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Tissue Engineering Applications in Maxillofacial Surgery

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Abstract

Nowadays, oral and maxillofacial surgeons face serious difficulties in reconstruction of large defects caused by trauma, cancer, or congenital deformities. Considering each part of oral and maxillofacial region consisting of several tissues, it is necessary to reconstruct these architectures layer by layer. Through years surgeons use different forms of grafts to reconstruct these defects. As these grafts and techniques are well described and used routinely, it should have been noticed that they are not without complications. This is where idea behind tissue engineering steps in. "Tissue engineering" due to its multi-aspect properties can be defined as application of methods and science of engineering toward the understanding of structure-function relationships of mammalian tissues in both normal and pathological forms to improve and develop biologic substitutes to reach the main goal of restoring, maintaining, and stabilization of tissue function. From standpoint of surgery, tissue engineering is not considered as a potential step anymore, but as an available approach to reach the ultimate goal of reconstruction procedures. The aim of this chapter is to defne concepts and advances in tissue engineering (TE). Also, review TE applications in the field of oral and maxillofacial surgery with bolding its clinical applications and complications based on novel and high-quality published researches.

Keywords: tissue engineering, scaffolds, bioprinting, stem cells, regenerative medicine, oral surgery, maxillofacial surgery

1. Introduction

For the first time, Langer and Vacanti introduced the definition of tissue engineering [1] to explain the basics of functional substitutes for tissue damage and how to reconstruct and regenerate these tissues based on principles of biology and medical engineering. This new field in contrast to the former biomaterial thoughts presents incredible disciplines which diverse the goal of regeneration induction of traumatized or damaged tissue rather than substitution with inert parts. In recent decades, a number of articles were being published about the tissue engineering and regenerative medicine (TERM) field over 360 yearly just at the beginning of the twenty-first century. Just in 2010, the number of original articles in this field reaches 4000. This over-increasing attraction to this field—involving almost all tissues even whole organs—leads to researches across the world [2].

Herein, we review latest scientific researches and recent advances of tissue engineering in major field of oral and maxillofacial surgery by subtopics categorized by facial complex parts.

2. Basic principles of tissue engineering

Tissue engineering is composed of three pillars: the cells, scaffolds, and growth factors. The combination of cells in a suitable scaffold was designed by the appropriate biochemical signals that can facilitate and make possible growth, so it could be a treatment option that is very suitable for clinical application. Various studies have shown that one of the important issues is proper design of scaffolds and associated mechanical signals to regulate tissue that is engineered. Scaffold that can be temporarily or permanently used for three-dimensional porous can also be natural or artificial, which in any case must be biocompatible [3]. A biocompatible environmental issue is crucial importance because it facilitates progenitor cells for migration and differentiation [4]. Some of the important issues that include the physical properties of the scaffold such as biodegradability, porosity, hardness and strength to be as much in excess of migration, cell adhesion, and proliferation (such as osteoconduction), which reflects the influence of signals on the cell is followed by the clinical efficacy of chemical signals and ultimately success factor for the link to be followed. Perhaps the problem for surgeons and maxillofacial surgery is more important than other counterparts, being careful scaffold designing on human anatomy for the repair of any defects in the face. Various studies designed to use the computer in the exact scaffold have shown promising results and have built a biomimetic scaffold that has special significance [5].

To complement these three pillars, tissue, cell lines that require ease of access and availability, differentiation capacity, and lack of stimulation of the immune system or have tumor genesis [6]. Choosing the right cell lines in tissue engineering is still under discussion. New research hopes to use stem cells and gene therapy with viral vectors to express growth factors in cultured cell lines successfully, but stem cell research is outside the scope of this topic [7]. Today, the laboratory of tissue engineering that leads clinicians to living tissue is a concept

that has the potential to create a great impact on the future treatments. One of the major obstacles to the proper functioning of the tissue outside the body is to understand the way in which cells can be set in niches under certain physical and chemical conditions which would be difficult [8, 9]. In this case, bioreactors can control the situation and imitate the natural environment. Bioreactor devices can control and adjust the physiological conditions. With advances in tissue engineering, scaffold design could put several layers of cells onto scaffolds for three-dimensional position. That purpose requires a microenvironment for growth in vitro. The mathematical model was able to calculate the fluid flow rate for scaffold to provide nutrients and remove wastes and release oxygen used. As well as other variables such as external mechanical force needed to stimulate the proliferation of osteoblasts and then followed it can also be provided. Another alternative method that involves the cultivation of graft in vivo using animal models or humans as a bioreactor to simulate the growth of cells is provided. The remainder of this chapter presents various examples discussed regarding various tissues of the jaw and face [9].

