2025 • Vol. 3, No. 2 • pp. 57-70
Future Dental Research (FDR)

Print ISSN: 3006-0516
Online ISSN: 3006-0354
NABEA AL-AJYAL FOUNDATION PRESS
Future Dental Research (FDR)

3D Bioprinting in Oral and Maxillofacial Tissue Engineering: Progress, Challenges, and Future Prospects

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Access this article online

REVIEW ARTICLE
Received: 21.8.2025 **Revised:** 26.09.2025
Accepted: 05.12.2025
DOI: 10.57238/fdr.2024.152576.1019

OPEN ACCESS

ABSTRACT

3D bioprinting holds significant promise for regenerating complex oral and maxillofacial structures. This review provides an in-depth analysis of current bioprinting strategies, including inkjet, extrusion, and laser-assisted technologies, and their applications in bone, cartilage, and soft tissue reconstruction. Key considerations such as cell viability, scaffold design, and vascularization are examined. The combination of bioinks with stem cells and growth factors has opened new avenues for patient-specific treatments. However, technical challenges such as mechanical strength, integration with native tissues, and regulatory barriers persist. This paper concludes with a vision of clinical translation supported by interdisciplinary collaboration and innovation in biomaterials.

Keywords: 3D bioprinting, tissue engineering, oral surgery, biomaterials, regenerative medicine.

1 Introduction

The complexity of oral and maxillofacial (OMF) defects following trauma, cancer, and congenital malformation raises a greater need for a more functional reconstruction of the OMF region, one of the most promising solutions for the reconstruction of the facial skeleton is the development and use of scaffolds that can replace even difficult anatomical [1]. Till date, the majority of scaffolds developed to replace OMF bones match the biological and mechanical properties of bone tissue, while their complexity, shape, and architecture remain un-investigated, complex scaffolds with predetermined mechanical and biological properties could be obtained by 3D printing using sequentially prepared multi-phase and multi-filled bioinks for 3D bioprinting, combined with a polydimethylsiloxane-based microtransfer molding technique, 3D bioprinting will be the center of attention for potential manufacturing methods due to the ease of controlling parameters for printing complex shapes that match the tissue of interest [2].

Biomaterials, specially designed bioinks, and 3D cell printing technology are the three key aspects bringing the application of 3D bioprinting technology in hard tissues [3]. Several natural and synthetic materials have been explored as potential biomaterials for hard tissue bioprinting individually or in combination forms. Incorporation of bioactive factors into bioinks is a means to modulate cellular behavior and enhance the osteogenic competency of bioinks. Providing 3D bioenvironment and possesses similar composition with natural bone, cell-laden hydrogel constructs would be a promising additively manufactured graft, meanwhile, significant attention is given to the progresses and advancements of inkjetbased, extrusion-based, and laser-based bioprinting technologies [4]. The potential obstacles for broad application of 3D bioprinting technology in hard tissue engineering are also discussed in terms of biomaterials, bioinks, and printing technologies, this review intends to provide insight and practical guidance for the future studies of advanced bioinks and bioprinting technology for hard tissue engineering [5].

Array of pioneering investigations has focused on the preparative approaches of constructs[6].The laboratory studies employing 3D printing for oral soft tissue modeling, including the use and fabrication parameters optimization of tailored inks, preparation and characterization of 3D printed scaffolds for gingival tissue modeling, as well as the employment of automated cell seeding and bioreactor systems for engineered gingiva are outlined [7]. The research gaps in oral soft tissue bioprinting, the future potential of bioprinting for precision and personalized gingival reconstruction treatment, as well as the perspective of the clinical translation of additive technologies are discussed [8].

2 Overview of 3D Bioprinting

3D bioprinting is a novel and rapidly developing bio-manufacturing system for precisely controlled 3D structures to improve the efficacy of tissue engineering and regenerative medicine, scaffolds for drug delivery, and models for disease research and therapeutic screening, 3D bioprinting was developed to solve the limitations of existing technology. In 3D printing, only scaffolding material is fed to the printing nozzle, as a result, some bioactive compounds or drugs remain non-uniformly distributed in the scaffolds. Furthermore, complicated preparation steps may lead to cell lysis and compound inactivity [6]. The process involves providing one or more bioinks—viscous mixtures of biomaterials, bioactive molecules, and cells—to a feed reservoir. Unlike 3D printing, inkjet bioprinting uses liquid bioink, which is printed as discrete droplets, paving the way for the development of tissue engineering, applications of 3D bioprinting in creating prevascularised muscle, bone, and cartilage structures are well documented, prototypes for drug testing, development, and delivery; organs-on-a-chip for drug efficacy screening; and biomimetic models for cancers and organoids are other applications of 3D bioprinting[9].

In 3D bioprinting, bioinks are echogenic biofunctional inks designed for various applications in regenerative medicine and bio-imaging, the fabrication of bioinks comprising vesicle-forming materials with gas microbubbles or nanobubbles provides 3D bioprinting constructs with both imaging and therapeutic properties [7]. 3D bioprinting is meant for minimally invasive bioprinting using highly viscous bioinks at relatively low printing pressures, with functional post-print processing of the bioink constructs, in bioprinting, engineered cells capable of undergoing dynamic behaviour upon extrinsic stimulation can be produced to generate anisotropic tissues such as heart valves and contractile cardiac tissues, g- Bioprinting is another extension of bioprinting where cells can be extruded using external g-field guidance and an acoustic field [10].

