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Review Article

Bioengineering from the laboratory to clinical translation in oral and maxillofacial reconstruction

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ABSTRACT

Background: Conventional techniques used in oral and maxillofacial reconstruction focus mainly on utilizing autologous tissues that have unquestionably improved function and esthetics for many patients, worldwide. However, the success depends on countless factors such as: donor and recipient sites conditions, patient's medical history, surgeon's experience, restricted availability of high-quality autogenous tissues or stem cells, and increased surgical cost and time.
Materials and Methods: Lately, teaming researchers, scientists, surgeons, and engineers, to address these limitations, have allowed tremendous progress in recombinant protein therapy, cell-based therapy, and gene therapy.
Results: Over the past few years, biomedical engineering has been evolving from the laboratory to clinical applications, for replacement of damaged body tissues due to trauma, cancer, congenital or acquired disorders.
Conclusions: This review provides an outlook on the content, benefits, recent advances, limitations, and future expectations of biomedical engineering for salivary glands, oral mucosa, dental structures, and maxillofacial reconstruction.

1. Introduction

Oral and maxillofacial (OMF) impairment greatly impacts oral functions and esthetics, whereby, reduces the patients' quality of life, and affects their psychological and socioeconomical status [Berebichez-Fridman and Montero-Olvera, 2018, Berthiaume et al., 2011, Dave and Tomar, 2018]. Tissues damage can be caused by trauma, cancer, congenital or acquired disorders. To restore the patients' quality of life, interdisciplinary accurate planning, and performance of OMF reconstruction is a must. Such reconstructive surgeries require precise restoration of the fine details of multiple body tissues forming the affected area [Andrades et al., 2011]. During recent decades, autogenous grafts have been the benchmark of reconstructive surgeries [Berthiaume et al., 2011]. However, donor site morbidity and limited availability of transplanted tissues restricted the achievement of desirable outcomes [Dave and Tomar, 2018]. Thereafter, scientists and clinicians tested allografts, xenografts, or synthetic substitutes in a search to address these limitations. Tissue engineering is a quickly evolving field that involves biomaterials, cells, and relevant physical and biochemical elements, to build up a tissue-like construct. Scientists and clinicians aim to include this tissue-like construct within the damaged body site to restore its functions and esthetics [Berthiaume et al., 2011]. However, the shortage of the clinical applications is caused by the limitation in proliferation and differentiation capacities of stem cells, cost, and time needed for the *in vitro* work. In this review, we shed light on the current biomedical engineering content, applications, recent growth, limitations, and future predictions, hoping to motivate scientists and clinicians for the advancement of reconstructive surgeries. Due to the wide range of the basic and clinical studies in the biomedical engineering field, detailed information about the basic laboratory work will not be included in this review. This review summarizes the current research in the field of bioengineering and its applications in the oral and maxillofacial area.

2. Tissue engineering basic content

Tissue regeneration is achievable by three main components: the cellular elements, the scaffold, and the ligands (chemical molecules such as: growth factors) [Yazdanian et al., 2021a]. It is a complex process that involves inflammation, proliferation, and tissue remodeling. During

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regeneration, the signaling molecules start cell proliferation to fill in the tissue defect, then, induce cellular differentiation [Langer and Vacanti, 1993]. These biological events are achieved by growth factors, which are secreted by the cells *in situ* or by some circulating blood cells. In addition, growth factors are stored in the extra-cellular matrix (ECM) to be released during tissue repair and remodeling. The extracellular matrix acts as a 3D scaffold to facilitate cell migration and tissue-specific orientation [Mosaddad et al., 2020]. Thus, cells, ligands, and ECM work together to achieve tissue homeostasis and regeneration [Langer and Vacanti, 1993]. Of much importance, angiogenesis and tissue vascularization play a crucial role in cells manner, thus, controlling tissue repair. In addition, intact circulation is important for cell survival and tissue supply with undifferentiated progenitor cells, necessary for tissue repair [Schliephake, 2010].

Over the past few years, autografts have been the benchmark for tissue reconstruction in the OMF area. However, surgeons are still looking for other alternatives to overcome donor site morbidity and obtain better constructs. Allogeneic grafts were introduced as an alternative to repair simple defects, but several shortcomings could not be eliminated, such as the higher cost, the difference in tissue quality/strength, the possibility of cross contamination, and the limited availability of cadaver [Costello and Kail, 2007]. Recently, researchers have developed the 3D biocompatible and bioactive scaffolds to support cells and signaling molecules, and to deliver them to where they should carry out their functions [Costello et al., 2010]. Different biomaterials have been employed as scaffolds to enhance tissue regeneration and cellular functions [Khayatan et al., 2024]. These scaffolds can be either organic or inorganic elements. The organic elements are either natural, such as collagen, chitosan, and silk, or synthetic, such as polylactic acid and polyglycolic acid. The inorganic elements are either minerals, alloys, or metals [Salgado et al., 2004]. The success of tissue engineered constructs depends mainly on the viability, longevity, and performance of its cellular component.