3. Oral and maxillofacial bone defects

3.1. Mandibular defects

The atrophic mandible presents its own unique set of challenges in reconstructive maxillofacial surgery. A mandibular vertical height of less than 2 cm (20 mm) is universally considered atrophic and presents with characteristic anatomic and physiologic features, such as hypovascularity, which might contribute to tooth and alveolar process loss. The atrophic resorption patterns also contribute to the consistent anatomic changes, such as prominent mylohyoid and internal oblique ridges, which are covered with a thin mucosal lining, contributing to an increased risk of soft tissue breakdown and dehiscence. These anatomic changes happen secondary to a deficiency in blood supply from the lack of muscle attachments in those areas, whereas the areas that have a healthy musculature show an increased blood supply, making it more resistant to postdental extraction resorption. An important concept that reconstructive surgeons need to understand is that atrophic mandibles depend heavily on periosteal blood supply because of the narrowing of the inferior alveolar artery [10–12].

Cawood and his group from the United Kingdom found that alveolar bone resorption seemed to have a predictable pattern:

- Class I, dentate
- Class II, immediately post-extraction
- Class III, well-rounded ridge form, adequate in height and width
- Class IV, knife-edge ridge form, adequate in height and inadequate in width
- Class V, flat ridge form, inadequate in height and width
- Class VI, depressed ridge form, with some basilar bone loss evident [13]

This classification has more relevance to implant dentistry because it gives the operator an idea of whether an adjunctive bone graft would be necessary (classes IV and V).

Marx and colleagues [14] published a novel soft tissue matrix expansion also known as the "tent pole," where the dental implants effectively "tent" the soft tissue envelope up to maintain the bone graft volume and prevent soft tissue collapse. The original description used an extraoral submental approach, and the bone graft material of choice was the anterior iliac crest bone graft, with four to five implants placed (each one 15 mm in height), with a 1-cm interimplant distance. Primary stability was obtained by engaging the inferior border of the mandible with the implants. Autogenous corticocancellous bone graft is then packed around the implants.

Patel et al. reported that the addition of rhBMP in the tent pole technique had a favorable impact on bone healing and allowed substitution of the posterior iliac crest as a donor site with the anterior iliac crest bone graft because of the enhanced osteoinduction that happens with rhBMP. Furthermore, the authors rarely use the classical anterior iliac crest bone grafting approach, instead opting for the trephine to harvest the bone from the anterior iliac crest, with excellent increase in vertical bone height and final implant placement. This translated to less donor-site morbidity and earlier mobilization [15].

Many surgeons have modified Marx's original tent pole technique, and some have replaced dental implants with bone screws; this modification seemed to improve the buccolingual orientation of the final implant placement, because the dental implants would be placed at a second procedure, when all of the bones have been consolidated, and the position of the implants is more ideal. A second advantage of this modification is that it allows the use of surgical implant guides, especially if a maxillary prosthesis exists. Another commonly used method is the use of a titanium mesh to tent the soft tissue and maintain the bone graft and the contour of the ridge. However, the main disadvantage of this technique is that the surgical site must be reentered to remove the titanium mesh before implant placement. This has presented its own set of challenges, especially when the graft grows over the mesh, and the procedure requires excessive soft tissue reflection.