2.1 Definition and Principles

Three-dimensional (3D) printing allows the production of an individualized 3D object based on a desired shape through a computer-aided design and a material of choice through a computer-aided manufacturing, the numerous advantages of 3D-printing technologies encourage further investigations and the development of innovative applications in various biomedical fields, it offers an easy, fast, flexible, inexpensive and accurate way to produce precisely designed personalized objects from a large variety of biomaterials[11]. Moreover, 3D printing could result in substantial changes in health care systems. Currently, the time frames and costs of surgical guides, dental models, orthodontic appliances or implant prosthesis production had already been dramatically shortened, a shift towards "off-the-shelf" products is likely to happen in the wake of automation, new developments in demand-responsive printers, biocompatible polymers, and high-quality sensors pave the way for the production of patient-tailored and patient-implanted devices in a dentist's office[12]. Three-dimensional (3D) printing is a rapid prototyping technology, by layer addition, can produce three-dimensional devices through physical and chemical processing without using machining or auxiliary craft. It is based on computer-aided design and composed of various procedures, 3D printing technology in dentistry was developed in the late 1990s with the introduction of stereolithography to produce a non-removable partial denture and framework. Since then, considerable progress has been made in terms of both equipment and materials [13]. Many 3D printing techniques have developed into dental applications and have gained FDA regulatory approval, currently, most of the commercialized 3D printers are an indirect printing method and require a post-curing process [14].

2.2 Types of 3D Bioprinting Technologies

3D bioprinting technologies can manufacture both cell-laden and non-cell-laden structures, non-cell-laden structures can be used as temporary 3D scaffolds to help cell adhesion, growth, and migration for in vitro and vivo applications, after proper surgical procedures, non-cell-laden bioprinted constructs can be placed inside the body to promote tissue regeneration [15]. Cell-laden bioprinting can be classified into direct cell-encapsulation and modular bioprinting. As an advanced extension of traditional 3D bioprinting, microphysiometric tissue chip technology uses a modular approach comprising multiple 3D bioprinted microenvironments, which can mimic a full organ or tissue system in vivo, it can also be incorporated with devices to

allow precisely controlled environments for drug screening/testing or for cell therapeutic applications [16].
Depending on the modes of material dispensing, 3D bioprinting approaches can be categorized as extrusion-based, inkjet-based, laser-based, and other photo and multi-material bioprinting [17]. Depending on the state of the material at room temperature, most techniques can be further divided into the following four groups:

(1) bio-ink materials in a liquid state (bio-ink gelation should be triggered after bio-printing), such as extrusion inkjet and laser bioprinting.
(2) bio-ink in a heated liquid state (gelation should be triggered by cooling down the bio-ink after bioprinting), such as thermos-curable material based-3D bioprinting.
(3) bio-ink solid state (three-dimensional (3D) structures could be formed by fixing and dispensing bio-ink materials), such as computer-controlled programmable 3D printing or fused deposition modeling (FDM)-based bioprinting.
(4) a mixture of bio-ink with gel wires (sol-gel mixing) [13].

3 Applications in Oral and Maxillofacial Tissue Engineering

Tissue engineering and regenerative medicine are two interconnected and diverging disciplines that promote the engineering and repair of different tissues and organ systems, according to the engineering approach, the idea is to replicate or engineer tissues using the three main components of cells, scaffolds, and biological signals in such a way that the resultant engineered tissue will be similar to the native tissue in terms of structure and functionp18]. The scaffold of biomaterial origin assists in shaping and housing cells while providing a bio conducive environment for the initial attachment of cells. Meanwhile, depending on the type of tissue, a right mix of biological signals such as chemical, biological, or physical such as electrical and magnetic will be chosen to induce cellular function such as migration, proliferation, and differentiation for tissue formation [19].
Advances in bioengineering, specifically 3D printing and biomaterials, combined with the development of advanced cellular therapy or cell-based therapy techniques, have brought this science within near reach. Bioprinting is defined as a 3D printing technology for the biofabrication of organs and tissues that incorporates living cells and biologically active molecules to produce 3D structures [20]. Bioprinting systems in combination with biomaterials (bioinks) are exploited for the tissue engineering of different tissues such as skin, cartilage, bone, intestine, salivary glands, tooth, and vascular grafts, among various printing techniques available, extrusion-based printing that prints bioink filament/extrudates through a nozzle in predetermined conveyor paths is most commonly used followed by inkjet-based and laser-assisted methods, this is followed by the selection of biomaterials used to formulate bioink for desired bioprocessing and final in vitro function of bioprinted constructs, finally, there has been an operative switch toward newer materials such as photosensitive hydrogels and bio-ceramics for bioprinting, as well as combining different scaffolds to design hybrid tissue constructs [21].

3.1 Bone Regeneration

Bone tissue engineering is a viable alternative to grafting and metal implants because of the disadvantages of these techniques. Bioprinting is currently a very evolving field in bone regeneration methods that allows for the addition of living cells and vascularization to the prints, after initial considerations of the need of bone regeneration and the use of existing grafting techniques, a large section will introduce the new bioprinting technology with a possible final thought of its big prospects in this area[22]. Remarkably, one of the beauties of 3D bioprinting is that the resultant living printed tissue can be implanted in situ in a defect site, avoiding the need of invasive surgery to harvest tissue and reducing the waiting time of tissue availability, depending on the technology choices, cells can also be added to the print in the form of bioinks, providing a significant advantage over current printed available scaffolds[23].
The need for bone regeneration is rising as defects are becoming more frequent with resulting greater patient suffering, more surgeries, and rising social costs. Bone tissue engineering is an innovative way of addressing this need, one of the problematic aspects of grafting techniques is the limited acceptance of synthetic grafts, while others are not as easy obtainable or / and have complications of donor-site morbidity, possible resorption, and ethical/legal issues. Bone tissue engineering aims to find new potential methods to treat bony defects which can be repaired with a printed living tissue by overcoming the major limitations of conventional treatment options [12].
These are enhancing both osteoinduction and osteoconduction on the one hand while avoiding all this on the other by using bioprinting of bone grafts bringing well-proven bone biomaterials into the scaffold/native tissue interface on a multi-scaffolds level. Use of engineering techniques to fabricate a suitable scaffold to be populated with cells in a bioreactor has always been attempted for bone tissue engineering. Within this respect, many promising scaffold techniques such as salt-leaching, polymer foam, gas foaming, supercritical CO_2 foaming, freeze foaming, and many others based on a sacrificial pore former or template technology have been proposed during the past decades. Advantages of these methods include unlimited freedom to choose the polymer and solvent, easy production of spongy scaffolds, simple downscaling for clinical use, and the flexibility of mixing bioactive materials to the polymer [13].

