective cohort study that 3D-printed hydroxyapatite holds potential advantages as a bone graft material in socket preservation.[71]

Despite these promising findings, there is a notable absence of clinical studies with long-term follow-up data in this area. Thus, future research should prioritize conducting such studies to provide a comprehensive understanding of the efficacy and long-term outcomes of using 3D-printed scaffolds for socket preservation.

2. 3D printed scaffold for guided tissue regeneration:

Recent advancements in tissue engineering have led to the development of 3D printed scaffolds tailored for guided bone and tissue regeneration. These scaffolds are designed to mimic the multiphasic nature of the periodontium, incorporating both hard (bone and cementum) and soft tissues (gingiva and periodontal ligament).[72] They exhibit tissue-specific characteristics and possess mechanical competence, making them suitable for various periodontal procedures such as socket preservation, guided tissue and bone regeneration, sinus augmentation, and vertical bone augmentation.[73,74]

The primary goal of these scaffolds is to facilitate the formation of bone, periodontal ligament, and cementum while promoting the reestablishment of connections between these tissues. Polycaprolactone (PCL) stands out as a commonly used scaffold material due to its documented success in promoting bone regeneration. These scaffolds offer advantages such as a 3D architecture closely resembling the extracellular matrix, leading to enhanced regenerative capabilities.[75]

Literature review indicates that most studies in this area are preclinical, involving in vitro, in vivo, and case reports, all of which demonstrate promising results in periodontal regeneration. For instance, Rasperini et al. reported the use of a 3D-printed scaffold in a human periodontal defect, showing favorable outcomes up to 12 months post-treatment.[76] However, longer-term follow-up revealed a decline in results. Similarly, Lei et al. reported significant reductions in pocket depth and bony fill in a 15-month follow-up case using a 3D-printed scaffold and platelet-rich fibrin for guided tissue regeneration.[77]

In a randomized clinical trial by Sumida et al., a custom-made 3D-printed device for bone defect management resulted in shorter procedure times and required fewer screws for retention compared to a commercial mesh group.[78] However, there remains a shortage of randomized control trials and clinical studies with long-term follow-up data, highlighting the need for further research in this area.

3. 3D printing in sinus lift procedure:

After tooth extraction, the loss of vertical bone height is a common occurrence, particularly impacting the treatment of partially dentate patients, especially those requiring implant placement, which necessitates adequate bone height and width. Additionally, the position of the maxillary sinus further limits available bone height.[79] Various methods have been explored in the literature for bone and sinus augmentation, including bone grafting, distraction osteogenesis, and guided bone regeneration.

Recent technological advancements, particularly in 3D printing, have introduced new possibilities for bone and sinus augmentation, showing promising outcomes. One notable advantage of 3D printing is its ability to replicate bony architecture and create a macroporous internal structure of graft materials with minimal wastage, owing to the additive manufacturing technique. Other benefits include the absence of ethical concerns, ample availability due to alloplastic materials, reduced risk of infection transfer, and decreased chairside surgery time.[80]

While randomized controlled trials are lacking, multiple case reports and in vivo studies have reported successful outcomes following the use of 3D scaffolds for sinus and bone augmentation.[79,81] Various materials have been utilized for printing bone grafts, including monolithic monetite (dicalcium phosphate anhydrous) and biphasic calcium phosphate. These materials demonstrate potential for effectively addressing vertical bone height loss and enhancing bone regeneration.

4. Three- dimensional printing for dental implants:

Implant placement is a common procedure performed by dental professionals to replace missing teeth, renowned for its predictable outcomes.[82] However, it is also technically demanding, and improper execution can lead to various complications such as poor esthetics, damage to anatomically important structures, infections, and implant failure.[83] Guided implant placement, facilitated by the fabrication of surgical guides using 3D printing technology, has emerged as a solution to prevent these complications. These surgical guides enable accurate 3D placement of implants, thereby minimizing the risk of unwanted damage to anatomical structures and reducing surgical time.

Numerous studies, including in vitro, in vivo, case reports, prospective and retrospective studies, as well as clinical trials, have investigated guided implant placement and consistently reported positive outcomes.[84-86] Two main protocols for guided implant surgery have been described in the literature: static and dynamic.[87] The static approach, also known as the stereolithographic guide, utilizes a static surgical template and does not allow for changes in the planned implant position during surgery. In contrast, the dynamic approach incorporates motion tracking technology, enabling adjustments to implant positioning during the procedure. These guides are typically produced using photopolymerization techniques.[88]

Although both static and dynamic protocols have been employed, the static approach is more commonly used due to its lower cost and reduced technique sensitivity.[87] Importantly, both protocols demonstrate comparable failure rates, highlighting the efficacy of guided implant placement regardless of the specific technique employed.

Conclusion:

Aliterature review was conducted, to explore the potential benefits of 3D printing in the field of periodontal regenerative therapy. As highlighted by dental tribune, the review was prompted by the significant global prevalence of periodontitis, affecting approximately 19 percent of the population worldwide. This prevalence underscores the necessity for effective treatment strategies.

While conventional therapies such as bone grafts, guided tissue membranes, growth factors, and stem cell technology have been utilized, the review points out that, 3D printing has recently emerged as a promising approach facilitating optimal cell interactions and fostering biological tissue regeneration in periodontal defects.

The review aimed to evaluate various 3D printing technologies, each offering unique advantages in general dentistry as well as for reconstructing or regenerating lost periodontium. However, 3D-printed scaffolds are pivotal in periodontal regeneration, providing a framework for cell attachment, migration, proliferation, and differentiation.For these scaffolds to be efficacious, they must meet specific requirements, including biocompatibility, porosity, and mechanical strength.

While 3D printing has made significant strides in meeting these criteria and addressing the medical demands of periodontal regeneration, the review acknowledges that certain aspects of the technology still require further development. The report underscores that 3D printing is "far from perfected" in terms of periodontal regenerative therapy, citing challenges such as high costs, biocompatibility concerns, and the need for suitable biomaterials.

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