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3D Printed Scaffolds For Periodontal Regeneration : An Overview On Fabrication And Biomaterials

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Abstract

Periodontal disease is a multifactorial disease resulting in loss of supporting structures. All periodontal therapies aims to regenerate both hard and soft tissue but fails to achieve complete regeneration. Hence, Tissue Engineering and Nanotechnonology utilizes signaling molecules and scaffolds in the periodontal therapies to achieve three dimensional regeneration by enhancing maximum cellular interactions, differentiation and proliferation.3D printing technology fabricates growth factors and osteogenic cell enriched scaffolds by additive manufacturing process for precise replication of defect area to be regenerated. Biomimicry, Autonomous self assembly and Mini tissue building block are the three approaches by which 3D scaffolds functions. 3D printers dispenses biomaterials following the instructions of STL format and uses ultraviolet laser beam to harden the material to form CAD designed scaffolds. Inkjet, Microextrusion and Laser assisted are the three types of 3D printers used commonly for scaffold fabrication. Polymers and Bioceramics are the most common biomaterials used for fabrication. Various studies have used composites, metals and hydrogels also for scaffold fabrication. This article intends to focus primarily on 3D printed scaffolds, biomaterials used for scaffold fabrication and its fabrication process in detail.

Keywords: Bioceramics, Periodontal regeneration, Polymers, 3D printed scaffolds, 3D printers.

Introduction

Regeneration of lost hard and soft tissues is the utmost aim of any periodontal therapy[1]. Though conventional grafting procedures proves to be successful in many clinical trials, complete regeneration is not evident [2]. Tissue Engineering and Nanotechnology paves its way in the field of Periodontics and Implantology for the reconstruction of lost periodontium utilizing signaling molecules, cells and scaffolds. Regeneration of hard and soft tissues by either indulging biomaterial in the graft form in vivo or fabricating growth factor and osteogenic cell enriched scaffolds for osteodifferentiation and angiogenesis in vitro and implantation of fabricated scaffolds in the defect site for complete regeneration are the focal intentions of periodontal tissue engineering [3,4]. Nanotechnology has also shown beneficial impact on three dimensional periodontal regeneration by assimilating stem cells in the scaffolds and by cell differentiation in various clinical trials [5,6]. Various researches are in the limelight for the conclusive evidence regarding the design parameters for scaffold fabrication and nanotechnological therapeutic application for periodontal regeneration[7]. The scaffolds or matrices were fabricated previously by subtractive manufacturing technique, but because of its restricted implementation in reproducing intricate anatomies and material wastage during fabrication process , 3D printing / Additive manufacturing / Bioprinting /

Rapid prototyping was invented [8]. This 3D printing extracts the data from CAD software and fabricates scaffolds layer by layer with various biomaterials in precise dimensions [9]. Current clinical trials have proven that these 3D printed scaffolds are superior to traditional grafting materials regarding three dimensional regeneration and the biomaterials used also optimistically influences the scaffolding properties. The added merit is that it restores the defect area with functional periodontium and structural hierarchy in tone with the original without scar formation [10].

What is 3D or bio printing?

Bioprinting is the process of printing live tissues [11]. Vijayavenkatraman S et al described 3D printing as a technology which fabricates multicellular and biomimetic tissues with complicated cytoarchitecture, hierarchial structure and functional homogenicity, intricate microenvironment and tissue specific mechanical and compositional heterogenicity in a multi scale domain. 3D printers fabricates scaffolds using computer aided design model by measuring thousands of cross sections, in turn constructs the exact replica of the desired area of regeneration by additive manufacturing approach i.e. layer by layer addition of material for fabrication[9]. It deposits and polymerizes various biomaterials, which are bioinks simulating cells incorporated extracellular matrix, to form scaffolds [12].