3.2. Cartilage Repair

Articular cartilage is defined as a thin tissue, roughly 1–4 mm thick, comprising hyaline (articular) cartilage lining the bone epiphysis of synovial joints, fracture and degeneration of cartilage or bone triggers repair responses involving inflammation, fibrous repair tissue formation and subsequently cartilage, synovial changes and bone pathology, treatment of cartilage defects is performed by several methods including microfracture, drilling, abrasive methods of debridement, and harvesting and implanting osteochondral grafts[19]. To utilize bone tissue engineering methods to regenerate cartilage, adequate architectural design and fabrication techniques that can produce a highly porous scaffold with a complex 3D structure are a prerequisite, whilst sustaining a certain degree of mechanical stability, there has been little success in regenerating cartilage with these methods, however, rapid prototyping techniques for the fabrication of scaffolds or templates for cartilage regeneration are promising research domains[24].

3D scaffold architectures have a large surface area for cell attachment, whilst their cyclic loads and stimulations have significant influence on cartilage formation from the endochondral ossification. however, scaffolds replicating the topography of natural cartilaginous structures, sufficient curbide strength and suitable dynamic stimulations are hard to employ using conventional procedures [25].

A temperature-sensitive HPMA–OA copolymer solution was jammed into a chondrocyte-laden porogenic mold in which aggregate gels were formed. With an improved method, pre-fabrication for chondral repairs using multi-material cartilage scaffolds with a spatial gradient bio-composition and bio-activity was realized (20). A ChitNC-hydrogel scaffold was printed, exhibiting a suitable elasticity and stability in physiological conditions with a low bio-resorption rate and controlling the degradation rate of antibiotics, via 3D bioprinting technology, chondrocyte suspension containing gellan gum gel as a building ink was printed to prepare cartilage constructs facilitating cellular activity and cartilage matrix synthesis [26].

3.3. Soft Tissue Reconstruction

Gingiva, the masticatory mucosa surrounding the teeth, is made up of stratified squamous keratinized epithelium and lamina propria-like connective tissue, it plays a crucial role in the adhesion of teeth and limiting the spread of microorganisms or pathogens, gingival recession, the exposure of cementum or root dentin, can lead to the development of cervical dentin hypersensitivity, root caries, periodontal disorders, and compromised implant aesthetics[27]. Normal wound healing in the gingiva is slow and complicated, existing treatments, such as free gingival grafts (FGGs), subepithelial connective tissue grafts, and coronally advanced flaps, have drawbacks in tissue availability, healing, and esthetics, therefore, the development of biomimetic gingival substitutes is of great interest[28].

Research on tissue engineering has progressed in the last decade, tissues consisting of biomaterials, cells, and components of the extracellular matrix (ECM) have been fabricated. Tissue-engineered gingival equivalents (TEGEs) consist of another culture dish and a porous scaffold to support human gingival fibroblasts (HGFs) and human gingival keratinocytes (HGKs), respectively[22]. Organotypic co-culture models have been established, consisting of a porous scaffold and HGF/epithelial cell mixture, co-culture models have been co-cultured directly and indirectly through a membrane with porous scaffolds of various materials, the limitation of these is that the aerial side of the scaffold is completely open, due to the fibrous structure of these scaffolds, they can be hard to detach from the culture dish [29].

Three-dimensional (3D) bioprinting has emerged as a promising tool for soft tissue reconstruction, it allows the precise deposition of cells and biomaterials in a layer-by-layer manner. Pulp fibroblasts, adipose-derived stem cells, and denatured gelatin have been used as bioprintable materials for 3D bioprinting. An orthogonal collagen gel delivery system of electrohydrodynamic printing and fused deposition modeling printing has been developed (30). Bio-ink hydrogels have included gelatin methacryloyl, hyaluronic acid, and acrylated gelatin modified with hydroxyphenylpropionic acid, bio-inks bioprinting inkjet printing for skin engineering mostly includes alginate and gelatin. However, bio-inks for gingival tissue engineering have not yet been investigated [31].

4 Materials Used in 3D Bioprinting

3D Bioprinting achieves the fabrication of scaffolds for tissue engineering, through printing cells, growth factors, and biomaterials as bioinks, the materials used to formulate these bioinks must ensure good printability, biocompatibility, and facilitate bio activity protection, these three aspects are greatly impacted by the physical and chemical properties of the bioink material, among others, alterations in physical properties including viscosity, elasticity, shear thinning, and rheological transition are directly related to the formulation and composition of bioink [20].

Hydrogels are the most prevalent bioink material due to their biocompatibility and ability to mimic the native ECM, natural hydrogels are widely used, including alginate, gelatin, hyaluronic acid, collagen, and chitosan. These naturally derived materials provide a rich ECM for cell adhesion and proliferation, but their poor mechanical properties and fast degradation rate limit their use for certain applications [22]. A common approach to tackle these issues is hybridizing natural polymers with synthetic ones, such as polycaprolactone, poly-lactic-glycolic-acid, or polyethylene glycol, so that the mixture combines the best from both types of materials, advanced bioinks using blue-rray gel or tunable mechanical properties are lately developed to control cellular behaviors and tissue development[32].

Despite the wide usage of natural polymers in bioink formulations, many synthetic materials have been extensively studied as bioinks in the past decade. Through click-chemistry or post-printing crosslinking, poly(ethylene glycol), poly(ethyl methacrylate), poly(ε-caprolactone), and poly(2-hydroxyethyl methacrylate) can be safely polymerized to form hydrogel scaffolds[33]. However, these synthetic biomaterials usually lack bioactivity and long-term cytocompatibility, which may hinder cell attachment and new tissue formation. extensive research on the development of bioinks derived from composite materials or hybrid complexes that combine the properties of synthetic and natural hydrogels is needed. Implementing bioactive-agent-releasing or -decorating materials into the existing bioink would be helpful to enhance bioactivity, biocompatibility, and tissue regeneration performance of synthetic bioinks[34].