Another bioactive agent that has been studied in maxillofacial reconstructive surgery is recombinant human platelet-derived growth factor. This is a product of platelets and functions as a chemotactic and mitogenic factor for osteoblasts and is critical for angiogenesis and thus can be applied to treating ridge defects [16]. This growth factor has been combined with several different types of grafting materials and carriers, such as mineralized and demineralized FDBA [17], xenograft (specifically deproteinized bovine block graft), equine block graft [18], and bTCP [19], in multiple case series and has been shown to help produce intact woven and lamellar bone contributing to an increase in vertical ridge height in humans, which was of appropriate quality to accommodate the placement of dental implants at a second stage. The concept of engineered heterotopic bone formation has also been studied; however, this has not yet gained much notoriety. In 2004, it was studied in the reconstruction of large segmental mandibular defects by way of an engineered growth of a mandibular transplant within a muscular environment (in this case the latissimus dorsi muscle) with the help of BMPs, with subsequent free tissue transfer of the bone-muscle flap approximately 7 weeks later [20].

A prefabricated titanium mesh was filled with bone mineral blocks, BMPs, and the patient's own bone marrow. Although a clinically successful result was obtained, this procedure may not be as cost-effective as some of the more traditional and established methods of free tissue transfer for mandibular reconstruction and does carry with it significant morbidity related to the surgery itself and potential complications, such as brachial plexus injury and shoulder drop [21]. Nonetheless, it certainly does open up a different aspect of tissue engineering and strategies for maxillofacial reconstruction [22, 23].

3.2. Maxillary sinus augmentation

It is challenging to reconstruct the edentulous posterior maxilla with dental implants due to insufficient bone height after crestal bone resorption and also maxillary sinus pneumatization [24, 25]. In recent years, with aid of existing space in the maxillary sinus, clinicians introduced techniques for surgical augmentation that use to restore bone height and also create a sufficient implant bed area which seems to resolve patient's treatment difficulties [26, 27]. Researchers suggested a variety of modifications in original sinus augmentation technique to ease different difficulties for clinicians and also patients [28, 29], but the basic principle of each technique remained unchanged which is to increase maxillary bone height with aid of placing graft material in the maxillary sinus after attending to detach the sinus membrane [25, 28, 29]. Nowadays, for rehabilitation of the posterior maxilla with dental implants, the use of maxillary sinus augmentation (MSA) is considered as a standard procedure [24, 25].

In original technique, before dental implant insertion, MSA was performed with the autogenous bone [25, 30]. Autogenous bone has usually been cited as the most eligible material to achieve predictable and favorable results in MSA. It is due to the fact that autogenous bone contains living cells and growth factors which cause osteogenic ability [25, 30]. In contrast, it should have been noticed that available supplies for autogenous bone are limited. Also, as disadvantage, harvesting autogenous bone is painful and includes procedures with risk of infection. With these in mind, it is necessary to investigate and develop alternative techniques to overcome these drawbacks [24, 25, 31–37].

Introduction of different osteoconductive biomaterials such as allogeneic bone [31, 32], xenogeneic bone [32–34], or alloplastic or composite materials [34, 35] which are cell-free and due to that require more time for bone healing. This is a disadvantage that none of mentioned materials have biological and structural properties similar to the native bone [24, 25, 34–37].

The modern science of bone tissue engineering, a fusion of recent discoveries in the field of molecular cell biology with the most innovative methods of reconstructive surgery, aims to overcome these boundaries [38].

In **Table 1**, studies of stem cell approach for tissue engineering dealing with sinus augmentation were illustrated.

A major disadvantage of potential bone substitutes is their inherent slow ability to induce new bone at a foreseeable rate. By advances and innovation in technology in tissue engineering, introduced alternative materials which are used as bone show significant advantages in

