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Three-dimensional printing for craniomaxillofacial regeneration

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Abstract (J Korean Assoc Oral Maxillofac Surg 2017;43:288-298)

Craniomaxillofacial injuries produce complex wound environments involving various tissue types and treatment strategies. In a clinical setting, care is taken to properly irrigate and stabilize the injury, while grafts are molded in an attempt to maintain physiological functionality and cosmesis. This often requires multiple surgeries and grafts leading to added discomfort, pain and financial burden. Many of these injuries can lead to disfigurement and resultant loss of system function including mastication, respiration, and articulation, and these can lead to acute and long-term psychological impact on the patient. A main causality of these issues is the lack of an ability to spatially control pre-injury morphology while maintaining shape and function. With the advent of additive manufacturing (three-dimensional printing) and its use in conjunction with biomaterial regenerative strategies and stem cell research, there is an increased potential capacity to alleviate such limitations. This review focuses on the current capabilities of additive manufacturing platforms, completed research and potential for future uses in the treatment of craniomaxillofacial injuries, with an in-depth discussion of regeneration of the periodontal complex and teeth.

Key words: Three-dimensional printing, Periodontium, Hydroxyapatite, Biomaterials

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I. Introduction

Although the patterns of incidence and their causes have changed over the decades, craniomaxillofacial (CMF) injuries still occur worldwide. The most common causes include traffic and sports-related accidents, assaults, falls, civilian warfare[1-3], as well as diseases, congenital disorders and surgery[4]. CMF injuries are typically characterized by bone fractures in the frontal, orbital, nasal, maxillary and mandibular regions[2] and soft tissue damage such as complex lacerations, tissue avulsions, nerve and vessel injuries, and burns[5-9]. These complex injuries can compromise vital structures. Consequences of CMF injuries are disfigurement and dysfunction, including compromised airway, hemorrhaging, infection, scarring, nerve damage, and non-union fractures[2]. These disfigurement and dysfunction contribute to acute and long-term psychological problems as well to social and economic burdens[8,10,11] since these detrimental outcomes are largely due to lack of full restoration of function and aesthetics found in the available treatments.

Due to the complexity of CMF injuries, the affected hard and soft tissues within the wound environment are unsuitable to support proper healing[4,12,13]. Moreover, management of CMF injuries is extremely challenging and involves a multidisciplinary team of professionals for the treatment of facial bone fractures, dentoalveolar trauma, and soft tissue injuries as well as associated injuries, mainly to the head and neck regions[3,11,14,15]. Major bone and soft tissue reconstruction often requires the use of autografts or allografts. Although autografts—considered the "gold standard"—and allografts are very attractive for their resorption, mechanical properties and immunological characteristics, both approaches have multiple limitations related to tissue availability, donor site morbidity and infection[4,16-19]. Since major drawbacks for using autografts and allografts include the need to manually sculpture the grafts in the desired shape[4,20], synthetic alternatives using additive manufacturing have become an attractive option[4,12,17].

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As mentioned before, the primary goals of CMF repair are restoration of aesthetics and function, both requiring precise pre-surgical planning as well as prostheses and implants fabricated in very unique geometries and sizes[15,18,20,21]. In the past decade, techniques such as additive manufacturing (e.g., three-dimensional [3D] printing) have been explored for tissue engineering purposes, especially for dental and CMF repair. This review focuses on tissue regenerative strategies for the CMF as a whole along with a focused discussion on 1) the regeneration of the periodontium and teeth within the oral cavity, and 2) providing an outlook on the advantages and limitations of current additive manufacturing, treatments and tissue regenerative research. The ability to harness the successes of tissue regeneration within specific regions of the CMF, such as the periodontium and teeth, could lead to a combined approach for regeneration of a larger region. This review will also discuss that potential and the ability of 3D printers to create a platform for manufacturing rather than the multiple manual manufacturing techniques currently used.