Stem cells are undifferentiated or partially differentiated, self-renewable cells that may differentiate into many cell types and can be extracted from embryos and adult tissues [Jaenisch and Young, 2008]. The highest differentiation capacity is seen in the totipotent stem cells of the zygote. While the embryonic stem cells are pluripotent, the hematopoietic and mesenchymal stem cells are multipotent, the myeloid stem cells are oligopotent, and the epidermal stem cells are unipotent [Zakrzewski et al., 2019]. Current research has targeted three groups of stem cells: somatic/adult stem cells (ASCs), pluripotent stem cells (PSCs), and cancer stem cells (CSCs). Adult stem cells are scarce undifferentiated cells that reside among other specialized cells in different tissues [Chagastelles and Nardi, 2011]. With their limited proliferation and specialization capacities, ASCs supply the damaged tissue with precursor cells that perform repair and regeneration [Pekovic and Hutchison, 2008]. ASCs include mesenchymal stem cells (MSCs), hematopoietic stem cells, skin stem cells, and neural stem cells [Gurusamy et al., 2018]. These cells are the main source of stem cell research and therapy in countries that have ethical concerns related to the use of embryonic stem cells. Pluripotent stem cells (PSCs) can be found in the cells of the embryo; they include the embryonic stem cells that reside in the inner blastocyst cell mass of preimplantation embryos, the epiblast stem cells and embryonic germ cells that can be extracted from post-implantation embryos, and the induced pluripotent stem cells that are obtained from direct reprogramming of postnatal/adult somatic cells, *in vitro* [Singh et al., 2016]. Cancer stem cells (CSCs) are tumor initiating cells that reside within tumors, but they develop from normal stem cells or tissue progenitors, following mutations, microenvironmental or epigenetic changes, and gene transfer [Soltanian and Matin, 2011]. In addition to proliferation and differentiation potentials of stem cells, CSCs can metastasize, suppress the immunity, enhance cancer growth and resistance to chemotherapy or radiotherapy [Atashzar et al., 2020].

Growth factors are proteins secreted by certain cells to send signals to specific cells to perform certain actions, such as cell proliferation, ECM secretion, and differentiation, which form the necessary steps for tissue repair and regeneration [Gerstenfeld et al., 2003]. There are six growth factors that participate in tissue regeneration, especially bone, and were applied in OMF reconstruction in some animal models [Rutherford et al., 1993; Khayatan et al., 2023; Mosaddad et al., 2024]. These growth factors include platelet-derived growth factor, basic fibroblast growth factor, insulin-like growth factor, transforming growth factor beta, vascular endothelial growth factor, bone morphogenetic proteins. In general, regeneration of OMF tissue was based on three main therapies: 1) recombinant protein therapy, 2) cell-based therapy, and 3) gene therapy. Recombinant protein therapy aims to deliver certain growth factor/s contained within a scaffold, to induce certain cells residing in the selected site. Employing this technique might help to decrease the need for autogenous grafts [Seeherman et al., 2003]. Cell-based therapy is based on direct involvement of added cells to tissue repair, regeneration, genetic alterations, and differentiation into different cell types [Gafni et al., 2004]. Gene therapy is a relatively recent technique that has an immense therapeutic capacity where a specific gene data can be transferred into cells to stimulate the secretion of targeted proteins [Hannallah et al., 2002]. In OMF construction, gene therapy was used in a few preclinical trials and some animal studies have tested genetically modified human bone marrow and MSCs for possible bone regeneration and further tissue engineering applications [Peterson et al., 2005].

