Int J Med Rev 2017;4(3):81-85

doi 10.29252/ijmr-040305

INTERNATIONAL JOURNAL OF MEDICAL REVIEWS

Narrative Review

"Three-Dimensional Printing" – A New Vista for Periodontal Regeneration: A Review

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Received June 12, 2017; **Accepted** August 02, 2017; **Online Published** August 29, 2017

Abstract
Periodontitis is a multi-factorial disease with a broad spectrum of inflammatory and destructive responses leading to loss of periodontium and tooth-supporting bone. The aim of periodontal therapy is to regenerate the periodontium lost due to periodontal disease. Tissue regeneration in the oral cavity is regulated by signalling molecules, cells, and by matrix formation. Maintenance of the integrity of healthy periodontium and regeneration of the periodontium are achieved by a balance between bone formation and bone resorption termed as bone coupling. Traditional regeneration techniques using grafts and membranes were unpredictable and could not achieve complete regeneration. Periodontal tissue engineering focuses on regenerating the form and function of hard and soft tissues using signalling molecules, scaffolds, and cells. Bony defects may vary in size from small intrabony defects to large horizontal and vertical bone defects in periodontal diseases that prove critical for implant rehabilitation. For decades, efforts have been made to achieve predictable and reliable bone regeneration using various methods. This review focuses on the various materials and methods that are currently being used and which are in the research stage for 3D printing of patient-specific custom-made scaffolds for periodontal regeneration.
Keywords: Guided Tissue Regeneration, Periodontal; Tissue Engineering; Stem Cells
Citation: Lakkaraju RB, Guntakandla VR, Gooty JR, Palatarthy RB, Vundela RK, Bommireddy B. "Three-Dimensional Printing" – A new vista for periodontal regeneration: a review . Int J Med Rev. 2017;4(3):81-85. doi: 10.29252/ijmr-040305.

Introduction

Periodontal fibroblasts, osteoblasts, and cement oblasts are principle cells in periodontal regeneration. Stem cells are a renewable source for these cells. Cell-adhesion, migration, proliferation, and differentiation are the various steps involved in periodontal regeneration.[1] The ultimate goal of periodontal therapy is to regenerate the lost periodontal tissue caused by periodontitis.[2] Different clinical trials have demonstrated that grafting procedures for the regeneration in intrabony defects are achievable, but complete and predictable reconstruction of periodontal tissue is still difficult to obtain.[3] The cause of this is that damaged periodontium has a limited capacity for regeneration.[4] Tissue engineering/regenerative medicine targets the regeneration of tissue and organs either by implanting biomaterials in the form of grafts for in vivo regeneration or by constructing substitutes enriched with cells and growth factors in vitro and transferring them into the defect site for regeneration.[5] Tissue engineering is an interdisciplinary branch involving stem cell biology, material sciences, medicine, chemistry, and biomaterial manufacturing.[6] Emerging studies have proven that nanoscale topography and nano-geometry-based scaffolds have a positive influence on cell differentiation and behavior, leading to enhanced regeneration.[7, 8] A recent study by Van Dyke et al. showed that proresolving nanomedicines designed specifically for the treatment of inflammation-induced bone loss resulted in increased bone formation in a large animal model.[9] Ongoing research into the importance of nanoscale features for regeneration of periodontal complex tissue will further elucidate the required scaffold design parameters and therapeutic capabilities of nanotechnology-based applications. A wide range of materials, such as autografts, allografts, and xenografts, are used alone or in combination with platelet rich fibrin, growth factors, and bone morphogenic proteins which have been tried with limited success and predictability.[10-17] All tissues

originate from stem cells. A stem cell is defined as a cell that has the ability to retain the capacity to divide and produce progeny cells that differentiate (develop) into various cells or tissues, including periodontium. Strategies are being developed to incorporate these stem cells into scaffolds for regeneration.[18-23] There is a need for effective strategies for implementation of tissue engineering into day-to-day practice. These strategies may be a hurdle with regulatory agencies, as they represent tissues, biological products, and drugs requiring evaluation to be done in all of the applicable pathways.[6] The USFDA has approved 28 tissue-engineering products for clinical use, and they are commercially available for various applications.[24]

3D Printing

The term 3D printing describes a manufacturing approach that builds objects layer by layer. This manufacturing procedure is described as additive manufacturing or as rapid prototyping.[25] Powder or liquid resins are used for 3D printing in a layer-by-layer manner. To construct each layer, 3D printers use 3D CAD software that measures thousands of cross-sections for a precise output. The 3D machine dispenses a thin layer of liquid resin and uses a computer-controlled ultraviolet laser to harden each layer in the specified cross-section pattern. After the construct is fabricated, excess resin is removed using a chemical bath.[26] Resins, super alloys, plastics, titanium, polymers, nickel-based and cobalt chromium, stainless steel, ceramic composite materials, and polycaprolactone are some of the materials used in 3D printing.