II. 3D Printing Technology for CMF Surgery

Additive manufacturing techniques, such as 3D printing, use the process of joining materials to create objects from digital 3D model data[20]. For biomedical applications, 3D printing can be used for the fabrication of complex scaffold shapes that are specific to patients using computer aided design (CAD) and advanced medical imaging techniques such as magnetic resonance imaging and computed tomography (CT)[12,18,19,22-29].(Fig. 1)

Although many industries have benefited from the development of additive manufacturing technologies since the mid-1980s, their applications in the biomedical field have been slow due to technical challenges such as limited accuracy, low mechanical properties and lack of biomaterial availability. All of these limitations have been investigated over the last two decades in order to address stringent performance and safety concerns[12,19,22,27]. As a consequence, 3D printing technology has become more popular in tissue engineering and has found many applications in the fabrication of custom implants for the reconstruction of CMF defects[26]. This has allowed for precise adaptation of the implant to the region of implantation, reducing surgical times and leading to lesser chances for infection, faster recovery and better cosmesis[15,18,19,25,28]. 3D printing has also been introduced into the surgical field as a tool for pre-surgical planning[25,29], allowing surgeons to review and interact with the anatomical models, thereby facilitating the understanding of the morphology and making it easier to perform complex surgeries in less time[18,24,27,30,31]. The uses of 3D printing for preoperative planning have been previously described in literature[26,32]. While these planning techniques have expanded the knowledge in both the scientific and medical communities, the use of 3D printing towards tissue regeneration focuses on the need for specific biomaterial-based printing rather than rapid prototyping for surgical guidance.

1. 3D printed biomaterials for CMF repair

Early 3D printing research focused on the use of metals and ceramics[12] for bone tissue engineering. Ceramic scaffolds have been 3D printed and tested *in vitro* under static and dynamic conditions, achieving high printing resolution, structural mechanical support and cell growth[20,23,33]. Today, 3D printing applications are investigated not only for bone reconstruction but also for replacement of soft tissues, using a variety of synthetic and biological materials including metals, ceramics and polymers[12,18,20,22-24,27-29,33]. Although most known biomaterials can be processed using 3D printing, extensive optimization of processing and post processing

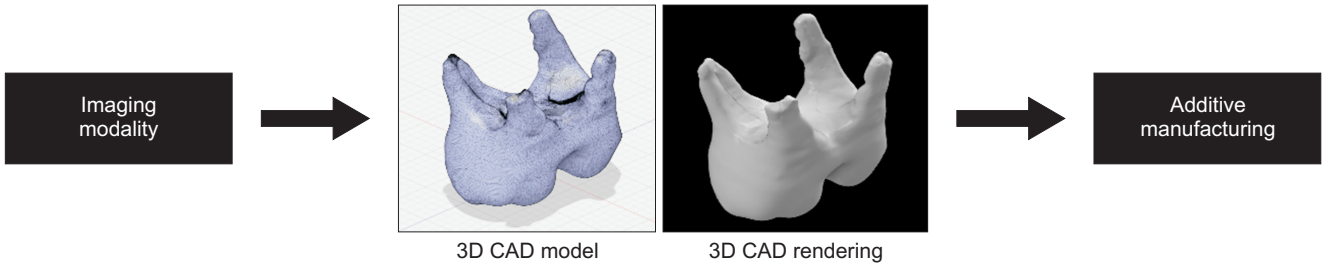

Fig. 1. The advent of additive manufacturing allows for the use of medical and research based imaging modalities to create three-dimensional (3D) computer aided design (CAD) models. These models can be rendered for visual enhancement and surgical simulation or the models can be converted to proper code for additive manufacturing into a graft, prototype or surgical model.
Laura Gaviria et al: Three-dimensional printing for craniomaxillofacial regeneration. J Korean Assoc Oral Maxillofac Surg 2017

parameters are needed to produce complex structures (e.g., interconnected porosity) with structural integrity, high quality and safety (e.g., sterility)[12,14,22]. The following sections will describe the different types of materials used in CMF repair and approaches for 3D printing them.

1) Titanium

Titanium has a long history as a bone implant material because of its biocompatibility, strength to weight ratio and osteoconductive properties. In cranioplasty, titanium has been used in the form of sheets and meshes prefabricated using 3D printing techniques such as direct metal laser sintering[15]. Dental and CMF implants, plates and screws have been fabricated using titanium[4] and although the use of this material has proven to be useful and clinically established, titanium implants cannot be replaced by ingrowing bone or function as a carrier for bioactive molecules[14,18].

