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Application of the Biological Substitutes and Tissue Engineering in Maxillofacial Regeneration

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Abstract

Tissue engineering has revolutionized the field of maxillofacial reconstruction with innovative solutions to restore tissue lost or damaged due to trauma, congenital defects, infection, or tumor resection. The basic principles of tissue engineering revolve around a triad of combining biomaterials, stem cells, and bioactive molecules to regenerate functional maxillofacial tissues. This emerging field of tissue engineering offers an exciting and innovative facial and jaw reconstruction alternative. Traditional reconstruction techniques, such as autografts, allografts, and prostheses often impose limitations, including donor site morbidity, immune rejection, and inadequate tissue integration. Advanced techniques like 3D bioprinting, gene therapy, and bioreactor-based tissue maturation have significantly improved the precision and effectiveness of engineered tissues. Incorporating tissue engineering into maxillofacial reconstruction offers promising personalized, biocompatible, and durable solutions, enhancing both functional and aesthetic patient outcomes. Tissue engineering represents the latest advancement that enhances current treatment strategies for reconstructing or regenerating the oral and craniofacial complex. This encompasses the teeth, periodontium, bones, oral mucosa, salivary glands, and temporomandibular joint (including bone and cartilage), along with associated blood vessels, muscles, tendons, and nerves. This article reviews the principles of tissue engineering and its various applications in oral and maxillofacial surgery.

Keywords: Reconstruction, regeneration, Scaffolds, signaling molecules, stem cells, tissue engineering

1. Introduction and review

Tissue engineering was initially defined as the generation of tissues in culture media by cells cultivated on porous, absorbable matrices. Research has demonstrated that various cell types, including bone cells, can proliferate and retain their phenotype

when cultured in vitro in three-dimensional porous matrices and gels. This discovery has laid the foundation for tissue engineering, which now encompasses the implantation of porous matrices, either alone or seeded with cells, to promote tissue regeneration [1-2]. Tissue engineering strategies typically include injecting isolated cells or their substitutes, implanting tissue-stimulating materials such as polypeptide growth factors, or embedding cells within matrices. The basic concept behind these strategies is that stem cells cultured from different tissues have the inherent ability to develop into tissues and organs when provided with the appropriate environment where they can be exploited in maxillofacial reconstruction surgery [3].

Various alloplastic materials have been utilized as scaffolds along with a few growth factors to regenerate tissues. However, incorporating cultured stem cells into this approach would result in a significantly more predictable procedure [4]. Three main approaches have been considered in tissue engineering: conduction, induction by bioactive agents, and cell transplantation, which are likely to be associated with the repair and replacement of calcified tissue and enhancement of oral wound healing [5]. There is great hope that pluripotent embryonic stem cells (ESCs) can develop into nearly any tissue including neurons, muscles, and teeth. This underscores the integration of biological, chemical, and engineering in the restoration and regeneration of tissues through the use of cells, scaffolds, and growth factors, either separately or in combination. At the cellular level, growth factors and cytokines regulate signaling pathways to control bone growth and resorption by inducing the migration of host cells to the bone defect site, promoting cell proliferation, and facilitating their differentiation into mature osteoblasts [6]. Craniofacial tissue engineering deals with the regeneration and new formation of oral and craniofacial structures lost due to congenital deformities, trauma, and tumor eradication. Most craniofacial structures originate from mesenchymal cells (MCs) derived from the embryonic neural crest of the inner cell mass of the blastocyst, which migrate, differentiate, and contribute to the morphogenesis of nearly all craniofacial components, including cartilage, bone, ligaments, muscles, tendons, the periodontium, and teeth [7-8].

1.1 *Sources of Tissue Engineering:*

Tissue engineering relies on three main sources: stem cells, bone morphogenetic protein (BMP) therapy, and platelet-rich plasma (PRP). Stem cells are unspecialized pluripotent cells that can differentiate into any formative cells in the human body. Mesenchymal stem cells, derived from the mesoderm, serve as the common progenitors for various lineages of the musculoskeletal system, including bone, cartilage, ligaments, muscle, and tendon [9]. A signaling molecule is a chemical that facilitates cell communication by being released from the signaling cell, crossing the gap between cells, and binding to receptors on a neighboring cell to trigger a response. Bone marrow has been claimed to be the most abundant source of MSCs, which have a high proliferative ability and great capacity for differentiation. From a practical perspective, bone marrow is an accessible source of osteogenic cells, as it can be collected through a relatively simple aspiration procedure, making it less invasive than obtaining osteogenic cells via biopsies from the calvarium, periosteum, or trabecular bone [10-14]. Several prerequisites are necessary for a successful outcome, including an adequate number of cells with bone-forming potential, a suitable scaffold for cell implantation, and a sufficient blood supply. Expanding the trials to humans presents a significant challenge due to the limited clinical reports available. The failure of bone tissue engineering (BTE) in humans is generally attributed to inadequate vascular supply, leading to immediate cell death after implantation. In contrast, the success of BTE in ectopic rodent models is due to the more favorable biological environment for implanted cells [15]. Future research should aim to overcome the challenges of limited proliferation and insufficient oxygen and nutrient supply in cell-based approaches or to develop constructs that can recruit the appropriate bone cells after implantation. The optimal survival of transplanted cells depends on the rapid formation of a sufficient number of new blood vessels, as research has shown that enhanced vascularization of engineered tissues improves the functionality of living cells [16].