Bioprinting Approaches For Scaffold Fabrication:

The 3 bio printing approaches are Biomimicry, Autonomous self assembly and Mini tissue building block where Biomimicry is the capability of synthesizing biological tissues with bioinks mimicking the biological functions. Autonomous self assembly approach is the formation of extracellular matrix in which the proliferation of cells were regulated by signaling molecules to their tissue of interest [13]. The third one is where structures are developed from mini-tissue functional component and converting them into a larger structure with desired characteristics [14].

Properties Of 3d Scaffolds:

1. 3D matrices should be entirely biocompatible and bioactive for bone tissue bonding.
2. The porosity of matrices should be 30-90% identical to that of cancellous human bone as high porosity reduces the compressive strength of the scaffold in turn reduces the mechanical stability.(Asa'ad F, Rasperini G et al)
3. For enhanced vascularization and new cell infiltration into the scaffolds to bind with the ligands, the interconnected network of pores should have diameter ranges from 150 to 500µm.(Asa'ad F, Rasperini G et al)
4. Mechanical strength of 3D scaffolds should be adequate enough till complete tissue formation is obtained and should also possess adequate degree of hydrophilicity.
5. Optimal degradation time of matrices should be 5-6 months in order to match the natural bone remodelling process.(Titsinides S, Agrogiannis G et al)
6. Scaffold architecture should have resemblance to native extracellular matrix for enhanced cell adhesion, differentiation, proliferation and regeneration.(Seunarine K et al)
7. It should exhibit specific surface topography and nanotopography as it increases the overall surface roughness, surface area and surface to volume ratio for osteoblast & scaffold surface adhesion, nutrient diffusion, organized cell growth and extra cellular matrix formation.(Webster TJ et al, Hollister SJ et al, Woodard JR et al).
8. Scaffolds should permit stem cell and mesenchymal incorporation and stem cell culture within it.
9. It should be rigid enough for surgical handling and for easy placement into the defect area without collapse.

Scaffold Fabrication Process:

Three principles by which scaffolds have been fabricated are MODELLING, PRINTING & FINISHING. [15]

1.Modelling:

This is a pre printing process where the defect area to be regenerated is scanned using Computed Tomography (CT) OR Magnetic Resonance Imaging (MRI) Scans. The scanned image is then transferred to a computer for further scaffold designing and analysis. Computer Aided Design (CAD) software is used for scaffold designing process where the area of

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regeneration is reconstructed in the scanned images as a 3D structure / model. This process from scanning of defect area till designing of scaffold is termed as Modelling [15,16] .

2.**Printing**:

The Printing process starts by the conversion of Computed Aided Designed 3D model into a G - code file format or Surface Tesselation Language (STL) format. The STL file sections the 3D model into multiple thin sections so that the 3D printers can deposit bio inks layer by layer for fabrication[15]. Bio inks, are nothing but biomaterials which are used for scaffold fabrication, are selected based on the morphological and molecular composition of the structure to be regenerated and are loaded into the 3D printers. The 3D printer dispenses the material in a layered fashion following the instructions of STL format. The Biomaterial is hardened by a computer controlled ultraviolet laser in a specified cross section manner to form scaffolds [9].

3d printers and technologies:

These are the machines used for the printing of designed scaffolds. Inkjet based printers, Micro extrusion printers & Laser assisted printers are the three types.

Inkjet based printers:

These printers dispenses bioinks as ink drops in non - contact mode over the platform for scaffold fabrication[11]. Thermal, Piezoelectric and Mechanical are its types. In thermal inkjet printers, the bio inks are dispensed from the nozzle by the pressure created by heating the printhead[17]. In piezoelectric type, the acoustic waves produced by voltage applied to the piezoelectric materials forces the bioinks from the nozzle [18]. In mechanical type, the bioinks are dispensed by the application of pressure [19]. Cell laden scaffold for soft & hard tissue printing are printed by these printer commonly [20].

Micro extrusion printers:

These printers dispenses biomaterials by a fluid dispensing system and an automatic robotic system attached to the printer. Fluid dispensing system is of pneumatic or screw driven or piston type where pneumatic type uses pressure air for dispensing bioinks and Piston and screw type uses mechanical pressure to jet the bioinks respectively[18]. These printers can print bioinks with high cell densities but it requires high pressure to extrude bioinks with high viscosity resulting in cell death[11, 21].