3. Oral and maxillofacial engineered tissues

1. Salivary Glands

Dry mouth or xerostomia is known as salivary gland hypofunction, that is caused by tissue damage due to head and neck cancer radiotherapy, Sjogren's syndrome, aging, or medications. Dry mouth causes various oral complications that decrease the patient's quality of life, such as bacterial and fungal infections, increased dental caries, chewing and deglutition difficulties [Maria et al., 2012]. These complications directed the attention of scientists towards salivary gland regenerative potentials [Zufferey and Aebischer, 2004]. Thereafter, Salivary glands 3D cultures aimed at producing functional salivary-like structures, for future use in repair and regeneration of damaged glands [Shin et al.,2017]. Different hydrogel types that are made of fibrin, collagen, or Matrigel were studied for their possible salivary gland regenerative potential [Ozdemir et al.,2016; Maria et al.,2011a; Maria et al.,2011b]. When salivary gland cells were cultured on gel, they could multiply into sphere-like structures, then differentiate into acini-like forms and exhibit salivary gland specific proteins [Ozdemir et al.,2016; Maria et al.,2011a; Maria et al.,2011b; Iyer et al.,2023]. Although ECM could reinforce salivary cells and help them to polarize and aggregate into sphere-like structures, the degradation rate of these spheres is not controllable, and the presence of certain xenogeneic substances is unavoidable [Ozdemir et al.,2016; Iyer et al.,2023]. Salivary gland suspension cultures use no scaffolds and no animal serum for production of sphere-like structures, which make it very suitable for clinical applications. However, the produced spheres take longer time to form and has no uniform shape or size [Iyer et al.,2023]. Due to the uncontrollable increase in their size after 5–10 days of culture, central apoptosis starts in the middle of the sphere; in the inner cells which are devoid of oxygen and nutrition. On the other hand, 3D ECM-produced salivary spheres can preserve their structure, viability, and unity for more than 10 days [Lilliu et al.,2016; Seo et al.,2019]. Bioprinting techniques employed magnetic labelling of cells with nanoparticles for easier and faster assembly into uniform-shaped and −sized salivary sphere [Ferreira et al.,2019]. Offering a compatible approach of producing uniform salivary spheres, nevertheless, bioprinting is uneconomical and biologically incompatible [Ferreira et al.,2019; Charbonneau et al.,2019; Charbonneau and Tran, 2020]. The production of fully functioning salivary spheres is still in progress. Once achieved, it would assist in the analysis of different medications, such as radiation protective drugs.

On the other hand, gene therapy has been employed to improve saliva secretion [Shan et al.,2005] and more work is in progress, for future human trials [Voutetakis et al.,2005].

2. Oral Mucosa

Various oral mucosa designs have been produced to test the biocompatibility of different materials [Rahimi et al.,2018]. Collagen gel was proved to enhance cell adhesion, multiplication, and differentiation into keratinocytes and fibroblasts [Zurina et al.,2018]. A double-phase culture technique was invented to produce a stratified epithelial structure from oral mucosa epithelial cells with the aid of a non-adhesive agarose, a hybrid matrix of poly lactide-coglycolide and collagen. This stratified epithelial structure contained polarized cells with epithelial intercellular connections and phenotype [Basso et al., 2018]. Epithelial tissue engineering continued to improve and was able to produce more complex structures which combines a stratified epithelium with a continuous basement membrane, and a subepithelial fibrous connective tissue layer, which reinforces and stabilizes epithelium during the regeneration process. This full thickness tissue engineered mucosal construct has been clinically used in vestibuloplasty, restoring superficial mucosal defects, and for "prelamination of free radial forearm flaps with subsequent transfer to the oral cavity". Clinical results have revealed acceptable to outstanding integration degrees with successful blood supply extending from the recipient bed and reduced healing time [Hotta et al.,2007].

3. Tooth Complex

Tissue engineering of the dental complex has targeted the complete functional dental unit, as well as, a single dental tissue, such as enamel, dentin, cementum, dental pulp, periodontal ligament (PDL) and alveolar bone. For example, pulp regeneration is limited, owing to its limited blood supply through the apex, and enamel does not regenerate on its own. However, cement and dentin are self-healing structures, owing to odontoblasts and cementoblasts continuous sources; the dental pulp, and sac, respectively [Yen and Yelick, 2011]. In 2007, the first complete incisor was formed after combining mesenchymal and epithelial cells that were extracted from a tooth germ [Nakao et al.,2007]. Two years later, a fully functional mouse tooth was produced as a transplant of an engineered dental germ; this tooth showed successful eruption and occlusion [Ikeda et al.,2009]. Thereafter, decellularized porcine dental buds were implanted with dental cells and have successfully developed and mineralized into complete teeth, in Yucatan mini pigs [Zhang et al.,2017]. Scientific trials to regenerate enamel were not successful until the assembly of bone marrow MSCs, tooth mesenchyme and epithelial cells into a dental crown within 20 days [Jayasudha et al., 2014]. Odontoblasts were successfully obtained and induced to produce healthy tubular dentin when human exfoliated deciduous teeth stem cells were suspended in an injectable scaffold and planted into human teeth pulps [Rosa et al.,2013]. For years, the standard pulp damage therapy has been root canal treatment [Jang et al.,2017]. Nowadays, based on the limit and sort of pulp damage, various pulp regeneration techniques can be applied, such as, pulp circulation reestablishment, stem cell treatment, implantation or injection of different scaffolds, gene therapy, and 3D cell-scaffold printing [Jung et al.,2019]. Self-assembled 3D-printed cell sheets were employed to regenerate pulpectomized teeth using human dental pulp stem cells (DPSCs) [Chandki et al.,2012]. In addition, certain scaffolds produced favorable clinical applications in regenerating teeth pulp [Colombo et al.,2014]. Many research groups have reported the safety and capacity of human and non-human DPSCs and other MSCs to regenerate dentin-pulp complex, produce semi-dentin tissue, and repair pulp [Chandki et al.,2012]. In addition, reports on the use of different growth factors with pulp capping have revealed successful pulp regeneration [Dissanayaka et al.,2014].