Study	Control	Type SC	Scaffold	Evaluation	Follow-up	Complications
Gonshor et al.	Allograft	MSC (bone marrow)	Allograft (Osteocel)	Histology after 3–4 months		None
Voss et al.	ABG	MSC (periosteum)	Polymer fleece	Radiography, histology on 18 patients	24 months	A
Shayesteh et al.	None	MSC (bone marrow)	HA/TCP	Histology after 3 months	12 months	None
Yamada et al.	None	MSC (bone marrow)	PRP	Radiography	2- to 6.3-year	None
Rickert et al.	30% ABG and 70% BBM	MSC (bone marrow)	BBM	Histology after 13–16 weeks		None
Schimming et al.	None	MSC (periosteum)	Polymer fleece	Histology after 3 months	6 months in 9 patients	B
MacAllister et al.	None	MSC (bone marrow)	Allograft (Osteocel)	Histology after 4 months		None
Mangano et al.	Calcium phosphate	MSC (bone marrow)	Polymer fleece	Histology after 6 months, CT scan		C
Zizelmann et al.	ABG	MSC (periosteum)	Polymer fleece	Radiography after 3 months		D
Ueda et al.	None	MSC (bone marrow)	PRP	Radiography	2–5 years	None
Sauerbier et al.	MSC (bone marrow) vs. BMAC	MSC (bone marrow)	BBM	Histology after 3 months	12 months	None
Fuerst et al.	None	Autogenous culture-expanded bone cells	BBM	Histology after 6 months		None
Trautvetter et al.	None	MSC (periosteum)	Polymer fleece	Histology after 6 months	5 years	None
Schmelziesen et al.	None	MSC (periosteum)	Polymer fleece	Histology after 4 months		None
Hermund et al.	50% ABG + 50% BBM	Autogenous culture-expanded bone cells	50% ABG + 50% BBM	Histology after 4 months	8 months	None
Sauerbier et al.	30% ABG + 70% BBM	MSC (bone marrow)	BBM	Histology after 3–4 months		None
Springer et al.	BBM	MSC (periosteum) (l) Autogenous culture-expanded bone cells (2a)	Collagen [1] BBM (2a)	Histology after 6–8 months		None

Study	Control	Type SC	Scaffold	Evaluation	Follow-up	Complications
Beaumont et al.	None	MSC (periosteum)	BBM + polymer fleece	Histology after 4 and 6 months	18 months	None

Adopted from Jakobsen et al. [39]

BBM, bovine bone mineral; HA/TCP, hydroxyapatite/tricalcium phosphate; NA, data not available; MSCs, mesenchymal stem cells; PRP, platelet-rich plasma; RCT, randomized clinical trial

A: 11 augmentations failed in test group, none in control group

B: Histology shows little or no bone formation in 8 of 15 patients, when a two-stage protocol was used.

C: Less bone and more medullar spaces were found in test group compared with control group.

D: 13 of 14 sinuses showed insufficient bone formation. Resorption 90% in test group after 3 months, 29% in control group

Table 1. Studies regarding cell-based sinus lift procedure.

their bone-inductive capabilities. These results are similar to the result of study conducted by Neiva et al., which revealed favorable outcomes with the use of PepGen P-15 Putty. They conclude this result from initial osteogenesis of intervened group which is guided by the putty and achieved an additional mature trabecular pattern in shorter period of time comparing to the control group. Earlier bone formation is evaluated and revealed in 3D radiographic assessment as early as 8 weeks [40].

A variety of study designs used in cellular studies on sinus grafting techniques outcome the square measure constituent. Briefly, most studies comparing cell therapy with a traditional grafting technique showed similar results [41–44].

3.3. Dorsal augmentation in rhinoplasty

As application of allografts for dorsal augmentation seems to have serious disadvantages [45], it appears that we might tend to observe the appliance of tissue engineering in rhinoplasty; Kim et al. in 2014 within the article made a case for the chondrocytes and porcine cartilage substance (PCS) construct as an attainable dorsal augmentation material in rhinoplasty cultured with a porcine cartilage-derived substance (PCS) scaffold as a potential substitute for normal tissue use for augmentation in rhinoplasty. A scaffold is derived from decellularized and fine-grained porcine articular cartilage prepared. The use of the rabbit articular cartilage was due to ability to supply homologous chondrocytes, which for 7 weeks were enlarged and polite with the PCS scaffold. The chondrocyte-PCS constructs were then surgically implanted on the nasal dorsum of six rabbits. Four and 8 weeks after implantation, complete evaluations such as the gross morphology, radiologic pictures, and microscopic anatomy options of the location of implant were analyzed. The rabbits showed no signs of surgical inflammation and infection. The degree of dorsal augmentation was maintained throughout the 8-week surgical observation amount. Surgical examinations showed chondrocyte proliferation while there was no inflammatory response. However, neo-cartilage formation from the constructs was not confirmed. The biocompatibility and structural options of tissue-engineered chondrocyte-PCS constructs indicate their potential as candidate dorsal augmentation material to be used in rhinoplasty [46].