Direct 3D Printing

Various cells, extracellular matrix, and bioactive molecule deposition can be done with fine-tuned control with this method. Living cell peptides, proteins, and DNA plasmids have been printed for various purposes.[27] 3D scaffolds with extra cellular matrix and cells have been printed by direct 3D printing technology.[28]

Indirect 3D Printing

Indirect printing involves the printing of a mold that is then cast with the final polymer. The scaffold for gene therapy and a growth factor delivery system are casted with this method. A computed tomography scan of the patient's defect acts as a template for making the 3D mold. Park et al. [29, 30] designed a 3D wax mold for periodontal regeneration to produce a fiber-guiding scaffold to improve integration of PDL fibers into bone and cementum. Alveolar ridge architecture can be maintained by placing an indirect 3D-printed scaffold in post-extraction sockets, resulting in normal bone healing and better maintenance of the alveolar ridge compared with extraction sockets without scaffolds.[31]

Fused Deposition Modelling

The fused deposition modeling technique for 3D printing uses a thermoplastic material, such as Polycaprolactone and poly lactic-co-glycolic acid (PLGA). These scaffolds have mechanical strength, high porosity, and controlled morphology. Cell and biomolecule incorporation may not be possible as this technique requires high temperatures for fabrication.[27]

Hydrogel Scaffolds

Soft tissue scaffolds can also be fabricated using hydrogels. Cell incorporation can be done into these hydrogel scaffolds.[27] Cell-to-cell interactions are restricted in these scaffolds, which can influence cell-to-cell signaling that may be detrimental in regeneration.

3D Printing with Live Cells

Living cells, either in cell aggregates or seeded onto 3D-printed scaffolds, may enhance cell signaling and promote tissue formation. The scaffold-free approach is defined as layer-by-layer additive biomanufacturing using live cells.[32] Spheroids of cells are used as building blocks that fuse to form a tissue in the minitissue-based approach. Blood supply to newly formed tissue can also be provided using vascular spheroids which assemble together to form vascular channels.[33] Recent research has focused on using 3D printing in building complex tissues, such as constructing periodontium-like tissue.[34]and patient-specific constructs such as temporomandibular joints.[27]

Emerging Concepts of Tissue Engineering in Periodontology

Advanced biomedical imaging such as cone beam computed tomography used for pathology visualization, implant placement, and to visualize the topography of bone has paved the way for better diagnosis and treatment planning in periodontology. CBCT imaging provides a scope for developing personalized scaffolds. High resolution three-dimensional imaging of bony topography obtained by CBCT allows the development of image-based scaffolds which can fit precisely in defect morphologies around teeth.[34] Polymeric or ceramic scaffolds can be developed using 3D printing, and three-dimensional printing has been utilized to make surgical guides and some first-generation regenerative scaffolds for clinical use. These scaffolding technologies can be used in combination with either biologics or cell therapies to create "bioactive scaffolding systems" intended for tissue repair and regeneration.[34]

Periodontal Scaffold Design and Fabrication with Additive Biomanufacturing

Periodontium is a complex tissue in its shape and structure. Designing scaffolds which mimic the complex periodontal shape and organization represents a significant challenge in regenerative periodontology. Although additive biomanufacturing may help

surmount this hurdle, the adoption and long-term success of these strategies rely greatly on the biomaterials being used. Ceramics and polymers are the most commonly used materials for the preparation of scaffolds.[35] These scaffolds can be synthetic or natural and can be resorbable or nonresorbable. Ceramic biomaterials simulating bone, such as CaP, calcium sulfates (CS), and bioactive glass (BG), are ideal candidates for hard-tissue engineering. They restore lost function with their stimulating effects on cell proliferation and differentiation and their relatively low degradation rate. Prolonged guided tissue remodeling and structural support for regeneration is achieved using these scaffolds. Brittleness and low ductility are concerns when using these materials.