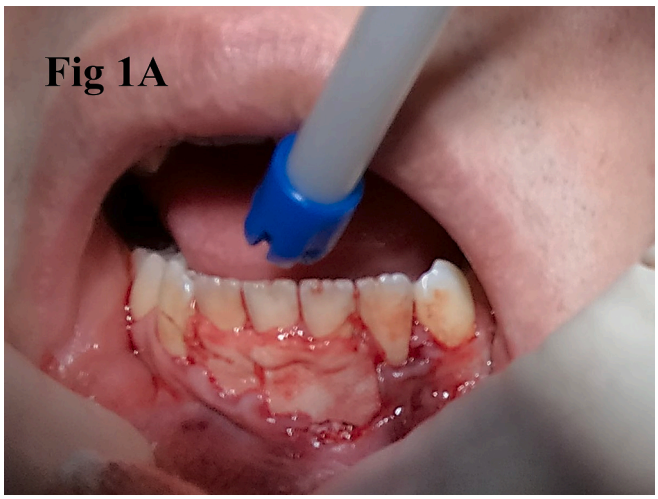
In the complex process of root formation, multiple cell types play important roles inside the highly vascular and innervated dental sac [Jamal, 2016]. A group of researchers were able to produce a thin layer of acellular cementum at the root cervix and a thick layer of cellular cementum at the apex, simulating the regular tooth cementum [Liu et al.,2019; Soudi et al., 2021]. Cementoblasts isolated from the dental follicle were able to repair periodontal defects in a rat model [Zhao et al.,2004]. Another group obtained PDL tissue from PDL stem cells implanted on a hydroxy-apatite scaffold [Bakhtiar et al., 2018]. In addition, fat-derived stem cells and dental follicle stem cells were reported to produce cementoblasts and reform PDL tissue [Liu et al.,2019]. Various growth factors, such as platelet-derived growth factor, recombinant bone morphogenetic protein, and transforming growth factor-β3 could stimulate cement-forming cells to deposit cementum and could form regular PDL, and Sharpey's-like fibers [Zhang et al., 2016]. Furthermore, MSCs showed high potential for PDL regeneration through immunomodulation and revascularization of the inflamed PDL [Monsarrat et al.,2014].

Recently, the connection of the gingiva to dental implants has withdrawn the scientists' attention, and different models have been employed to analyze this connection. A human gingiva construct was produced to test the epithelial attachment to the implant-abutment surface; natural gingival margin, junctional epithelium, and gingival sulcus were formed around the implant-abutment surface and expressed keratin 4 and 19 epithelial proteins [Roffel et al.,2019]. Gingival recession is a common oral problem with different causes, such as mechanical or occlusal trauma, anatomical, inflammatory, chemical, or biological factors [Chan et al.,2015]. The standard treatment of gum recession is the connective tissue graft. Recently, coronally advanced flap was used with platelets-rich plasma [Li et al.,2019], advanced platelet-rich fibrin [Sameera et al.,2018], leukocyte platelet-rich fibrin [Sameera et al.,2018], and all showed promising gingival regeneration outcomes. Collagen membranes were proved to be the best matrix that supports the gingiva during regeneration [Buskermolen et al.,2016]. Free gingival graft (FGG) surgery is the standard technique to increase the attached gum thickness and width, but recently, an allograft prepared from acellular skin matrix revealed promising clinical outcomes [Shah et al.,2014], Fig. 1A and Fig. 1B. The esthetic outcomes of porcine xenogeneic collagen matrix combined with apically positioned flap (APF) were better than FGG combined with APF around human mandibular back implants, however, gum shrinkage was higher [Qiu et al.,2023].