Laser assisted bio printing:

These printers uses Lasers to deposit bioinks. It comprises of a 'ribbon' containing bio inks which is supported by Titanium or Gold layers which absorbs and transfers energy. Bio inks are vaporized by laser pulses, in turn it produces a pressure bubble which later exerts pressure on biomaterial to get deposited for bioprinting process at high resolution. Prevention of biomaterial clogging is one of its advantages as it is a nozzle free technique but the presence of metal absorbing layer may leave metallic residue in the fabricated scaffold[11, 22].

Though all 3D printers works by Additive Manufacturing technology, recent studies have utilized various techniques for scaffold fabrication.

Stereolithographic technique is the most common where a perforated platform is placed under a polymer container and a beam of laser is used to harden the biomaterial. When the first layer of biomaterials gets hardened, the platform lowered and an another layer is deposited and hardened. The procedure is repeated until the entire designed model has been printed[23,24].

Direct light processing is an optical technique where a light projector is used to polymerize the biomaterial by projecting voxel (Volumetric pixel) data into the photopolymers at ultra violet wavelength[23].

Fused deposition modelling is a material extrusion technique where two materials called Modelling and Supporting material were used. Modelling material is the main biomaterial which gets deposited from the printer in layer by layer pattern along with the Supporting material which is a gel like material, acting as scaffold and will be removed once printing has been completed and exposes the modelling material for use[23,24].

Inkjet powder printing technique uses inkjet styled printhead which jets Glue or Binder (Gypsum based composite) to bind the successive layers of deposited powdered material. Few printers create 3D structures with high resolution by jetting both binders and coloured inks.[23].

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Selective laser sintering technique binds the powdered material by heat rather than binders and it uses laser to fuse selective particles and when scaffolds are fabricated with metals, then it is termed as Direct Metal Laser Sintering[23,24].

3.**Finishing**:

Finishing the printed scaffold is the final process of scaffold fabrication where removal of extra material from an oversized printed material and removal of surface roughness for the accurate fit of scaffold to the defect area has been undertaken. Chemical bath can also be used to remove the excess soft resin from the fabricated scaffold[15, 23].

Biomaterials Used For Scaffold Fabrication

Since biomaterials influences the scaffolding properties in the aspect of cell adhesion, proliferation and regeneration, selection of biomaterials is considered a key factor for successful scaffold designing. Polymers and bioceramics are the most commonly used materials.

1.**Polymers**:

Natural polymers:

Various clinical trials suggested the use of natural polymers because of its biocompatibility, cellular recognition, cellular interactions and hydrophilicity.

Collagen, a protein which provides structure and stability to the tissues, is the most commonly used natural polymer since it represents the major constituents of Extracellular Matrix. An invitro study conducted by Pastorino L et al have documented that 3D printed collagen scaffolds promoted cell adhesion, cell proliferation and osteodifferentiation of Bone marrow stromal cells. It is one of the choice of materials in non load bearing areas because of good biomimetic property, biocompatibility and cell remodelling capacity.But has to be cross linked with other biomaterials to enhance its weak mechanical property[25, 26].

Similarly, Gelatin, a denatured form of collagen exhibits excellent biocompatibility and it is water soluble in nature. It also has better flowing property hence blends with other biomaterials too but it lacks rigidity. Studies have stated that it enhances osteoblast adhesion, osteoblastic migration and mineralization [26,27].

Silk fibroin, a natuaral polymer obtained from Bombyx mori species can also be used for scaffold fabrication as spider silk has better mechanical strength and printability. Added advantage is that it maintains the viability of mesenchymal stem cells. But high shear application in the extrusion printing changes its dimensions before fabrication, hence it is printed using Direct Light Processing technique[26].