2) Ceramics

Ceramics are commonly used in biomedical applications due to their high stiffness and bioactivity. Currently ceramic-based inks are available for direct 3D printing to fabricate patient specific bone grafts for dental and CMF repair applications[4,24]. The most popular ceramics are calcium phosphates such as tri-calcium phosphates (TCP) and hydroxyapatite (HA) because of their excellent bioactivity, osteoconductivity, similarity to the mineral component of bone and bioresorptive properties[12,16,17,19,22,34]. Previous studies have demonstrated their suitability for the build-up of 3D printed structures with resolutions of ~50 μm[16] as well as structures with controlled open pores that are capable of increasing osteoconduction *in vivo*[12]. Also, evidence has shown the printability of a combination of TCP and bioactive glass which can be compositionally optimized for tailored biodegradation[16,19]. Extensive research of 3D printing parameters such as powder packing, drop penetration, particle size, and calcium phosphate ratios has to be done for optimization of the 3D printed constructs[17,24,34,35].

3) Polymers

Blends of natural and synthetic polymeric biomaterial inks are adequate for printing scaffolds used in medical applications and can be customized for individual needs and applications in the CMF region[22]. In general, synthetic polymers are often poorly soluble in aqueous media, meaning that organic solvents must be used which raises concerns related to biocompatibility and large scale production of implants. Nonetheless, synthetic polymers are of great interest due to their biocompatibility properties, ease of use, cost and degradation kinetics[24]. The most used polymers in 3D printing for hard and soft tissues are polylactic acid (PLA), poly(caprolactone) (PCL), polyether ether ketone (PEEK)[24].

4) Composites

Although the initial 3D printing focused on pure materials, composite materials appear to be a most promising approach for the improvement and optimization of biomaterials at the engineering level[22]. The main goal of using composite inks is to enhance ink properties such as synthesis, printability, mechanics and bioactivity[24]. Commercial 3D printers can be adapted for co-printing of polymer blends (polymer-based composites) and hydrogel-based composites[24]. Other alternatives to improve mechanical and biological properties have been to add powdered ceramics as well as metals to pure polymers or polymer blends which can be printed using 3D printing nozzles[17,22-24,34].

III. Advantages and Limitations of 3D Printing Technology

3D printing offers outstanding possibilities in many aspects when compared to other methods, because it is more precise, faster, easily produced and cost-effective in a limited number of cases[16,26], eliminating highly specialized manual labor. 3D printing also offers advantages such as high versatility and capability to print complex designs[20,27] using a large variety of biomaterials that can be printed individually or in combination[18,21,22].

Although industrial 3D printers, such as Stratasys Polyjet printers, have reached extremely high resolution (~16 μm) in the past few years[4,16,21,23], the use of 3D printing technology for implantable biomedical devices is still severely limited by available printable materials that cannot compete with traditional biomedical treatments. The main challenges are the use of processing methods required to work with materials that are not easily printed[12,23,24,35] with the use of organic solvents and high processing temperatures which can harm and reduce the working life of 3D printers that are not specifically optimized for those very narrow uses[23,35]. In summary, the main issues to be addressed in 3D printing of biomaterials are:

• The feasibility of low temperature 3D printing, especially for ceramic materials to make them more stable (control shrinkage) with the potential of incorporating biomolecules and polymers[12,17,34].

• The development of aqueous binder solutions used in scaffold fabrication to avoid the use of organic solvents that can compromise not only the biocompatibility of the scaffold but also the lifespan of the printer heads. This idea has been gaining attention because of its significant contribution to large-scale manufacturing[12,17,34,35].

• Achievement of high resolution and accurate porous interconnected structures with adequate mechanical and degradation properties. This approach can be optimized using composite biomaterial blends, as well as post processing treatments[12,14,16,22-24].