4. Dental Implants

Dental implants have been the standard treatment for most edentulous adults. For ideal esthetic and function outcomes, the alveolar ridge preparation to receive an implant is standardized with certain bone quality and dimension [Lafzi et al.,2016]. Alveolar ridge augmentation is necessary when limited gum or bone quality and quantity presents at the future implant site [Pandit et al.,2011]. Guided bone regeneration [Larsson et al.,2016] and guided tissue regeneration are the standard techniques for alveolar ridge preparation to receive an implant. The bone source in these techniques might be autogenous, allograft, or xenograft [Cho et al.,2019; Yazdanian et al., 2021b]. Owing to their excellent osteogenic capacity, MSCs originating from bone marrow, present the main cell source to enhance bone quality and quantity with different bone grafting techniques [Marolt et al.,2014]. Recent studies have used different proteins, minerals, and recombinant growth factors in conjunction with MSCs to regenerate the alveolar bone and have showed promising outcomes [Shimizu et al.,2019]. These and other studies present a new hope for restoration of damaged jaw bones due to trauma, cleft palate, and for maxillary sinus lift before implant placement [Schimming and Schmelzeisen, 2004].

5. Maxilla/Midface



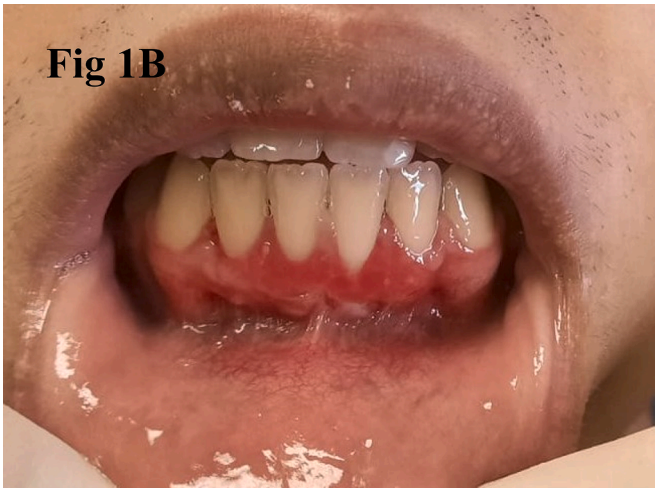


Fig. 1. (A): photograph shows acellular skin matrix allograft placed during a free gingival graft surgery for the treatment of thin receded gingiva at teeth 31, 41, 42 (buccal aspect), in a 16-year-old male, after the completion of orthodontic treatment. (B): photograph shows nicely healed attached gingiva with complete root coverage of the lower incisors, three-months post-operative. Photo courtesy to Dr OMM.

The current available cancer treatment includes surgical resection and reconstruction, radiotherapy and/or chemotherapy [Elkashty et al.,2019]. Resection of the tumor produces a defect that can adversely affect the patients' quality of life; by reducing the ability to chew, deglutinate, breathe, and speak clearly [Irish et al.,2009]. Radiation and chemotherapeutics reduce speech and chewing capacities within the first 24 weeks of treatment. Sometimes, the patient might recover within 12 months, however, his quality of life remains reduced through the entire time of recovery [Rogers et al.,2002]. In addition, treatment with high radiation doses can damage the healthy bone, blood vessels, endosteum, and periosteum [Shenoy et al.,2007], thus, limiting tissue repair and regeneration. Intensity-modulated radiotherapy (IMRT) has been used for years, to limit the risk of damaging healthy tissues surrounding the cancerous tissue. In IMRT, computer modeling and beam modifiers are used to control the doses of radiation delivered to specified cancer regions, thus, reducing the dose delivered to the surrounding healthy tissues [Boyer et al.,2014]. IMRT has reduced osteonecrosis and salivary glands damage [Bucci et al.,2005]. In the same way, chemotherapy causes multiorgan damage and fibrosis [Trotti, 2000]. Surgical cancer resection of the maxilla creates huge tissue defects that need to be restored with free tissue grafts or prosthetic obturators, however, both techniques have limitations that include compromised blood supply, increased risks of infection, and impaired healing [Javed et al.,2010]. In addition, with reduced quality of life and post-operative facial deformation, patients develop psychological problems [Irish et al.,2009]. Autologous free tissue flaps are the standard treatment of most maxilla defects, as they restore the oral and nasal cavities, allowing no crossing of food or drinks between the two cavities. However, obtaining a free tissue flap means a second surgery site, this increases morbidity and mortality rates [Peng et al.,2005]. In addition, sometimes the autogenous free flap is not the good match for certain maxillary defects reconstruction. Thereafter, tissue-engineered constructs have replaced autogenous free flaps. However, being directly exposed to oronasal normal flora, and lacking well-established initial blood supply, increase the risk of tissue-engineered construct failure.