4.1. Bioinks and Their Composition

Bioinks are usually biomaterials encapsulating cells, which will then be deposited on a substrate to form three-dimensional constructs, these materials are in direct contact with the cells, therefore, one of the most important qualities they must possess is biocompatibility(35). In the context of bioprinting, biocompatibility encompasses both absences of cell toxicity and the presence of cell adhesion cues, this is significantly influenced by the water content, facilitating the transfer of oxygen and nutrients to the cells, furthermore, these materials need to be biodegradable, as they need to be replaced by extracellular matrix components produced by the cells, as a result, it is important for the degradation profile to match the regeneration rate of the extracellular matrix (ECM) by the cells, furthermore, mechanical properties, such as stiffness, must match those of the target tissue to provide a favorable environment for cellular activities, moreover, the possibility of rapid gelation is of extreme importance in order for the bioink to keep its shape upon deposition on the substrate[20].

In extrusion-based bioprinting, the material needs to form a filament upon ejection from the nozzle, during the process, shear stress is applied to the cell encapsulating material introducing the possibility of damage to the cells, thus, properties such as shear thinning and yield stress of the material must be considered, while in extrusion-based bioprinting the viscosity of the material should be in the range of 30 to 60 × 107 mPa/s, the viscosity in inkjet technique has to be much lower and in the range of 3.5 to 12 mPa/s, furthermore, bioinks for this printing modality need to have rheopectic properties rather than shear-thinning properties, meaning there needs to be an increase in viscosity upon application of shear force, leading to droplet formation (36). As for laser-based bioprinting, the bioink should be able to adhere sufficiently to the sacrificial layer and spread uniformly on it. Additionally, it needs to possess high viscoelasticity, enabling formation of material jets. The viscosity of the material used for this bioprinting modality is usually in the range of 1 to 300 mPa/s 10 [37].

4.2. Natural vs Synthetic Polymers

Most of the polymers used as biomaterials for scaffolds are naturally occurring, synthetic biodegradable, and synthetic non-biodegradable polymers, naturally occurring polymers are polymers that exist in the nature, for tissue engineering applications, naturally occurring polymers are a good choice as they are biocompatible and biodegradable, however, their use is limited due to unwanted properties such as low solubility, low mechanical properties, batch variability, and rapid degradation rates as compared to biodegradable synthetic polymers [38]. Aside from naturally occurring polymers, there are also synthetic polymers, synthetic polymers can be adapted for obtaining singular desired characteristics by applying various fabrication techniques, for these motives, the use of synthetic polymers has enormously increased in the biomedical field, particularly in the field of dentistry, however, synthetic polymers show several drawbacks that can limit their use in clinical applications, such as lack of cellular recognition, biodegradability, and biocompatibility, moreover, concerning biodegradable synthetic polymers, the time for matrix resorption is not predictable, and hence non-resorbable matrices are preferred for soft tissue augmentation in the oral cavity[39]. On account of the latter limitation, researchers have recently proposed a novel non-resorbable composite membrane manufactured via electrospinning that has allowed the obtaining of remarkable in vivo outcomes concerning angiogenesis and immunomodulation throughout the polarization of macrophages, tissue engineering is a multidisciplinary field that prioritizes the healing and regeneration of tissues and organs with the use of biomaterials, cells, and biochemical factors, in this sense, one of the most important biomaterials for scaffolds in tissue engineering is the polymeric matrices, indeed, the success of scaffolds in tissue engineering applications is based on their capability to provide an appropriate environment for cell attachment, migration, propagation, and differentiation [40].

4.3. Cell Sources for Bioprinting

Cell sources for bioprinting include one of the primary elements of bioinks, as cells are the functional agents for the biomanufacturing of living tissues, various cell types have been bioprinted for different applications, such as skin, blood vessels, and bone tissues, a number of original cell lines, commercially available cell lines, nor cellularized constructs would induce cellular toxicity, leading to the loss of cellular structure and/or morphology as well as bioactivity [41]. Maintenance of cellular integrity and viability post bioprinting remain significant hurdles, especially for cells required to undergo later stages of mammalian development. Factors influencing mammalian cell viability include printed construct height, nozzle diameter, temperature, flow velocity, and surface characteristics of the printing chamber, early work in bioprinting focused on the printing of immortalized or continuously cultured cell lines, which is compatible with complex 3D printing systems, however, bioprinting of immortalized cells alone can create constructs with limited biological functionality[42].

Addressing this need, both mouse and human multicellular 3D spheroids were bioprinted into a variety of configurations with high viability, modifications to early work included increasing the printing temperature from room temperature to 37 ◦C, inherent differences between cell lines used (human vs mouse, osteoblast vs fibroblast cell types, etc) ,resulted in a systematic difference in spheroid structure, such as size or compactness, in printed constructs[43]. Notably, cell spheroids were produced rapidly and at high density with low cell culture requirements, excess cells were removed without damaging spheroids, and a wide variety of rigid as well as soft hydrogel bioinks were printed. Recent advances have seen the bioprinting of multiple types of cell systems, including stem cells and primary cells, such as human dental pulp stem cells and primary human osteoblasts, into bioinks compatible with sugar templating methods to create vascularized bone scaffolds [44].

Additionally to their normal physiological functions, stem cells possess unique self-renewal and pluripotency features that have drawn attention from biomedical researchers, stem cells can be classified as embryonic stem cells, fetal stem cells, and adult stem cells based on the embryonic origin, adult stem cells include somatic stem cells, tissue stem cells, or organ stem cells [45]. Salivary gland stem cells are a rare population of multipotent stem cells that are maintained in the postnatal salivary glands, and their de-regulation is closely related to sialorrhea and systemic salivary gland diseases, human salivary gland stem cells can safely induce amelioration of sialorrhea following intraglandular injection in rabbits, with the evidence that restored glandular morphology and function and replaced degenerative saliva-secretion duct cells, newly formed progenitor cells undergoing a differentiation process towards acinar cells were observed less post injection, bioprinting of salivary gland organoids or human salivary gland stem cell sheets can be favorable candidates for the treatment of xerostomia [46].