Several strategies can enhance oxygen and nutrient supply, with the first being the stimulation of blood vessel growth by incorporating the angiogenic growth factors or endothelial cells into the tissue-engineered construct. This approach is especially effective in cell-based methods, where vessel growth is initiated immediately after application. The second approach circumvents the challenges associated with orthotopic bone formation by generating an engineered bone construct within a muscular environment, facilitating ectopic bone formation. The successful reconstruction of a large mandibular discontinuity defect through the growth of a custom bone transplant within the latissimus dorsi muscle of an adult male

patient. The third approach involves delaying the application of human MSCs for a few days after scaffold implantation, allowing a hematoma to form immediately, followed by the proliferation of blood vessels and fibroblasts within the fibrin clot during the chronic inflammation phase on the third or fourth day, leading to granulation tissue formation. Injecting culture-expanded MSCs at this stage ensures that new blood vessels invade the hematoma, providing a sufficient supply of oxygen and nutrients, which supports the survival of the implanted cells [2].

1.2 *Stem Cells:*

There are three main types of stem cells, each with various applications. Embryonic stem cells, derived from the early stages of embryo development, have the ability to differentiate into any cell type in the human body, offering potential solutions for thousands of disorders and biomedical challenges [6]. Adult stem cells can be harvested from fully grown adults, though not all of their cells are stem cells, as most have already undergone differentiation. These stem cells are located in specific areas of the body, such as bone marrow or early stages of tissue development, where they remain undifferentiated; they are not fully pluripotent and can differentiate into only a limited range of tissues. The third type of stem cells, umbilical cord stem cells, are harvested from a newborn's umbilical cord and are multipotent, providing more potential than differentiated cells but less than pluripotent cells.The umbilical cord stem cells can be stored in a bank and later used for treating bone marrow disorders, anemia, and cancer therapies. There is little controversy surrounding this type of stem cell, as the umbilical cord is typically discarded after childbirth. Thus, the concept of a stem cell bank effectively transforms what would otherwise be waste into a potentially life-saving resource [12-13].

Characteristics of the stem cells for cell-based therapies:

- The ability to be harvested from patients.
- High proliferative capacity in culture, allowing the production of numerous cells from a limited source.
- Manipulability for gene transfer, enabling the replacement of non-functional genes.
- Capacity to migrate to the target tissues of the host.
- Ability to integrate into the host tissue and interact with the surrounding environment [17].

1.3 *Bone Morphogenetic Proteins:*

Bone morphogenetic proteins (BMPs) are human genes that encode growth factors and cytokines capable of stimulating bone and cartilage formation. The proteins encoded by these genes belong to the Transforming Growth Factor-β (TGF-β) superfamily and play a crucial role in differentiating mesenchymal cells into bone and cartilage cells. At least 11 BMPs have been cloned and recognized for their osteogenic activity, with BMP-2 being one of the most osteo-inductive agents in humans. Also, BMP7 treatment is capable of inducing all genetic markers of osteoblast differentiation in various cell types. BMPs interact with specific cell surface receptors known as bone morphogenetic protein receptors [18].

1.4 *Transforming Growth Factor-β:*

The TGF-β gene superfamily is one of the largest and most diverse groups of related growth factors, playing a crucial role in tissue formation and wound healing. TGF-β was initially purified from human platelets and later identified in various normal tissues, including cartilage and bone. TGF-β1 promotes woven bone formation in vivo when injected into the cranial periosteum or the ear perichondrium. Additionally, when combined with a demineralized bone matrix carrier, both TGF-β1 and TGF-β2 enhance osteo-induction in the craniofacial region [16-18]. These factors regulate bone metabolism, as well as the differentiation, proliferation, and expression of extracellular matrix proteins in cells. Growth factors like TGF-β, insulin-like growth factor (IGF), and BMP are stored within the matrix and osteoid of the skeleton. During the continuous process of bone turnover, osteoclast activity releases these factors in their biologically active form [7].

1.5 *Osteoinductive and Osteoconductive Growth Factors:*

Osteoinductive and osteoconductive growth factors are two key concepts commonly utilized in bone regeneration for tissue-engineering constructs. These types of growth factors are defined as the ability to cause pluripotential cells, from a non-osseous environment to differentiate into chondrocyte and osteoblast cells, culminating in bone formation. The osteoinductive

material promotes healing in an area that would otherwise not heal on its own if left untreated, whereas the osteoconductive material supports repair in a location where normal healing would occur without intervention [16]. Various types of osteoconductive materials, designed to guide new bone formation, have been extensively studied for use as bone tissue replacements. Both naturally derived and synthetic osteoconductive materials have been shown to support bone formation. Optimizing the scaffold architecture may also enhance the conduction of these materials in vivo [18-19]. Barrier membranes are often used alongside osteoconductive materials to fill defects, support the membrane, and promote bone healing [20].