Radiation therapy following surgical resection and reconstruction further compromises the site vascularity. Therefore, careful preoperative planning is needed for considering all the compromising factors and obtaining the best clinical outcomes. Included in tissue-engineered constructs, bone marrow MSCs were found to migrate preferentially to the site defect [Zhou et al.,2011], MSCs are attracted by certain inflammatory mediators which are produced by cells residing in the wound site, these mediators are similar to those secreted in the tumor microenvironment [Belmar-Lopez et al.,2013]. These MSCs showed bone regeneration potential, which can subsequently limit the need for multisite surgeries. However, tissue engineered construct preparation in the laboratory is time consuming, plus, being non-vascularized, the risk of construct failure increases when the defect site has compromised vascular supply, due to major surgical resection or pre-operative radiotherapy or chemotherapy [Schimming, 2004].

Maxillary sinus lift has been a standard technique to augment bone necessary for dental implant placement at the posterior maxilla. A group of researchers successfully augmented significant bone masses for implants placed in many patients. They used hydroxyapatite and tricalcium phosphate combined with autologous bone marrow MSCs. After 3 months healing period, 93 % of their patients showed significant new bone formation that made implant placement a big success [Shayesteh et al.,2008]. MSCs can differentiate into bone cells and regenerate bone, which is a promising potential for future clinical applications. Inclusion of growth factors, such as bone morphogenetic protein-2 (BMP-2) and β-fibroblast growth factor, highly improved the quality of regenerated bone, which could be employed in surgical defects reconstruction [Urkmez et al.,2008; Saleh Hasani Jebelli et al., 2024]. Recombinant human BMP-2 was proved to be safe and efficient when contained within absorbable collagen sponges to be used for maxillary sinus floor augmentation. These sponge scaffolds showed successful outcomes compared to autogenous bone grafts [Boyne et al.,2005], with the advantages of circumventing long-term pain, paresthesia, and walk troubles related to the autogenous bone grafting from the hip or the lower leg bones [Triplett,et al.,2009].

6. Mandible

The periosteum-derived progenitor cells (PDPCs) can differentiate into osteogenic, adipogenic, chondrogenic, and myogenic cells [Park et al.,2007]. The interconnection between endothelial and bone progenitor cells can mutually enhance angiogenesis and osteogenesis [Rouwkema et al.,2006]. In addition, PDPCs can secrete certain growth factors, such as BMP-2, that might improve the clinical outcomes of a tissue-engineered construct [Cheng et al.,2003]. Furthermore, PDPCs have chemotactic capacity, if employed in clinical applications, may direct PDPCS to migrate to the defect sites for better regenerative outcomes [Stich et al.,2008]. However, harvesting PDPCs, laboratory expenses, and the necessary time for construct preparation, should be planned early enough before the surgical resection to avoid possible morbidity. When PDPCs were seeded into polyglycolide-co-polylactide