5 Current Progress in Research

This section discusses the current progress of research on 3D bioprinting in oral and maxillofacial tissue engineering. In recent years, there has been significant advancement in the field of 3D bioprinting technology for oral and maxillofacial tissue engineering, however, the adoption of commercially available bioprinting technology for dental applications is still limited [47-48]. The progress in this research area is analyzed in four categories, including strategies to achieve proper architecture and dimensions of tissue replacements, 3D bioprinting of soft to hard composite tissues, innovative materials and biomolecules employed in 3D bioprinting or in bioink formulations, and the possibility of 3D bioprinted tissues for clinically relevant preclinical models, challenges and exciting opportunities for using bioprinting technology in patient-specific oral and maxillofacial tissue engineering are further discussed [20].

As a rapidly maturing technology, 3D bioprinting is distinguished from other tissue engineering technologies. It is an additive manufacturing technology to create living tissue that closely simulates natural tissue architectures and microenvironments in a personalized manner, based on the most current research literature, ongoing research projects, and patents, bioprinting for tissue engineering applications is reviewed, the knowledge gap on the usage of bioprinting in dentistry applications is highlighted, as well as the types of materials, the 3D bioprinting technologies, and strategies converting 3D structure into 3D bioprinting models [6].

Most of the existing review articles focused on the bioprinting technologies. 3D bioprinting to fabricate highly porous scaffolds with controlled architecture and porosity for bone, cartilage, and vascularization tissue engineering applications is summarized. Current challenges in bioprinting technology for biocompatibility and bioprintability are elaborated, and future directions to stimulate further development in more complex tissue or organ engineering are suggested. Other literature reviews highlighted the material types for bioprinting and bioprinting strategies [49].

5.1 Recent Advances in Techniques

3D Bioprinting, which has been referred to as "three-dimensional bioprinting," is a rapid prototyping process using biomaterials to create three-dimensional structures, bioink or biomaterial threads containing cells or growth factors are laid down on a substrate layer to produce a bioprinted structure [4]. Here, the term bioprinting refers to "3D bioprinting" or "3D bioprinting," including 3D printing, which uses biocompatible materials capable of not compromising formulation materials, component fabrication, or direct cell incorporation or post-fabrication treatment, the first 3D bioprinter was developed in 2006 by a team at the North Carolina State University in Raleigh, this printer, capable of forming tissue-like structures using alginate as the primary biopolymer, laid the foundation for this growing field [50].

Engineered three-dimensional tissues and organs represent a promising design in tissue engineering and regenerative medicine. However, engineering a three-dimensional well-organized and functional highly vascularized tissue construct is still a challenging task, recently, 3D-bioprinter-based technologies and bioprints, specifically developed biomaterials or bioinks, have opened up new opportunities for comprehensively designing biomimetic tissues/organs with spatial complexity at the microscale and macroscale levels [38].

The field of bioprinting has rapidly developed and steadily advanced over the past 10 years, several major advances include not only multi-material bioprinting technologies but also bio-inks for challenging bioprinting biomaterials, the recent progress in bioprinting techniques for the tissue engineering field is reviewed, focusing on more advanced bioprinting techniques, bioinks, and engineered vascularization design, the challenges and future research directions for bioprinting are also included [51].

5.2. Case Studies and Clinical Trials

To restore maxillofacial defect practitioners employ autologous bone grafts, but this method often leads to insufficient volume/quality, using 3D bioprinting and additive manufacturing, personalized tissue constructs can be fabricated based on a patient's anatomical data, several studies have been conducted to recreate 3D printed, bone-like scaffolds and to develop a computer-aided design flow using STL and PLY formats, Cal58 osteosarcoma cells were implanted onto scaffolds and characterized in vivo in a mouse model and in vitro with a profiled bioreactor to research performance, statistically relevant results demonstrated 3D bioprinted bone-like constructs display essential components and porosity for osteogenic behavior of implanted cells [4].

Tissue engineering initializes the rationale approach for bone grafting, biocooperating scaffold materials can influence the odontobiological capacity of CD34+ cells. In a canine model of 7 mm circumferential calvarial defects at four locations, CAD/CAM β-TCP scaffolds were implanted, on assessment day, bone formation was statistically significant, better scaffold biocompatibility provides insight into the use of synthetic materials for human reconstruction [51].

Reports, patents, and clinical investigations regarding the performance of 3D printed templates of bone and dental structures were evaluated, the models, biocompatibility, mechanical properties, and clinical trials were outlined, during manufacturing with Biomer, PLA, and hydroxyapatite filaments the surgical templates were printed within the metabolic protocols. Cone beam computed tomography and mimics quickly designed the models, an innovative material led to precise printing features, and the reliability of templates during actual surgeries was ascertained, the new material's resolution and biocompatibility could lead to safer printing in different medical fields [52].

6 Challenges in 3D Bioprinting

Some obstacles still need to be solved in the 3D bioprinting process of tissue engineering. This text briefly introduces some challenges that need to overcome further, a key limitation of the bioinks is that most hydrogels are mechanically weak and cannot meet the requirements for supporting structures; instead, hydrogels should be precisely positioned inside hard supporting structures, consequently, bioprinting of cartilage, which typically contains a high percentage of water and exhibits low shear-thinning features, has not yet been achieved due to a lack of strong bioink, bioprinting process of 1, 1′-Diethyl peroxydicarbonate is developed into rapid formation of the elastomeric hydrogel. If the economic viability can be demonstrated, 3D printing will bring automatic and reproducible stomatognathic applications to the market [53]. There may be no other tissue losing component material in bioprinting and biologically, the production of 3D printed scaffolds by a four-step process of polymer infiltration, photolithography, drying, and deionization would allow time-saving reconstruction of even complicated bone defects, there is a significant area needed for growth or degeneration, ensuring shape reproduction of implanted biomaterials, controllarily inducing the degradation rate of biomaterials for long time maintenance of ion release, and sensing body micromorphology change and illnesses [54].