Synthetic polymers, on the other hand, such as polylactic acid (PLA), polyglycolic acid (PGA), copolymer poly (lactic-co-glycolic acid) (PLGA), and PCL termed PLURONICS have highly adjustable characteristics, excellent production repeatability, and can potentially be mass produced. However, the high temperature required for printing makes the incorporation of cells and growth factors into the polymer mixture complicated if not impossible.[36] Laser-assisted printing, inkjet printing, and extrusion-based printing are various additive biomanufacturing techniques. Common to all these technologies is the use of CAD software or digital images for the design.[37]

Extrusion-based printing can be done using a wide variety of printers, which vary in the temperature-controlled material handling, dispensing system and stage, and an optional light source and piezoelectric humidifier. It is the most commonly used technique for fabricating additive periodontal scaffolds.[38] "An example of an extrusion-based printing technique evaluated for periodontal applications is fused deposition modeling (FDM). In FDM systems a thermoplastic material is fed from a filament coil and inserted into a heated nozzle head that enables the deposition of semi-molten state polymer struts onto a substrate".[39] The electrospinning scaffold fabrication method is also explored for periodontal applications. A syringe pump, a syringe that discharges the desired polymer, a high voltage supply, and a collector plate are part of the electrospinning setup. Electrospinning is also referred to as solution electrospinning if done with polymer solutions and melt electrospinning if done with polymer melts. Since melt electrospinning allows direct writing of the polymer melt, this method can be considered as an additive (bio) manufacturing technique.[40]

Multiphasic Scaffolding for Periodontal Regeneration

Periodontal tissue with its complex anatomy requires hierarchical tissue formation. Adequate periodontal ligament fiber orientation and its incorporation into the newly formed tissue establish strength and integrity, which are also key in periodontal regeneration. A PCL–PGA scaffold fabricated by computer-aided manufacturing addresses these problems. The scaffold consisted of both periodontal ligament-specific and bone-specific compartments. Indirect 3D printing was used to fabricate the hybrid scaffold. Pore size, channel orientation, and tissue specific compartments were carefully designed when preparing the mold. After fabrication, the molds were cast with a PCL or PGA polymer solution. To form a single scaffold structure, both compartments were fused with a thin layer of PCL. Biomimetic random hybrid scaffolds for engineering human tooth-ligament interfaces were evaluated in subcutaneous pockets of mice by Park et al. They demonstrated bone and periodontal ligament regeneration capacity and generation of parallel and obliquely oriented fibers. Adjustments were made to the design to further simulate periodontal tissues.[41] This approach demonstrated control over fiber orientation and facilitated the morphogenesis of periodontal tissue. Park et al. further evaluated the controlled channel architecture in the scaffold design on the periodontal tissue interface.[29] Compared with random scaffold architectures, in vivo evaluations of this scaffold in periodontal fenestration defects in athymic rats showed controlled and predictable periodontal fiber orientation, controlled tissue infiltration, and a better organization of the ligament interface. With this image-based, fiber-guiding scaffolding system, the authors intend to predictably facilitate regeneration and integration of dental supporting tissues.[30]

Cell Sheet Technology in Combination with Additive 3D Printing

Several groups of researchers have investigated the combination of additively manufactured scaffolds and cell sheet technology. Vaquette et al. [42] used a fused deposition-modeled component for the bone compartment and a more flexible solution electrospun component for the periodontal ligament compartments. It was a biphasic scaffold design for regeneration of alveolar bone and periodontal ligament simultaneously. Lee et al. [43] developed a triphasic scaffold as an extension of biphasic scaffolds. It aimed to integrate regeneration of various tissues. The scaffold was fabricated by using fused deposition modeling and consisted of compartments for the cementum/dentin interface, the periodontal ligament, and the alveolar bone. Regeneration of periodontal tissue was envisioned by a combination of biophysical properties and biological cues. Stiffness of the PCL scaffold impeded adaptability to the complex 3D anatomy of different periodontal defects and proved to be a limitation of this design. A case report of a personalized additively manufactured bioscaffold for periodontal osseous defect regeneration in humans was reported by Rasperini et al. Computed tomography scan of the patient's defect was used, and a 3D scaffold was prepared. PCL powder containing HA

was laser sintered to prepare this scaffold. Despite its promise, this scaffold became exposed after 12 months, which ultimately led to failure from a clinical point of view. Retrospectively analyzing this failure, a porous design for angiogenesis and a less bulky and easily absorbed scaffold might have provided better results as proven by various studies.[44-46]

Conclusions

3D imaging and modeling can have a huge impact on regenerative periodontics. Regenerative medicine and three-dimensional imaging allow more predictability in managing complex interdisciplinary clinical scenarios. These 3D scaffolding technologies can be used in combination with either biologics or cell therapies to create" bioactive scaffolding systems" for tissue repair.[47] A major hurdle in the usage of cell scaffolds in day-to-day practice is the difficult task of getting clearance from regulatory agencies as it involves cells and tissues.

Authors' Contributions

All authors contributed equally to this study.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

Funding

None.

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