scaffold to repair critical size bone defects in a rabbit model, they showed satisfactory outcomes [Redlich et al.,1999]. The success of surgical reconstruction relies on the potential of healthy patient's cells that surround the defect site, to infiltrate and vascularize the tissue engineered construct. To further reinforce the construct, multiple small bone implants can be grown in the laboratory and transplanted later to the defect site [Steinhardt et al.,2008]. However, this technique will increase the number of required surgeries, time, and cost. Reconstruction of critical size bony defects remains one of the biggest challenges to oral and maxillofacial surgeons. A major step in OMF reconstructive surgeries was achieved when stem cell therapy was used in combination with BMPs to prepare a custom bone graft that was implanted into the latissimus dorsi muscle of a patient to be transplanted along with its blood supply to reconstruct a critical mandibular defect [Warncke et al., 2004]. Mandible defects commonly result from trauma and surgical resection of benign or cancerous tumors. In most cases of cancer resection, radiotherapy is needed, but it might result in osteonecrosis. In addition, bisphosphonate that treats osteoporosis, is another cause of osteonecrosis [Otto et al.,2011]. In advanced osteonecrosis cases, segmental resection is the treatment of choice to eliminate dead bone segments, but it creates larger bony defects [Joo et al..2019]. If more than 10 % of the mandible is resected, spontaneous healing of the mandible fails [Brierly et al.,2016]. Currently, bone transplants, metallic appliances, and distraction osteogenesis are being clinically used, however, the free fibular flap transplant is the standard for mandible reconstruction [Kumar et al.,2016]. Such surgeries are complicated with possible bacterial contamination, donor site morbidity [Bede et al.,2019], and some patients might develop hyperalgesia (30.5 %) and neuropraxia (40 %) [Nørholt et al., 2011]. Metal appliances and osteogenesis distractors inevitably require numerous surgeries (with detailed presurgical planning), which raise both morbidity and esthetic problems [Pare et al.,2019]. MSCs derived from the mandible show distinctive osteogenesis capacity, owing to their neural crest neuroectoderm origin [Li et al.,2020]. Long bones which had originated from the mesoderm, form and heal by endochondral ossification, while craniofacial bones form and heal mainly by intramembranous ossification. Interestingly, the mandible distraction stimulates intramembranous ossification, while mandible fractures stimulate endochondral ossification [Achilleos and Trainor, 2012]. MSCs from tibia bone marrow have lower proliferation [Dong et al.,2014], pluripotency, and osteogenesis differentiation capacities compared to MSCs derived from the mandible bone marrow [Lee et al.,2019]. Clinically treated alveolar defects with autogenous mandibular bone grafts showed better outcomes compared to alveolar defects treated with autogenous iliac bone grafts [Barone and Covani, 2007]. Interestingly, grafting neural crest-originated MSCs into tibia defects and mesoderm-derived MSCs into mandible defects, resulted in intramembranous ossification in the tibia defects and endochondral ossification with fibrosis in the mandible defects [Leucht et al.,2008]. This means that MSCs keep the regenerative ossification pattern of their origin, which is very important to consider in planning and selection of stem cell source for regeneration and reconstruction of different defective sites.

Hydrogel scaffolds work as carriers and protectors for seeded stem cells, allowing them to restore the defect sites with less risk of immune rejection [Kurtz, 2008]. In addition, hydrogels may release certain growth factors to recruit the patients' own cells to migrate into the constructs [Ying et al.,2019; Ko et al.,2013]. Furthermore, hydrogels can control stem cells' function and fate through sending physical and biochemical signals [Ko et al.,2013]. Together with different stem cell types, hydrogels show promising potentials for reconstruction of the mandible defects [Liu et al.,2016]. Certain growth factors, such as bone morphogenetic proteins, insulin growth factor, fibroblast growth factor-2, transforming growth factor-β, stromal cell-derived factor-1, vascular endothelial growth factor, and nerve growth factor, hold osteo-inductive and angiogenic properties, and play important roles in mandibular regeneration when included within the hydrogel [Dreyer et al.,2020]. Holding the highest osteogenic potential, BMP-2 has been the most used growth factor in mandibular reconstruction [Sheikh et al.,2015]. Recombinant human bone morphogenetic protein-2 (rhBMP-2)-sponge collagen or poloxamer-based gel provided the highest outcomes in mandibular reconstruction when combined with regular titanium meshes, Fig. 2 [Tatara et al., 2019].

Mandibular reconstruction following trauma or deformation shows promising clinical outcomes, since seeding different stem cells into hydrogels simulates real life biology, stimulating construct mineralization and infiltration by the patient's own cells, thus, enhancing bone regeneration. On the other hand, mandibular reconstruction following osteonecrosis or severe infections, might face the challenge of antimicrobial resistance when antimicrobials were given systemically while the construct blood supply is impaired. Therefore, hydrogel constructs can act as biological carriers to provide continuous antimicrobials release into the infected defect to enhance bone regeneration. Recent studies have focused on producing an appropriate hydrogel bio-ink to simulate the natural tissue physical and chemical properties, necessary for supporting seeded cells and growth factors [Genova et al.,2020]. Three dimensional bioprinting is a developing branch of tissue engineering where the polymer concentration controls the viscousness and mechanical properties of the print. The polymer concentration needs to be balanced to allow easy printing and at the same time provide better environment for cell proliferation and differentiation at the reconstruction site [He et al.,2016]. It is challenging to obtain the ideal hard and strong construct by using 3D bio-printed hydrogel. Therefore, many reports suggested using stiff polymers, such as polycaprolactone, poly lactic-co-glycolic acid and polyvinyl alcohol in combination with the 3D bio-printed hydrogels [Lee et al.,2014]. Thus, 3D bio-printing provides new chances for fabrication of site-specific constructs using many cell types and production of fine tissue details within these constructs, for promising mandibular reconstruction outcomes [Gaspar et al.,2020]. This allows for production of bio-printed constructs seeded with primary arch osteoblasts, and vascular-like vessels lined with primary endothelial cells [Amler et al.,2021]. Moreover, 3D printed polycaprolactone/hydrogel including dual drugs release, such as, resveratrol and strontium ranelate, has significantly promoted *in vivo* mandible formation after 8 weeks of implantation [Zhang et al.,2020]. Besides, the perfect 3D cultural conditions supported by the bio-printed hydrogel constructs, they improved stem cells activity and directed their fate towards proliferation and differentiation [Kang et al.,2016].