Alginate or algin or alginic acid, a natural polysaccharide composed of alpha - L - Glucuronic acid or beta - D - mannuronic acid, obtained from brown algae has good cell encapsulation property as it enhances the cell growth by imbibing water and other nutrients required for the growth from the micro environment and also has better flexural strength because of its gel forming property. Disadavantages are its slow biodegradability and poor cell adhesion property. Since it has a structural similarity to human glycosaminoglycans, it can also be used for regenerative use [26, 28].

Agarose, a polysaccharide constituting D-galactose & 3,6 anhydro galacto pyronose extracted from sea weed can also be used because of its good mechanical strength and biocompatibility but has very poor cell adhesion and it is non- degradable [26].

Chitosan, a cationic polysaccharide obtained from chitin, has antifungal, antibacterial and analgesic properties and highly biocompatible. It accelerates wound healing by rapid blood clot formation and also reduces the post operative infection by minimizing the scaffold contamination. Also it forms stable hydrogels which enhances the cell affinity and increases the mechanical strength. It is the choice of material for Guided tissue regeneration[26, 29].

Cellulose, a polysaccharide exhibiting high cell viability maintaining property can also be used for scaffold fabrication process. Akizuki et al in their study have used Methyl cellulose scaffolds seeded with single layer cell sheets for periodontal regeneration[26, 30].

Hyaluronic acid or Hyaluronan, a natural polysaccharide present in the human connective tissue in the form of glycosaminoglycans has enhanced role in fibroblast and mesenchymal stem cell growth and its migration and maintains cell viability and stability at higher levels at higher

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concentrations. The only disadvantage of Hyaluronan is that it has low mechanical strength but can be made rigid by esterification and cross linking process[26, 31].

Synthetic polymers:

Scaffolds based on synthetic polymers are used for 3D scaffold fabrication to overcome the reduced bio activity, weak mechanical strength and rapid degradation rate of natural polymers to enhance better regeneration. Aliphatic Polyesters are thermoplastic semi-crystalline materials. Polycaprolactone (PCL), Poly Lactic acid (PLA), Polyglycolic acid (PGA) and Poly Lactic-co-Glycolic acid (PLGA) are the current most common polyesters used for scaffold fabrication.

PCL has excellent mechanical stability , biocompatibility, mouldability. It has low melting point which enables it to maintain the viability of live cells incorporated into the scaffolds during the deposition. The degradation of PCL is by hydrolytic mechanism within the interior part, keeping the exterior surface of the scaffold intact thereby maintains the contour of the regenerated bone volume over time. It is hydrophobic in nature which results in reduced cell affinity and cellular interactions [32, 33, 34]. It is considered as choice of material for multiphasic 3D scaffold fabrication [35]. Slow degradation rate is a major disadvantage which was evident from a study conducted by Rasperini et al where the histological and molecular analysis of a PCL scaffold implanted into a periodontal defect at 13 months revealed 76% scaffold mass remaining in the defect site [36].

PLA, PLGA are also hydrophobic in nature while PGA is hydrophilic and have higher degradation rate. PLA can be easily processed and it is metabolized easily in the body. PLGA can be used as a better co-polymer for PLA [26, 34].

Fluoric f-127 is an expelled component during polymer cross linking process which leaves pores on the scaffold structure in turn produces an enhanced environment for cell growth and nutrient diffusion[37].

2.**Bioceramics**:

These are inorganic biomaterials with excellent biocompatibility, hydrophilicity, mouldability, similar native bone composition where the cellular population is greater on the scaffold surface in turn increases the cell to cell interactions thereby promoting cell proliferation and differentiation[38]. Blokhuis TJ et al have documented even its osteoconductive & osteoinductive property in an in vivo study. Bioceramics have its applications in Guided Bone Regeneration and Socket Preservation procedures.

Coste PF et al have documented the use of Calcium Phosphates in 3D scaffolds for Periodontal regeneration.