Overcoming the above mentioned technological limitations will finally lead to the incorporation of cells and growth factors/drugs to 3D printed scaffolds, since most of the currently used processing techniques cannot sustain the viability of cells and biomolecules after printing. This approach can tremendously impact the performance of the 3D printed constructs by balancing mechanical, biological, drug delivery and degradation properties[12,20,22,30]. Future advancements in this field can be based on "multi-color" or "multi-component" printing, where each ink can be positioned on a precise location, offering the potential to simultaneously arrange multiple types of cells, deposit multiple extra cellular matrix materials, and exert point-to-point control over bioactive agents for biological tissue manufacturing[23]. However, this approach only relies on the modification of current 3D printing machines and processing temperatures in order to maintain adequate conditions for cells and biomolecules[23]. To date, some bioprinting technologies have been introduced and investigated in order to achieve this purpose[20], providing new insights into the future of complex tissue regeneration for bone, cartilage, muscles, vessels, ligaments, tendons and nerves in the CMF complex[23]. To such end, the following sections focus on specific treatments and approaches for regeneration of the periodontium and teeth within the oral cavity.

IV. Regeneration of the Periodontium

Periodontal disease afflicts approximately half of the population over thirty years of age in the United States. Genetic, environmental, dermatological and hematological factors all influence the high prevalence of this disease[36]. Around 30% of the cases are characterized by moderate periodontitis with mild and severe cases about even. However, the number of patients with moderate to severe periodontitis increase to 64% after 65 years[37]. This reduces the function of the periodontium (combined cementum, periodontal ligament [PDL] and alveolar bone) which is to secure the teeth to the mandible. In severe cases of periodontitis, the periodontium is destroyed and ultimately causing tooth loss[38,39]. This destruction also leads to various complications and medical intervention, highlighting the need for a viable tissue regenerative approach.

1. The periodontium and strategies for regeneration

The complexity of tissue regeneration of the periodontium lie within the tissues of which it is comprised. The periodontal structure begins with the PDL which is unique in its shape and function. The web-like PDL connects the alveolar bone root to the cementum of the tooth providing tensile strength in a gap less than half of a millimeter[38] and support for mastication. Unlike other ligament attachments to bone throughout

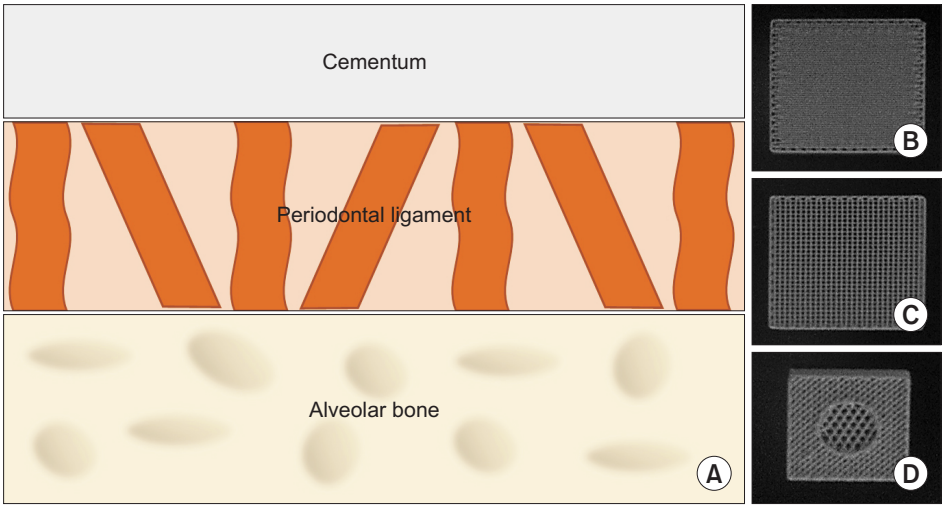

Fig. 2. The periodontium complex is comprised of cementum (A), the periodontal ligament and alveolar bone. These all have distinct porosity and strength. Additive manufacturing allows for different porosities and strengths (B, C) and the ability to create variations within the same grafts (D).
Laura Gaviria et al: Three-dimensional printing for craniomaxillofacial regeneration. J Korean Assoc Oral Maxillofac Surg 2017