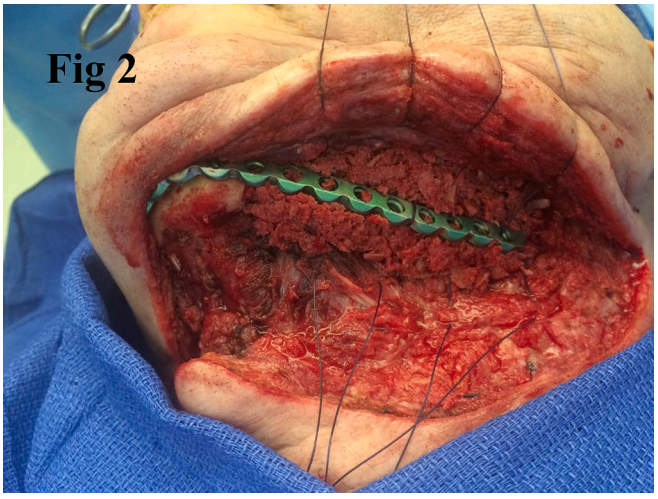


Fig. 2. A photograph shows left side hemi-mandibular reconstruction using bmp-2 and autogenous bone graft from the iliac bone, supported by titanium mesh, for treatment of osteonecrosis, in a 65-year-old male. photo courtesy to Dr AH.

7. Temporomandibular Joint

Temporomandibular joint (TMJ) tissue engineering might be very limited due to the complexity of TMJ anatomy, histology, and physiology, which make it a very specialized joint to withstand the huge forces of mastication, pressure, and tension, for proper long-term function. In 1960S, TMJ disc replacement was first introduced with Teflon implants that failed shortly and caused foreign body granulations, pain, and joint bone loss [Henry and Wolford, 1993]. In addition, fat tissue was used to alleviate joint pain with no success [Acri et al.,2019]. Thereafter, MSCs were used in TMJ disc engineering. In 2015, perforated TMJ discs were repaired with fibrous tissue, 8 weeks after being implanted with collagen scaffolds seeded with autologous bone marrow MSCs, in a rabbit model [Kobayashi et al.,2015]. Furthermore, hyaline cartilage was studied by many scientists in a hope for TMJ cartilage replacement, but satisfying results are still in progress [Almarza and Athanasiou, 2004]. In 2023, a group of researchers developed TMJ disc constructs from decellularized rabbit TMJ discs that were supported with polycaprolactone. When installed in a rabbit TMJ disc reconstruction model, these constructs restored the structure and function of the rabbits' TMJs and were stable for 6 months. In addition, similar disc constructs were produced from decellularized porcine TMJ discs and implanted in a goat TMJ disc reconstruction model. These xenograft discs were functional and could stabilize the goats' TMJs for 20 weeks post-operative. This shows the therapeutic potential of TMJ disc allografts and xenografts in the management of TMJ disc degenerative disorders [Jiang et al.,2023]. Hopefully soon, tissue engineering scientists can provide precise human TMJ models by employing bone inductive scaffolds and stem cells with potentials to differentiate into TMJ disc fibro-chondrocytes.

4. Conclusions & future expectations

Tissue engineering is developing at a fast pace. At present, in some cases, oral and maxillofacial reconstruction cannot achieve optimal functional and esthetic outcomes, especially in cancer patients. This has negative impacts on these patients' general and mental health. Nevertheless, each therapeutic approach has its beneficial outcomes, but optimization is necessary to achieve the ideal functional and esthetic outcomes in a reasonable time, with a reasonable cost, and the minimum number of surgeries, to improve the patients' quality of life. Tissue-engineered constructs can be optimized via customization of the used scaffold, growth factors, stem cell type and origin, for each individual patient. The *in vitro* cell expansion and construct processing time needs to be shortened for faster application and cost reduction. Further research is necessary to test possible immediate stem cells transplantation into the defect site at the time of resection, to possibly save time and reduce lab work cost. In the meantime, further research is needed to improve *in vitro* cell expansion and bone tissue formation (quality and quantity), in a shorter time by optimizing culture media and incorporation of different growth factors.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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