Cultured chondrocytes and porcine cartilage substance (PCS) constructs as an attainable dorsal augmentation material in rhinoplasty: preliminary animal study and, additionally Mendelson et al. in 2014 conferred this concept than designed nasal cartilage by cell homing: a model for augmentative and rehabilitative rhinoplasty. Bioactive scaffolds were developed that not solely recruited cells within the nasal dorsum in vivo, however, additionally induced chondrogenesis of the recruited cells. Bilayered scaffolds were fictional with alginate-containing gelatin microspheres encapsulating cytokines atop a porous poly(lactic-co-glycolic acid) base. Microspheres were fictional to contain recombinant human remodeling growth factor β3 at doses of 200, 500, or 1000 ng, with phosphate-buffered saline-loaded microspheres used as a bearing. A rat model of augmentation facelift was created by implanting scaffolds atop the native nasal cartilage surface that was scored to induce cell migration. Tissue formation and chondrogenesis within the scaffolds were evaluated by image analysis and microscopic anatomy staining with hematoxylin and eosin, toluidine blue, Verhoeff elastic-van Gieson, and aggrecan immunohistochemistry. Sustained release of increasing doses of remodeling growth factor β3 for up to the tested 10 weeks promoted orthotopic cartilage-like tissue formation in an exceedingly dose-dependent manner. It appears that these findings represent the primary commitment to engineer cartilage tissue by the cell orientating for facelift and will doubtlessly function as an alternate material for augmentative and rehabilitative rhinoplasty [46].

An important feature for rehabilitative and augmentative rhinoplasty is the ability of the graft to be tailored to the individual patient. Autologous graft area unit is stacked and sutured along in a very bundle before implantation. The bioactive poly(lactic-co-glycolic acid) scaffolds are simply changed to larger augmentations by varied the mold diameter wont to create the poly(lactic-co-glycolic acid) scaffold base. For associate degree off-the-shelf product, three totally different scaffolds can be generated with a variety of forms and sizes and simply cut for precise adjustments. Thus, the bioactive scaffolds might probably be used as completely unique various implant styles to current rhinoplasty treatment [46].

4. Skin

It seems that one of the important years for tissue engineering is 1975; in this year, some occurrence about skin engineering was evolved in this field even though the Washington National Science Foundation applied science panel meeting to formally adopt the term "tissue engineering" for this field a decade later in 1987 [47] and Langer and Vacanti explained the definition of this field later in 1993 [1]. The first step is ascribed to the actions of two teams in the United States 40 years ago. Rheinwatd and Green were the first team who are unskilled and ignored cultivation of human epidermal keratinocytes in vitro [48]; they also created potentially the enlargement of those cultivation of cells into numerous epithelial cells for graft in 1975 [49] from a little skin diagnostic assay. Today, the work that was done in those days is called "skin epidermis tissue engineering." At the same time, Yannas et al. worked on the features of scleroprotein and degradation mechanism [50] in 1975, which now

we believe that these efforts facilitate the way for the new generation of artificial dermal substitute, resulting in the "skin dermis tissue engineering" [51]. Fortunately, after 6 years, both of these groups independently revealed the clinical effect of tissue-engineered substitutes for the treatment of different grade burns, albeit in different approaches. The first graft of extensive burns with sheets of cultured epithelium (produced from epidermal cells which are autologous) was reported by O'Connor et al., two adult patients were experienced at the Peter Bent Brigham Hospital [52, 53]. Cultured epidermal autografts (CEA) were the next generation of cultured sheets which are autologous and also successively revealed to prepare cover of full-thickness burns in pediatric patients [54]. Meantime, only a short time after O'Connor et al.'s study, Burke et al. revealed that artificial dermis had experienced functional and physiological acceptable dermis in the treatment of extensive full-thickness burns on several patients [55]. These evidences resulted in randomized clinical trial for extensive burn injuries led by Heimbach et al. [56] about the application of artificial dermis; now new generation of artificial dermis is known as IntegraTM Dermal Regeneration Template. This study was done successfully by collaborating 11 centers, and other studies [57, 58] could inevitably demonstrate this dermal substitute a "gold standard" material treatment of full-thickness burns [59].