the axial skeletal in which the ligament generally forms one insertion point on the bone, the PDL lines the entire surface with multiple small fibrous units being inserted at varying angles. Connective tissue and vascularization are intertwined with the PDL[40]. Tissue regenerative approaches may seek to form a viable PDL structure, but most incorporate the entire periodontal complex or periodontium to combat the detachment of tissue caused by periodontitis[41]. The overall necessity for such approaches arises from the increasing concern of periodontitis described above and the lack of periodontium in current dental implants which will be discussed later in this review. Regenerative approaches for the periodontium have included growth factors, various cell types and materials that seek to provide adequate porosity and mechanics for the varying tissue types[42]. Moreover, additive manufacturing uses line spacing, line thickness and resolution to change mechanics and porosity.(Fig. 2) The advent of additive manufacturing platforms such as the EnvisonTec 3D Bioplotter have broadened the capacity to 3D print a variety of biomaterials through ink development, and the continued reduction in cost of these platforms will make these technologies more readily available and should further expand the additive manufacturing tactics to periodontium regeneration. The following are current approaches using several materials, growth factors and cells.

2. Materials, manufacturing and cells in periodontium regeneration

Several studies performed for the regeneration of the periodontum are summarized in Table 1. A recent study created Mg-calcium-silicate cements with varying amounts of Mg which were seeded with PDL cells and evaluated for both odontogenesis and angiogenesis, which is a vital component

Table 1. An overview of various regenerative approaches discussed in this review and the diverse additive and other manufacturing techniques

Author	Journal	Periodontium regeneration		
		Synthesis technique	Tissue	Regenerative approach
Gerçek et al.[45]	*J Biomed Mater Res A* (2008)	Solvent/lyophilization	PDL	Used different PCL concentrations in tetrahydrofuran that formed microspheres after undergoing lyophilization and exhibited higher mechanical properties.
Oortgiesen et al.[46]	*Tissue Eng Part C Methods* (2012)	Gel substrate	PDL	Encapsulated PDL cells in collagen gels and evaluated under mechanical and chemical (enamel matrix derivative) stimulus.
Li et al.[47]	*Tissue Eng Part A* (2008)	Cell/substrate	Periodontium	Created dentin with transforming growth factor-β1 loaded Millipore transfilters *in vivo*. Then the transfilters were removed and PDL cells were seeded.
Park et al.[48]	*J Dent Res* (2014)	Directional freezing	Periodontal tissue	Placed dry ice at varying locations surrounding a paraffin tooth mold in a gelatin bath allowing for directional control of fibers.
Hasegawa et al.[54]	*Tissue Eng* (2005)	Temperature release	PDL	PDL cell sheets were created using thermosensitive PIPAAm to allow release of the sheets without using trypsin-EDTA.
Dan et al.[55]	*Biomaterials* (2014)	Melt electrospinnning	Periodontal tissue	PCL with CaP coating scaffolds were implanted with either gingival, PDL or alveolar bone cell sheets.
Iwasaki et al.[56]	*Tissue Eng Part A* (2014)	Decellularization	Periodontal tissue	The decellularized amnion tissue was seeded with PDLSCs and assessed for cell viability with movement and surgery.
Lee et al.[60]	*Tissue Eng Part A* (2014)	3D printing	Periodontium	Three phase scaffolds (PCL with 10% HA) with different pores for the cementum, PDL and alveolar bone loaded with amelogenin, connective tissue growth factor and bone morphogenetic protein 2, respectively.
Pilipchuk et al.[61]	*Adv Healthc Mater* (2016)	3D printing, patterning	Periodontium	Printed regions for bone (PCL with 5% HA) and patterned ligament (PCL) for cell alignment compared to salt leached scaffolds.
Ma et al.[62]	*Biofabrication* (2015)	Dropwise 3D printing	Periodontal tissue	Printed hydrogels with gradients of GelMA and PEG with encapsulated PDLSCs.
Rasperini et al.[63]	*J Dent Res* (2015)	3D printing, SLS	PDL/alveolar bone	Utilized computed tomography images to create a patient specific graft with SLS of PCL with 4% HA.