Tissue regeneration is not only building the structures mimicking living tissues but also making the constructs function normally in the long term [55]. A key issue to the success of engineered constructs is to ensure sufficient nutrient and oxygen supply to the engineered constructs. In the past decades, many strategies targeting this issue have been developed, from implanting tissue into the host body to 3D bioprinting, but it is still a big challenge [56]. The regenerative medicine and tissue engineered technology and elements were classified and regulated in all manners of design, manufacture, transfer, and disposal [57].

6.1. Technical Limitations

In general terms, tissue engineering has proven to be instrumental in accelerating the tissue regeneration process. The viable tissue engineering strategies present various challenges and pitfalls for successful clinical translation and application 8. One of the main challenges is a lack of choice of appropriate materials. A suitable choice of biomaterials is crucial to construct scaffolds that can imitate the complex architecture and properties of the target tissues. Current research on dentoalveolar bioprinting is still in its infancy, and many aspects are potentially subject to further research. Overall, the choice of materials that is biocompatible with the current bioprinting technologies is limited. Different 3D printing modalities and their available biomaterials are summarized. More research on scaffold designs, bio-inks, crosslinking techniques, and post-treatment procedures is warranted to improve the dentoalveolar bioprinting technologies [58]. In most fields of additive manufacturing a limiting factor is finding an appropriate choice of materials. In bioprinting, this challenge is amplified, as materials need to support the encapsulation of cells, while being compatible with the bioprinting technologies itself. The field of technologies is still in its infancy. Looking at dentoalveolar bioprinting, the amount of material characterization studies and dentoalveolar tissue regeneration strategies currently examined is limited [59].

Further studies on the biocompatibility of the biomaterials for the strong hydrogel formulations are warranted, as well as on combining hydrogel with solid biomaterials [60]. Furthermore, the promise of complex architectures holds additional technological hurdles. As the current bioprinting methods typically use low viscosity and shear-thinning bio-inks that allow for a fast recovery after printing, it is much more challenging to introduce solid biomaterials in the traditional processes. Using, for example, material extrusion-based bioprinting to print high concentrations of PLA is feasible, but rapid recovery to printing viscosity after extrusion is hard to achieve [61].

6.2. Regulatory Hurdles

The rapid commercial and technological growth of biopanters and bioinks puts pressure on regulatory bodies to develop adequate frameworks to guarantee the safety and efficacy of these new technologies 6. Regulations should cover the entire bioprinting workflow from bioink formulation, production, and inspection, through biopattering, post-processing and storage, to the tests and characterization needed before human applications. These regulations must take into account the materials and their potential toxicological properties, as well as the cellular component of bioprinted constructs [62]. Standards must also be set in terms of equipment validation, bioprinting conditions adjustment, and product quality control, characterization, and testing. The heterogeneity of bioprintable smart hydrogels and bioinks may complicate standardization, and the awareness of mismatch between currently available bioprinters and biopatterning approaches must be acknowledged [55]. Access to multiparametric analysis of bioinks and bioprinting parameters would also be beneficial.

Existing regulations must also be adapted to bioprinting applications and products. Current standards, regulations, and guidelines aiming to ensure the quality, efficacy, and safety of bioinks, biopatterning equipment, and bioprinted products are very limited. As a result, multiple facets of the bioprinting workflow currently lie outside any regulatory framework[63]. This situation raises concerns, given the rapid adoption of bioprinting for clinical applications, and especially regarding bioinks composed of exotic components or manufactured using proprietary processes. Ethical concerns regarding bioprinted human tissues constructed from immortalized cell lines or human pluripotent stem cells exist [64].

Technological advancement combined with awareness of the limitations of existing regulations provides an opportunity for constructive discussions among bioprinting scientists and engineers, bioprinting companies, and regulatory bodies about how to best address these challenges [65]. Fine tuning of the rapidly evolving regulatory environment, as well as increased transparency and clarity regarding regulations, would also be beneficial for the growth and commercial success of bioprinting applications [66].

6.3. Ethical Considerations

Implementation of several bioprinting approaches in tissue engineering opens doors to the reestablishment of functionality in compromised regions, such as the head and neck area. Bioprinting enables the generation of complex 3D constructs containing not only bone grafts but muscle and skin tissue too, which have to meet both structural and functional requirements. Moreover, it allows obtaining multilayered constructs with multiluminal inner geometry that cannot be manufactured by other methods [67].

This will provide patients with complete restoration of tissue integrity and functionality at pre-trauma, pre-disease state. Unfortunately, the lack of standards as well as knowledge regarding technical, scientific, bioethical, and legal issues of the bioprinting approaches can hinder the implementation of this promising technology in clinical practice [68]. In this review, an outline of the state-of-the-art 3D bioprinting approaches used for oral and maxillofacial tissue engineering is presented, along with discussing the challenges faced and future perspectives for the implementation of bioprinting technologies in clinical practice. The regulatory framework for 3D bioprinting faces multiple challenges. Indeed, skilled personnel must be engaged for bioinks preparation and viability post fabrication. Due to the intricacy of the process, it becomes almost impossible to render reproducible bioinks without ensuring a high level of automatization. Nevertheless, standardization of testing methods for assessing both bioinks and bioprints are essential for versatility ahead. Regarding numerous bioinks, some are already approved for clinical practice, which clears the path for their use in bioprinters for creating custom 3D constructs that can be validly used in the clinics[69]. However, a co-dependence must be established between the ink and the printer design. 3D bioprinting allows achieving unprecedented levels of control over constructs. Bioperspectives can be manufactured incorporating hybrid approaches, with any commercially available 3D printer paired with the bioprinting capability by projecting an array of laser beam at a sequence of angles to produce minuscule droplets and even micron spheres in morphologies of tuneable gradation for drug delivery, stem cell or biological component entanglement with cellular lineage activation, etc. Expectations on a shorter time frame expect the arrival at the clinics of continuous liquid interface production technology, where a free-form polymer structure could be produced every 10 seconds. It shows how innovation in the field of bioprinting will carry exponential advances in regenerative therapies [70].

7 Future Prospects

Numerous potential strategies and tools for bioprinting in tissue engineering are anticipated due to a better understanding of the unique biological characteristics of oral and maxillofacial tissues, improved bioprinting capability, and novel bioprinting biomaterials [71].