Hydroxyapatite (HA) is the most commonly used Calcium phosphate in periodontal tissue engineering as its inorganic composition is identical to that of human bone and also had a positive effect on osteoblast adhesion & proliferation. Hydroxyapatite in amorphous form has higher degradation time than crystalline form[39]. Porous Hydroxyapatite scaffolds has greater cell viability than denser one[40]. Nanohydroxyapatite can also be used because of its excellent bone binding ability [41].

Beta Tricalcium phosphate (TCP) possess a strong bone binding capacity and biodegradability. Biphasic Calcium Phosphate (BCP), a combined form of HA and TCP has a very controlled bioactivity, stability, degradation and bone ingrowth in large defects when compared to other calcium phosphates. BCP degrades in a faster rate when compared to HA and slower than TCP[42,43].

Bioactive glass is a silicon oxide with calcium substitute which binds with the bone chemically by forming a layer of HA on the surface on contact with body fluids without intermediate fibrous connective tissue layer. Biodegradability is slow because of its conversion into HA in physiological environment[44].

All these bioceramics have excellent osteoinductive property as they absorbs osteoconductive exhibiting factor or differentiation of osteoprogenitor cell into osteoblasts by calcium and phosphate release into the microenvironment [45].

3.**Hydrogels**:

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Hydrogels are used for 3D scaffold fabrication because of its high biocompatibility, good rheological, better mechanical, clinical and biologic properties. Studies have encountered that scaffolds made up of microsphere encapsulated BMPs and Glycidyl Methacrylate Dextran + Gelatin has good tissue engineering applications for periodontal regeneration[46]. Cultured collagen gel seeded with cells can also be implanted into defect for better tissue repair and regeneration[47]. Gelatinous carrier retains signals like Arg-Gly-Asp (RGD) thereby enhances cell adhesion, migration, differentiation and proliferation. [37, 48].

4.**Metals**:

They usually possess high mechanical strength, toughness & hardness when compared to polymers and bioceramics. Titanium is the commonly used metal. Studies also reported that Titanium based 3D scaffolds possess good hydrophilicity thereby increases the mineral deposition and enhances better cell attachment and proliferation[49]. Another study conducted by Haugen HJ et al have also documented the new bone formative ability of titanium without any inflammatory signs. Since it non-degradable, it needs an additive surgery to remove the scaffold.

Magnesium and its alloys have excellent osteoconductive property hence increases the osteogenic marker expression but has high degradation rate[50].

5.**Composites**:

These are biomaterials where two or more different biomaterials are combined to enhance the advantages of properties for better scaffold fabrication. Natural polymers are combined with synthetic polymers or bioceramics to overcome its undesirable bioactivity and weak mechanical strength in GTR applications [51]. PCL combined with HA enhances HA's brittlesness and reduces hydrophobicity of PCL thereby increases the cell penetration into the scaffold[52]. Crystalline HA can be combined with Natural polymers to modify its degradation time[53]. Since, Bioceramics are brittle and has low flexibility and mouldability, it is combined with synthetic polyesters or metals for better applications in non-bearable areas[54]. Aliphatic esters causes tissue necrosis by releasing acidic products on degradation hence combined with Bioceramics to enhance its bioactivity[55]. Collagen combined with HA has enhanced tissue regeneration because of its compositional similarity to the bone[51]. Titanium coating in magnesium scaffolds may modify the degradability rate of magenesium[56].

Future Perspectives:

Though various biomaterials discussed have documented predictable outcomes in various literatures, efficacy and safety of biomaterials, biomaterial combinations, fabrication techniques used to construct scaffolds for every particular tissues and use of autogenous biomaterials are not assessed. Hence, research should be carried out to explore these aspects for better scaffold fabrication . Studies should be directed to focus on geometry and optical particle size of biomaterials for better spatial resolution of scaffolds. Apart from biomaterials, resolution can also be determined by printheads of 3D printers. More innovation can be made in printheads to reproduce finer details accurately and rapidly. Multicomponent printing where simultaneous printing of multiple cell types with different materials also need to be explored[57].