(PDL: periodontal ligament, PCL: poly(caprolactone), PIPAAm: poly(N-isopropylacrylamide), EDTA: ethylenediaminetetraacetic acid, CaP: calcium phosphate, PDLSCs: stem cells from the periodontal ligament, 3D: three-dimensional, HA: hydroxyapatite, GelMA: gelatin methacryloyl, PEG: polyethylene glycol, SLS: selective laser sintering)

in the periodontal complex[43] co-existing with the PDL between the alveolar bone and cementum. It was discerned that higher Mg content provided higher angiogenic expression and may be an option for future studies[44]. Another group lyophilized PCL in tetrahydrofuran to synthesize microspheres which could successfully maintain of PDL cells[45]. PDL cells have also been incorporated into a collagen gel delivery system and stimulated via mechanical and chemical means. The unilateral loading alone increased alignment and cell number while the combination of mechanical stimulus with Emdogain (a protein-based stimulus for periodontal regeneration) did not produce improved results[46]. In another study, PDL cells were cultured on dentin that was regenerated on readily available Millipore transfilters loaded with transforming growth factor-β1 to ascertain the ability of dentin to regenerate PDL tissue[47]. A unique approach to manufacturing periodontal scaffolds came from directional freezing followed by lyophilization. The approach used paraffin molds of the tooth and socket to form a gelatin periodontal complex which was frozen directionally by placing the ice at different regions surrounding the mold. This allowed for variation in the gelatin surface and the formation of a PDL template of fibers frozen in different directions which were lyophilized[48]. Other manufacturing techniques used in PDL regeneration are electrospinning and melt electrospinning which provide random fibrous meshes as platforms for regeneration. These manufacturing techniques, materials and mechanical stimuli provide a solid base with which to model future studies. Moreover, these techniques combined with cells such as stem cells from the periodontal ligament (PDLSCs), alveolar bone stem cells (ABSCs), and dental pulp stem cells (DPSCs), and other primary cells[49-51], growth factors and enhanced spatiotemporal control using additive manufacturing could lead to a regenerative solution for the periodontal complex. Also, as discussed earlier, the importance of vascularization in the regenerative process is essential when postulating cell type and culture environment[43], and as such, PDLSCs have also been evaluated for angiogenic response. When seeded with endothelial cells (ECs), the PDLSCs increased the expression of vascular endothelial growth factor compared to ECs alone[52]. On collagen gels, PDLSCs can also differentiate towards an osteoblastic lineage to form alveolar bone[53] which connects with the PDL.

One tactic for employing the regenerative capacity of cells is to create cell sheets from cells of each tissue type. This can be achieved by releasing the cell sheet from poly(N-isopropylacrylamide) (PIPAAm) which changes hydrophilicity at lower temperatures and allows the cells and extrcellular matrix to detach without using trypsin[54]. These sheets can be incorporated into porous scaffolds or electrospun meshes[55]. One study evaluated cell sheets formed from PDL, alveolar bone and gingival cells on a PCL scaffold with melt electrospun bone and electrospun PDL sections. The alveolar and PDL cell sheets produced periodontal regeneration whereas the gingival cell sheet did not[55]. PDLSC therapy has also been employed by seeding PDLSCs on decellularized amniotic membranes for transplantation[56]. These cells can be combined with growth factors delivered in scaffolds to enhance regeneration. The main concern is being able to spatiotemporally control the delivery of cells and growth factors. Although the complexity of the periodontium and current techniques make this difficult[42], additive manufacturing technology has the ability to improve the spatiotemporally control of tissue regeneration.

3. Additive manufacturing in periodontium regeneration

The continued advancement of additive manufacturing has allowed for printing of more materials and the printing of the same materials in conditions more relevant to tissue regeneration[57]. This section gives an overview of the many advantages of additive manufacturing for periodontium regeneration. The first example is a PCL/HA scaffold of composite material manufactured in a layer-by-layer fashion by 3D printing using a 3D model created from laser scanning. Then, the scaffolds were infiltrated with growth factors such as stromal cell-derived factor-1 (SDF-1) and bone morphogenetic protein-7 (BMP-7)[58] in a collagen gel solution, showing significantly higher cell infiltration and angiogenesis[59]. Other study printed PCL/HA composite scaffolds using the EnvisionTec 3D Bioplotter which is a pneumatic-based system that allows the user to vary parameters based on the solution viscosity. The scaffolds were triphasic in that the design changed mesh size for all three components of the periodontal complex with the alveolar bone and cementum having a smaller, stiffer mesh compared to the PDL. The scaffolds were loaded with poly(lactide-co-glycolide) (PLGA) microspheres with recombinant human amelogenin, connective tissue growth factor and bone morphogenetic protein 2 (BMP-2) in the cementum, PDL and alveolar bone sections respectively. *In vivo* evaluation with DPSCs found proper expression of bone and cementum tissues and alignment of collagen fibers in the PDL region[60]. Other examples are the use of selective laser sintering to produce a PCL/HA scaffold with grooved pat-