This review summarizes representative articles on the current progress of oral and maxillofacial tissue engineering over the past three years and emphasizes the future potential of hybrid bioprinting and organ-on-chip as alternatives for future personalized treatment strategies. While comprehensive progress has been made in current bioprinting development, there are still several challenges to overcome. The main challenges for oral and maxillofacial bioprinting can be divided into four categories: bioprinting process modeling, bioprinting biomaterials, bioprinting capability, and bioprinting scalability. First, bioprinting process modeling is indispensable for understanding how to modify the printed construct without affecting printability and bioactivity as well as predicting the printability of novel bioprinting biomaterials, which will significantly reduce trial-and-error in material formulation. The successful implementation of neural-network-based and finite-element-model-based bioprinting modeling has opened the door to a better understanding of the bioprinting process mechanism [72].

While numerous natural and synthetic bioprinting biomaterials are currently employed, there is still an urgent demand for bioprinting materials that meet widely accepted criteria, including printability, cytocompatibility, biocompatibility, mechanical strength, and degradation aspect. Most biomaterials employed for oral and maxillofacial bioprinting at the time of writing contain only two or three of the above criteria, including bioinks specifically designed for cartilage, bone, and muscle structures [20]. As the major innovation agent in tissue engineering, it is envisaged that more novel biomaterials or bioinks will be developed for more complex oral and maxillofacial tissue bioprinting. Large-sized constructs resulting from recent advancement in multi-head or multi-nozzle bioprinting systems have almost no length limit as to bioprinted construct size, while most recent artificial scaffolds used for patient-matched oral and maxillofacial tissue/organ regeneration are only designed to treat small tissue defects. 3D bioprinting is envisaged to manufacture large-sized scaffolds with high porosity to match the required standards for clinical translational studies [56].

7.1. Innovative Technologies on the Horizon

In a near future, various advancements in material manufacturing and processing techniques are anticipated for 3D bioprinting. One area of focus includes instant-printing devices made of grass or droplets, bioinspired with properties similar to skin and keratin. In parallel, ubiquitous manufacturing shows promise in real-time preparation of biological tissues through ultra-fast bioprinting [4]. Another element involves the ability of robots to redesign and construct their architecture and environment, moving toward a paradigm of self-assembly and bioinspired architectures created by filaments, droplets, sponges, bio-inserted scaffolds, or viruses. Progress in the development of hybrid scaffolds utilizing two-photon polymerization printing techniques and 3D ultrasonic projection printing is also on the horizon. There is ongoing research on new materials that do not contain thiols and temperature changes, or bio-supporting filaments designed for temperature-induced reversible gelatin polymerization [68]. Research is devoted to soft robotics predicted to access on-demand biodiscovery or create smart pollution collection structures through bio-inspired construction solutions such as self-healing drug-deliverer designs. Additionally, research on bioengineering and bioinspired scaffold architecture is expected to explore the principles of architectural design in nature to introduce pathways toward growth engineering. On the other hand, demand responses to several new technologies and advanced manufacturing techniques are being analyzed. The capabilities for the extended production of frozen structures and volumetric printing of complex biological tissues are also anticipated. Furthermore, there are initial steps in the development of 3D bio-revolutionary design software, with progress being made on neural structures producing memories. Finally, bioengineering synthetic Circulatory Systems that expand and contract, respond to the pH of the environment, or assist in the production of hair-paterials are predicted [73].

TABLE 1. Progress in 3D Bioprinting for Oral & Maxillofacial Applications

Progress in 3D Bioprinting for Oral & Maxillofacial Applications		
Application Area	3D Bioprinting Progress	Tissue Types
Bone regeneration	Bioprinted scaffolds with hydroxyapatite and stem cells	Mandible, maxilla, alveolar bone
Periodontal repair	Multi-material printing mimicking bone-PDL-cementum complex	Periodontal ligament, gingiva
Soft tissue reconstruction	Bioprinting of oral mucosa using keratinocytes and fibroblasts	Oral mucosa, gingiva
TMJ (Temporomandibular joint)	Printing cartilage-bone interfaces using chondrocytes and biomimetic gels	Condylar cartilage and bone
Tooth root and pulp	Bioinks developed to support odontogenic differentiation	Dental pulp, dentin-pulp interface

Chart 2: Challenges in 3D Bioprinting for Oral and Maxillofacial Engineering		
Category	Key Challenges	Examples/Notes
Bioink limitations	Difficulty in formulating bioinks that support cells, mimic ECM, and are printable	Lack of universal bioink
Vascularization	Creating vascular networks within thick tissue constructs	Limits nutrient diffusion and cell viability
Cell sourcing	Limited access to patient-specific, lineage-committed cells for oral/maxillofacial tissues	Especially for dental pulp, PDL cells
Structural complexity	Reproducing complex 3D interfaces (e.g., bone–ligament–cementum) with precise architecture	Multimaterial and gradient printing is still evolving
Mechanical properties	Achieving strength, elasticity, and integration post-implantation	Often inferior to native tissue
Regulatory barriers	Lack of FDA/EMA	Regulatory framework still

	approval pathways for bioprinted constructs	developing

Chart3: Future Prospects and Innovations

Emerging Strategy	Goal	Examples
4D Bioprinting	Dynamic constructs that change over time post-implantation	Smart scaffolds that adapt to healing stages
AI-integrated design	Optimize print parameters, scaffold geometry, and cell positioning	AI for automated patient-specific modeling
Organoid printing	Print tissue mini-organs for disease modeling and regenerative testing	Tooth buds, mini-TMJ, salivary gland models
In-situ bioprinting	Direct printing into the defect site during surgery	Real-time bone or mucosa repair in oral surgery
Advanced vascular bioinks	Incorporate endothelial cells and growth factors to promote angiogenesis	VEGF-loaded gels, microchannel printing
CRISPR-enhanced cells	Modify cells to enhance differentiation or resist inflammation	CRISPR-engineered MSCs or pulp stem cells
Progress in 3D Bioprinting for Oral & Maxillofacial Applications		