Conclusion:

3D scaffolds are excellent advancements aimed at multi tissue regeneration of periodontium by ensuring complete cell infiltration and migration, proliferation, vascularization, differentiation, scaffold degradation followed by new tissue formation and it is also proved by creating interconnected pores and surface topography which is exactly required for periodontal tissue engineering in various studies. Various researches in the biomaterial aspect, biological aspect and also in technological aspect are put forward to improve and develop the technology for precise scaffold fabrication . Even though, 3D scaffold is at the futuristic level, few concepts are still not been explored completely, It is an absolute need for clinicians and researchers to enhance the translation from preclinical level to clinical trials in humans. With that, definitely 3D Printed Scaffolds will be a future, fertile in periodontal regeneration.

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Figures

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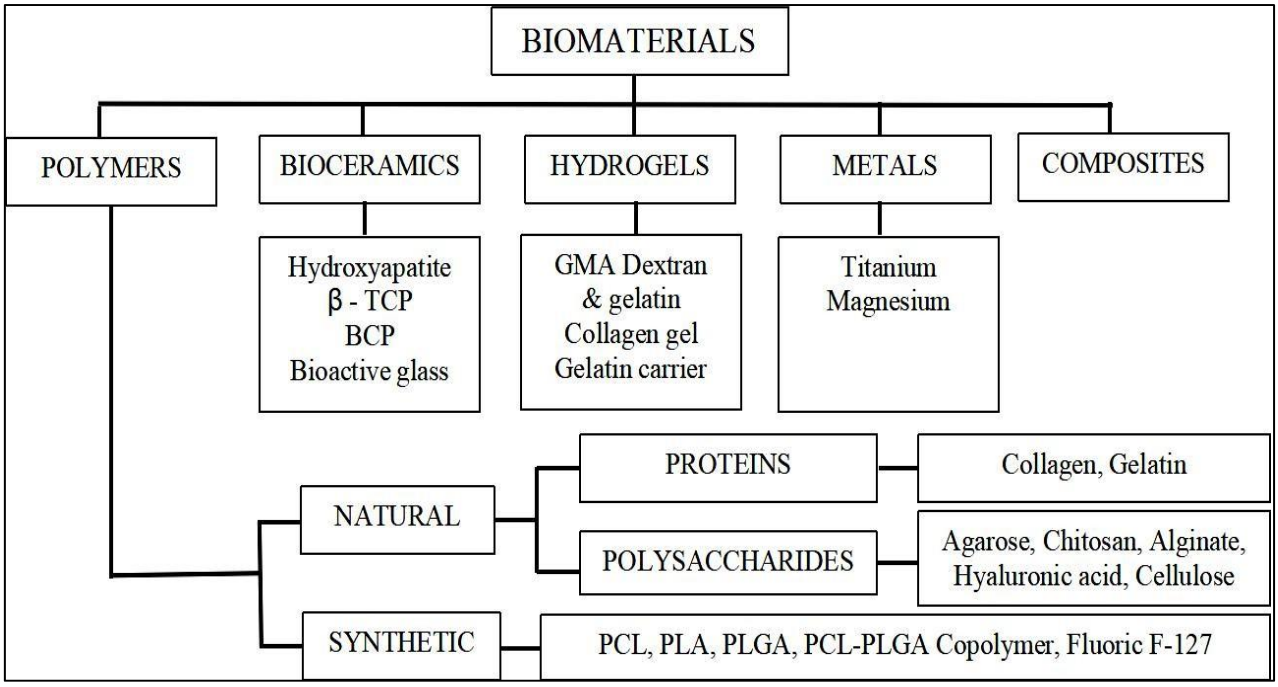

FIGURE 1: Biomaterials used for 3D Scaffold fabrication

ABBREVIATIONS:

β - TCP - Beta TriCalcium Phosphate

BCP - Biphasic Calcium Phosphate

GMA dextran - Glycidylmethacrylated dextran

PCL - Polycaprolactone

PLA - Poly Lactic Acid

PLGA- Poly Lactic-co- Glycolic acid

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