terning for cell alignment[61] compared to the previously discussed pneumatic approach, whereas another additive manufacturing technique uses a dropwise gel printing method with cell encapsulation. Using dropwise gel printing technique, one study printed PDLSCs dropwise in gelatin methacryloyl/polyethylene glycol (PEG) hydrogels with a gradient of the two hydrogel components (ratios for 0:5 to 5:0 across a well plate) and reported that the lower ratios of PEG increased cell viability, area and proliferation[62].

Some additive manufacturing approaches have moved beyond the periodontium to include a layer of native dentin to determine if the regenerated periodontium could form a function junction with the dentin of the tooth. The use of a native tissue also has the capacity to reduce immunogenic response once implanted. Studies have employed this dentin technique leading up to and following the first human trial of a 3D printed periodontium which was completed in 2015 with a PCL-based scaffold with specific bone and PDL sections and a burst release of platelet-derived growth factor (PDGF). The implant was removed at 12 months showing that the long PCL degradation timeline was not advantageous and that other materials, degradation profiles and inductive factors should be explored[63]. Moreover, additive manufacturing approaches for the regeneration of the periodontium and teeth combined can be very beneficial in this field. Next section of this review will discuss those approaches.

V. Regeneration of Teeth

The tooth is a complex organ formed by a variety soft (dental pulp) and hard tissues (dentin, enamel, and cementum)[64] which, in conjunction, maintain the physiological and biological environment[39]. Enamel cannot regenerate itself in an adult tooth[65]. If eroded, enamel can leave the tooth exposed and may lead to the need for tooth replacement with an implant or graft. These options for adult patients stress the importance of dental care and the ability to intervene with periodontium focused tissue regeneration as discussed above prior to the need for implants.

1. Dental implants, imaging and additive manufacturing

Dental implants are usually designed to allow for osteointegration and increased aesthetics. The process of implantation of synthetic implants takes months, with time taken for metal post integration after bone grafting and prior to final insertion of the abutment and synthetic crown. However, this standard implant does not provide or seek to replace the PDL. The abutment screw is designed to create a preload that often determines the success of the implant through load sharing and osteointegration. If the post does not integrate into the alveolar bone, the implant can loosen. Nonetheless, preloading of the screw to certain values and subsequent loading after initial positioning has been shown to increase success[66].

New imaging techniques such as cone-beam CT and 3D modeling can be utilized not only for manufacturing scaffolds, but also for prototyping and preparing the implant site. The surgeon can use a stereolithographic additive (SLA) manufacturing technique to make a tooth prototype and shape the alveolar bone to fit the tooth that is to be transplanted. This reduces the transplantation time and helps maintain the vasculature and cells in the tooth[67]. The prototypes can be directly printed through SLA manufacturing or resin cast into a 3D printed wax negative[68]. These techniques provide an outlook on what additive manufacturing can offer in tooth regeneration. These same strategies can be used to take images of the teeth of a specific patient and 3D print a tooth to those exact specifications. However, this would not restore function because the wax and resin prints currently used cannot form a functional replacement tooth. However, with the advancement of strategies to print a tooth with biomaterials, growth factors and cells could harness this approach and create a functional solution. Additive manufacturing approaches towards tooth regeneration are explored below.