7.2 Integration with Other Medical Technologies

Bioprinting involves the integration of cells and biological factors into a 3D scaffold. While attempts have been made to print cells and tissues in various sites of the body, bioprinting is still at its infancy in dentistry and oral-maxillofacial surgical site regeneration [74]. Various drug delivery systems, including hydrogels with controlled release, are either commercially available or in use in preclinical studies for periodontitis treatment. Photosensitive biocompatible hydrogels containing a wide range of drugs have been proposed as bioactive scaffolds for site-specific periodontitis treatment. Local sustained-release platforms coat hydrogels with antibacterial drugs and immunomodulatory molecules to prevent and treat periodontitis. Multi-printing of such sustaining drug release/delivery platforms could be attempted in order to provide a long-term effect against the regenerative tissue loss of periodontitis[4]. Furthermore, as CAD-based and 3D printing technologies are further developed, combination products with digital data transfer printing and manufactured in combination with other medical devices could open up new avenues for digital individualized craniofacial reconstruction. Similar types of HAp scaffolds have been commercialized for peri-implantitis treatment of dental non-union sites [74]. Besides usage in bone defect reconstruction, it will be beneficial to further evaluate the potential of combine bioprinting with soft/hard tissue junction clinics and other 3D printed CAD-based customized devices. Bio-inspired methods for better blood vessel reconstruction using microfluidic channels strictly controlled by computers and/or microscopic 3D resolution combined with various vasculature sources could be helpful to form a self-sustaining vascularized socket scaffold. How to adopt new biomaterials/new combined uses of old biomaterials/advanced fabricating techniques to tackle the challenges for improved functional scaffold design, while keeping in mind biological, mechanical, surface structure and architecture, interconnectivity robustness of the scaffolds, biocompatibility cladding coating degradation from all aspects need extensive research too. Screening of drugs at the tissue levels/in vivo, functional assessment of improved bioprosthetics grafts for stabilization/integration for calcitic/biomechanical competence at animal model, and especially functional assessment of currents carotid/cogonalt/foraminal arteries repair graft have never done. For further advancement of engineered bone graft, key concerns such as precisely tuning mechanical properties, biologically enhancing graft-mediated hosted-bone regeneration and angiogenesis for long-term stability, and graft-host integration/VFFR clinical monitoring all remain challenging [76].

7.3 Potential for Personalized Medicine

Although 3D bioprinting in medicine is still in its infancy stage, there is great potential for future applications. 3D bioprinting has been praised for years as a revolutionary technology that will change future surgical management and pathology treatment approaches [77]. No industry has so far engaged in extensive research efforts, and the medical bioprinting market is growing strongly with the introduction of new printing technologies. The rapid prototyping technology of CAD software in combination with 3D bioprinting is currently being explored and implemented into academia and clinics. Even though applying these tools for skeletal tissue engineering is complicated due to lower cellularity and perfusion of adult bone, early efforts have been made towards the printing of collagen, gelatin, and alginate scaffolds with cells[78].

In the craniofacial field, researchers are implementing 3D printed scaffolds for both hard and soft tissue regeneration. Because of their wide range of applications and enormous design flexibility, polycaprolactone (PCL) and polylactide (PLA) scaffolds have been printed using both standard fabrication methods and novel extrusion bioprinting

technologies. In contrast to powder–liquid bioprinting methods, melt-based extrusion and laser-assisted printing represent solvent-free and temperature-controlled scaffold fabrication methods to produce scaffolds for craniofacial tissue regeneration[60]. Due to the great potential of combine and multi-functional bioprinting technologies, researchers must thoroughly evaluate and analyze novel approaches including electrical and magneto induction, temperature determination, real-time quality monitoring, and smart materials towards integrated technologies suitable for the craniofacial field[79].
Exciting progress in bioprinting has been made and novel bioprinters with specialized ink dispensing modalities, measurement tools, and large-scale printing goals have surfaced. Multi-material flow, life-support system added, 3D printing of organ-on-chips, and hybrid bioprinting approaches have all shown great promise for the future applications 2. With the accumulation of knowledge, it is time to develop a multi-printer platform and miniaturized devices for implementation in small clinics, hospitals, and research facilities. Also, it is essential to shift from technology-driven printing paradigms to fabrication technology development driven by clinically relevant big data sets[80].

8 Conclusion

In recent years, tissue engineering has emerged as a promising approach to restore damaged or lost tissues, and cell printing technologies are advancing to allow spatially regulated assembly of cells and biomaterials. Medical weightlessness induced by microgravity, which is detected in spaceflight or can be created in parabolic flight, can induce various physiological responses in the human body. However, these effects of microgravity on cell cultures have hardly been studied in tissue engineering. For the first time, the effect of weightlessness on bioprinting system was examined in vitro. In summary, this review highlights the latest developments in 3D bioprinting technologies, biomaterials, and bioinks with an emphasis on bioinks based on hydrogels tailored for oral and maxillofacial tissue engineering applications.

Furthermore, recent advances in the biofabrication of multi-tissue constructs and their particular importance for OMF regeneration are critically reviewed. The challenges and future prospects for this rapidly evolving field are presented. A combinations of 3D bioprinting and hybrid approaches can be used to manufacture OMF grafts containing a bony core and mineralized collagenous tissue shell with the potential to integrate with the recipient site. In this regard, it is anticipated that combining 3D bioprinting with other technologies will help produce small-to-large, scaled constructs that can be effectively used in OMF regeneration. Finally, given the rapid advancements in 3D printing technologies and materials in recent years, it is anticipated that the first generation of patients with OMF grafts will be treated within the next decade.

Conflict of Interest: The authors declare no conflict of interest.
Financing: The study was performed without external funding.
Ethical consideration: The study was approved by Babylon University, Babylon, Iraq.

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How to cite this article

Al-Ameedee AH, Adeeb A, Al-Ameedee AA, Al-Ameedee AA; 3D bioprinting in oral and maxillofacial tissue engineering: progress, challenges, and future prospects. Future Dental Research (FDR). 2025;3(2):57-70. doi: 10.57238/fdr.2024.152576.1019