But there are still challenges, and those two groups are still far from reaching the final goal of replacing autologous skin for coverage of permanent deep dermal or full-thickness injuries in extensive burns.

Table 2 demonstrates the current status of available tissue-engineered materials and techniques for skin substitution.

	Skin substitute/ surgical technique	Structure	Advantage	Disadvantage
Epidermal	Cultured epithelial autograft (CEA)	Confluent autologous keratinocytes	In vitro expansion for large bum area, permanent	Fragility, infection, high cost, and variable take rate
	CUONO's method		Extensive bums	Two-stage procedure, precise grafting time coordination
	CEA with meshed split-thickness skin autograft		Expansion 1:4, no rejection	Beyond 1:4 expansion: poor cosmetic and functional results, delayed reepithelialization
	CEA with microskin autograft		Expansion 1:9–15, no rejection, high take rate, shorter epithelization time	Time-consuming, labor-intensive, hypertrophic scarring

		Skin substitute/ surgical technique	Structure	Advantage	Disadvantage
Dermal	Artificial biological materials	Integra™	Cross-linked bovine tendon collagen-based dermal matrix linked with glycosaminoglycan (GAG)		Two-stage procedure, infection, hematomas, seromas
		Integra™ with CEA		Good long-term esthetic and functional outcome	High cost, poor adhesion
		Integra™ with Meek			
		MatriDerm®	Bovine non-cross-linked lyophilized dermis, coated with alpha-elastin hydrolysate		
		Composite skin substitute	MatriDerm as a template, seeded with expanded autologous skin fibroblast and keratinocytes	Full wound closure	
		Blobrane®	Silicone membrane and nylon mesh impregnated with porcine dermal collagen	One-stage procedure, coverage of partial-thickness bums	Intolerant to contaminated wound bed
	Natural biological	AlloDerm®	Human acellular lyophilized dermis	Acellular, immunologically inert, provide natural dermal porosities for regeneration and vascularization on the wound bed	High cost, risk of transmitting disease, two-stage procedure
		AlloDerm® with CEA			Multiple applications
		Permacol™	Porcine acellular lyophilized dermis	Good esthetic and functional	Infection, hematomas, seromas
	Synthetic materials	TransCyte®	Porcine collagen-coated nylon mesh seeded with allogeneic neonatal human foreskin fibroblasts	Immediate availability, ease of storage	Temporary
		Dermagraft®	Bioabsorbable polyglactin mesh scaffold seeded with cryopreserved allogeneic neonatal human foreskin fibroblasts	Ease of handling, no rejection, chronic wounds—diabetic ulcers	Poor ECM structure, infections, cellulitis,

	Skin substitute/ surgical technique	Structure	Advantage	Disadvantage
Dermo-epidermal	PermaDerm™	Collagen-glycosaminoglycan substrates containing autologous fibroblasts and keratinocytes	Permanent replacement of both dermal and epidermal layers, one-step procedure	No clinical trial reported yet
	DenovoSkin	Plastically compressed collagen type 1 hydrogels engineered with human keratinocytes and fibroblasts	Near-normal skin architecture	Long culture time, no clinical series reported yet

Adopted from Chua et al. [60]

Table 2. Tissue-engineered materials and current surgical techniques for skin substitution.

The happen which facilitates efforts is that combination between a skin allograft bank and professional laboratory which culture autologous epithelial cell sheet could be an important step, and also we should gather many scientists and engineers and absorb finance in this field. The only way that can create the demand of engineered tissue for patients is through working and collaborating with clinicians, and also this expert team brings us innovation, novel technologies, and cost management and realizes the challenges in advancement of skin tissue engineering [61–65].

5. Oral mucosa

There is a recognized lot to reconstruct and restore advanced craniomaxillofacial (CMF) soft tissues that are broken and/or disfigured as a consequence of automobile accident, trauma, burn injury, or tumor surgery. In trauma, injuries usually produce extraordinarily advanced geometric and avulsion defects, and also the anatomic and purposeful intricacies of CMF composite soft tissue structures like the lips, eyelids, and nasal advanced create the reconstruction significantly difficult for maxillofacial surgeons (**Table 3**).