2. Additive manufacturing in tooth regeneration

Currently, tooth 3D printing is performed by different 3D printing technologies and extrusion methods[69,70]. Different biomaterials such as collagen sponge[71,72], agarose[73], alginate[74], hyaluronan-chondroitin copolymers[75], poly-glycolic acid (PGA), PLA[76,77], and fibrin[78] have been paired with dental stem cells to regenerate different components of teeth including dental pulp[79-81], dentin[82,83] crown[71,84] and roots[85-87]. From the wide variety of materials, ceramics such as HA and TCP are obvious candidates for regeneration of the tooth, alveolar bone complex due to their known osteoconductive properties[88].

3D printing techniques can manufacture scaffolds in the exact shape and size of the missing tooth using imaging the contralateral existing tooth[18,89,90]. Other materials such as 3D printed alumina coated with HA[70], silica-β-TCP, zinc oxide-β-TCP[91] and printable composites such as PLGA-β-TCP[69], as well as PCL-β-TCP[92] and PCL-HA[59] have also been evalu-

ated for 3D printed regeneration of the tooth/alveolar bone complex. In 2010, Kim et al.[59] were the first team to demonstrate tissue ingrowth (including PDL) in an anatomically correct 3D bioprinted tooth scaffolds *in vivo*.

The ultimate goal in the development of 3D printed tooth scaffolds would be the incorporation of stem cells since this is an area that attracts great interest from the regenerative medicine viewpoint[93-95]. The ability of stem cells to differentiate into different cell types makes them a viable candidate for therapies that could result in the regeneration of the different tissues that form the tooth complex[96,97]. Different types of stem cells have been investigated for their potential in tooth regeneration. DPSCs, as mentioned in periodontium regeneration, have also been identified to be capable of forming a structure similar to dentin lined by odontoblast-like cells surrounding a tissue comparable to dental pulp[98]. Stem cells from human exfoliated deciduous teeth (SHEDs) have the ability to differentiate into odontoblasts, osteoblasts and adipocytes[99] and are easily accessible[100]. When compared to DPSCs, SHEDs were shown to have a higher proliferation rate and differentiation capacity *in vitro* as well as a potentially higher mineralization capacity[101]. In addition, stem cells from apical papilla (SCAPS) have also been isolated from extracted wisdom teeth displaying greater potential for proliferation, stemness, and dentin regeneration than DPSCs[102].

Since embryonic stem cell research has raised ethical concerns[103], most efforts have been focused on differentiating stem cells obtained from adult tissues or inducing embryonic-like pluripotency on other cells. The combinational use of these cell types together with the above additive manufacturing techniques comprised of osteoconductive biomaterials, medical imaging and 3D modelling has the potential to produce a patient specific tissue regenerative approach for teeth.

VI. Conclusion

CMF defects caused by disease, surgery or trauma are complex in nature and involve repair of many different tissue types with unique properties and intricate geometries. Therefore, CMF surgery not only represents a challenge for CMF surgeons, but it also poses a multifaceted design problem to fabricate a complex, 3D biomedical tissue regenerative alternative to current treatments[23]. In recent years various tissue engineering approaches for CMF repair have been explored. Traditionally, the biomedical field has relied on manually fabricated scaffolds for hard and soft tissue. However, recent developments have adapted 3D printing into an increasingly common technique to fabricate scaffolds and devices for CMF applications due to its potential to provide patient-specific designs, high structural complexity, and relatively rapid, fully-automated fabrication at a low-cost[24,27]. Moreover, the long-term goal of 3D printing in tissue engineering will be to develop printable biomaterial inks capable of creating safe and reproducible scaffolds with tunable mechanical, biological and degradation properties[22,23,34]. To achieve that, 3D printers need to continue to be re-designed with the specific capabilities needed for multi-component printing of biomaterials, viable cells and biomolecules in order to mimic the physiological environment and enhance tissue repair[4,22-24].

As shown in this review, there have been strides in CMF repair, especially in periodontium and tooth regeneration in large part due to the advancement in additive manufacturing techniques. The periodontium scaffold combined with native dentin slices[63] gives an outlook of the potential combination of multiple tissue additive manufacturing strategies to regenerate complex defects with many tissue types. Although, 3D printing holds great overall promise due to its diverse applicability in routine and complex cases of dental and CMF surgery and planning[20,27], there are still many technical challenges to overcome before it can be recognized as a common biofabrication technique in medicine[24,26,29,104].

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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