Kenji Izumi et al. in 2013 within the article evaluated the appliance of tissue engineering in oral mucosa [67]; the first objective of this study was to gauge the security of a tissue-engineered human ex vivo produced oral mucosa equivalent (EVPOME) in intraoral graft procedures. The secondary objective was to assess the efficacy of the grafted EVPOME in manufacturing a keratinized mucosal surface epithelial tissue. Five patients World Health Organization based on inclusion criteria that defects in mucogingival region or an absence of gingiva which is keratinized on incisors and premolars teeth, together with radiographies of adequate bone height in interdental region, were used to expand the amount of keratinized gingiva in the defect site. A specimen was taken by a punch biopsy from hard palate to accumulate oral keratinocytes, which were enlarged, associate degreed cultured on associate degree noncellular matrix of the dermis for make of an EVPOME.

Approach	Advantages	Disadvantages
Free grafts (full-thickness skin grafts, split-thickness skin grafts, etc.)	Simply harvested, vital tissue accessibility	Poor color match, donor-site morbidity, lack of bulk, no performance
Local advancement and motility flaps	Sensible color match, functional	Restricted quantity, might need staged surgeries, will result in microstomia and associated purposeful deficits in speech and swallowing
Free vascularized tissue transfer	Wonderful tube peduncle, applicable tissue thickness, and a technique to suspend the lip with the incorporated tendon	Long recovery, donor-site morbidity, lack of performance, poor color match/esthetics, needs specialized surgical skills
Allogeneic tissue transfer/ face transplant	Sensible color match, purposeful tissue, esthetics	Needs long immunosuppression, facet effects of immunosuppression, long and troublesome recovery, donor accessibility, needs specialized surgical skills and facility

Table 3. The advantages and downsides of the contemporary approach to soft tissue reconstruction [66].

EVPOME grafts have special features which are used directly over associate degree healthy periosteal bed and preserved in situ. At 1 and at 7, 14, 30, 90, and 180 days postsurgery, Plaque Index and Gingival Index were recorded for every subject. Additionally, inquisitory depths, keratinized animal tissue dimension, and keratinized animal tissue thickness were recorded at baseline, 30, 90, and 180 days. Fortunately, there were no adverse outcomes or complications to EVPOME ascertained in all cases throughout the research. But the mean increased in keratinized animal tissue dimension was 3 mm (range, 3–4 mm), and no vital changes in depths were ascertained. According to our findings, we can terminate that EVPOME is useful for oral application and has the flexibility to reinforce keratinized gingiva. More randomized clinical trials in this field should be performed to demonstrate other dimensions of tissue engineering [67].

The maintenance of associate degree sufficient strip of attached gingiva includes a minimum of 2 mm of keratinized gingiva and has revealed that it could be necessary for preservation of periodontal tissue [68, 69]. Historically, FGGs' associate degreed grafts which were taken from connective tissue are applied to gain sufficient strip of attached gingiva [70]. Unfortunately, clinical evidence about the use of autologous and allogenic products confronts to some problems about FGGs, i.e., problems about morbidity around donor region and also amount of tissue for graft which is restricted [71]. Nevins [72] applied treatment by bilayered cell for mucogingival region, and this research revealed that adequate keratinized tissue was gained; however, the amount was not more than it gained with FGGs. Interestingly, each research tried to prove that clinical evidence such as texture and color have better results when compared with FGGs. Nevertheless, application of products that have allogenic cells could have important effect on the wound bed; the impact of treatment could be as a completely unique "biologic dressing" to motivate encompassing cells. One of the reliable materials was a scaffold which is biodegradable with gingival autologous fibroblasts which are cultured [73]. Another research in this field used oral mucosa cells to transplant directly to the cornea [74].

Another researchers believed that the long time (more than 22 months) existence of the cultured keratinocytes from oral cavity, expressed markers of stem cell. Also evidence tried to by pharmacologic approach produce cultured oral keratinocytes to produce stem cell population; and now all efforts focus on clinical application of this technology that has a lot of simply for the event of a lot of strong EVPOME for intraoral graft procedures [75]. As a result of oral mucosa keratinocyte area unit simply getable and expand quicker in vitro than skin keratinocytes [76], they will be a lot of efficacious to be used in future clinical applications in regenerative medicine. This platform technique might produce other potential extraoral uses, like repair of facial skin [77], reconstruction of eyelids and nose, or in situ tissue layer substitutes for the urethra and conjunctiva [78].

6. Temporomandibular joint disorders

The temporomandibular joint (TMJ) may be a synovial joint that has for articulator motion relative to the os base and distributes the traditional stresses of perform (chewing and speaking) and parafunction (clenching and bruxism). It is usually noted as ginglymoarthrodial joint attributable to its slippy performance and hinging. The temporomandibular joint links the condyloid process (mandibular bone) to the temporal bone. The cartilage disc is the middle of mandibular condyle and the glenoid fossa eminence of the temporal bone and separates the joint area into inferior and superior compartments, each of that area unit crammed with synovial fluid [79].

Because of the advanced loading patterns that designed tissues can expertise within the TMJ, acquisition of complete style parameters from the native tissue is important. Significantly, TMJ disc, condyle, and condylar cartilage replacement area unit in nice demand attributable to these tissues' poor regenerative capability and high rate of involvement in TMD. In response, many studies characterizing the properties of those elements are performed [79]. Though glenoid fossa and articular eminence are the concern in TMD, they need not be absolutely characterized. Within the following section, structural characteristics of the TMJ tissue area unit are summarized. Application of tissue engineering in the treatment of temporomandibular joint defects is rising as a progressive choice to substitute and remove the pathological defects automatically in the near future. Historically, basics of regenerative medicine are three necessary elements, cells, stimulator factors, and scaffolds. But new technology introduced novel methodologies and recommends how to manage TMJ disk and stimulate relevant cartilage [80]. This approach includes the scaffold-free and cell-based methodology and cells and stimulators that work together. But another approach is to construct a structure and render appropriate form of engineered tissues, permitting well-designed structure and simple handling [81]. Another mechanical feature may be appropriate for designed tissue. In the best manner the chemistry of scaffold that could be degradation with matrix synthesis. But the rate of scaffold degradation depends on the nature of scaffold and might be modified by manipulation. For induction of the mass of matrix synthesis, growth factors are added to the scaffolds. Today, all engineered tissue materials are used to regenerate condyle and TMJ disc; however, similar strategies for regeneration of mandibular fossa are not successful [82].

7. Conclusion

Unfortunately, limiting factors still existed; most of them could be the differences of lab environment and human body such as unknown exact dose of BMP and applicate high dose of this material to creation of bony scaffold [83]. On the other hand, unpredictable effects of BMP and complications about application of BMP together with oncogenesis. Based on these evidences, Food and Drug Administration (FDA) restricted application of BMP to sinus alveolar process augmentation in the United States; other substitute materials in maxillofacial region should be considered moral issues even if these materials reveal high level of evidence in several experimentations [84].

Another problem like tissue transfer decreases the chance of high-quality and priced experimentations [85], and also Ripamonti et al. study revealed that growth factor and signaling systems in animal and human are totally different and huge variation between them is observed. Unfortunately, there are few clinical trials in the maxillofacial region, but the question is what the obstacles are? The main obstacles are how to predict regenerate cells to not become oncogenesis and produce our wanted cells, how to manage signaling factors to facilitate the procedure of regeneration, and how to create the scaffold that permits cell growth in the best way. More clinical trials are needed to remove the obstacles [86].

Tissue engineering is the field that is surrounded by other fields like histology, medical engineering, and pathology that every progress in these fields could change principles of tissue engineering. Our goals are simple which are to know how to regenerate human tissues from host cells and somehow that these regenerates have desirable function and esthetics. To reach to this goal, we have long way, but today engineers progressed biocompatible scaffolds, increase the flexibility to 3D tissue constructs, and designed complex tissue for the different facial areas. The latest progress guarantees that tissue engineering is the trustworthy choice for the treatment of maxillofacial defects. In future, the role of tissue engineering will increase and become routine in surgeries.

Acknowledgements

Conflict of interest

Authors declare that there is no conflict of interest that may damage the integrity and validity of this research.

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