1.6 *Platelet-rich plasma:*

Platelet-rich plasma (PRP) is a volume of autologous plasma with a platelet concentration higher than baseline. In a platelet-rich clot, 4% consists of red blood cells, 95% of platelets, and 1% of white blood cells. In contrast, a natural blood clot contains 95% red blood cells, 5% platelets, less than 1% white blood cells, and numerous fibrin strands. The healing cascade of the tissues is initiated and controlled by bioactive proteins found in platelets, plasma, and white blood cells. It contains a high concentration of growth factors, which are universal initiators for almost all pathways of wound healing [21]. Because these concentrated platelets are suspended in a small volume of plasma, PRP is more than just a platelet concentrate. Additionally, it also contains fibrin, endogenous thrombin, Fibrinogen, fibronectin, and vitronectin. These types of proteins in the blood are known to act as cell adhesion molecules for osteoconduction. The use of PRP has an important advantage as it is a safe product of the patient's blood, thus eliminating transmission of blood diseases. PRP can also be generated and prepared in an outpatient clinic while the patient undergoes a surgical procedure, such as dental implant placement. The supersaturating of the wound with PRP and growth factors could produce an increase in tissue synthesis and faster tissue regeneration. Regarding cost-effectiveness, PRP harvesting requires only 55 cc of blood and is performed in an outpatient clinic, avoiding the additional expenses of hospital or blood bank procedures [22]. Platelet-rich plasma has become a valuable adjunct in wound healing in the maxillofacial region subjected to surgery, blood clots initiate the healing and regeneration of hard and soft tissues through the release of growth factors that initiate and support wound healing.

2. Application of tissue engineering in maxillofacial reconstruction

Tissue engineering could be applied clinically in either soft or hard tissues. Currently, there is great interest in oral and maxillofacial bone grafting procedures that involve using PRP to enhance the healing of the donor and recipient sites of soft tissue flaps and grafts including skin, mucosa, muscles, and dermal fat.

2.1 *Soft tissue engineering of the oral mucosa:*

A crucial aspect of oral tissue engineering is the rapid acquisition of viable basal cells from the oral mucosa. However, the current culture period remains lengthy, posing a challenge to meeting the demands of oral tissue engineering. To optimize the process of implanting and expanding oral mucosal tissue, specific criteria must be met, including the biological properties of the cells, the adhesion rate, the cell growth curve, and the population doubling time [23]. Studies have shown that isolated epithelial cells begin forming colonies within three days and reach confluence by the 10^{th} day.

2.2 *Soft tissue engineering of the skin:*

The skin is a multifunctional tissue that acts as a protective barrier against the external environment, and significant skin loss can pose a serious threat to life. Beyond serving as a protective barrier, the skin plays a crucial role in preventing water loss, providing immunological defense, and regulating body temperature. Extensive skin loss across the body is primarily caused by burns, trauma, surgical removal of neoplasms, and dermatological disorders [24]. Tissue engineers aim to address these challenges by developing skin-equivalent replacement tissues that are readily available in large quantities and require minimal surgical intervention. Engineered skin must securely adhere to the defect site for efficient nutrient diffusion, exhibit sufficient mechanical strength for protection, maintain flexibility to accommodate body movements, shield against ultraviolet radiation, regulate water, protein, and electrolyte loss, facilitate rapid healing, and help control heat loss [25]. Epidermal stem cells play a crucial role in providing cellular substrates for skin regeneration. Certain epithelial cells cultured from the skin possess proliferative potential, and for over 20 years, cultured human skin has been utilized as a source of new tissue for grafting onto damaged areas in burn patients. This approach represents one of the earliest therapeutic applications of stem

cells. The effectiveness of PRP in enhancing soft tissue healing has been assessed, particularly in the healing of split-thickness skin graft (STSG) donor sites. In this approach, a PRP gel is prepared, applied to the donor site, and secured with an occlusive dressing. Upon removal of the dressing, significant epithelialization of the donor site is observed. Revascularization is rapidly promoted due to the angiogenic properties of platelet-derived growth factor and TGF-β1. Fibrin serves as a scaffold for epithelial migration, facilitating rapid granulation of tissue and epithelialization, which accelerates healing, alleviates pain, and enables the patient to resume normal activities [20-25]. A bio-resorbable membrane is created from activated PRP gel to aid in wound healing. This membrane, which lasts approximately five to seven days, is formed by activating PRP into a gel and applying 3–4 ml onto a smooth surface. After about five minutes, the gel solidifies and can be removed as a membrane composed of fibrin with embedded platelets. It can be utilized in various applications, including covering sinus lift windows, sealing sinus membrane perforations, and protecting dental implant fixtures [21].

2.3 *Tissue engineering of the skeletal muscle:*

Human skeletal muscles have limited regenerative capacity, and severe trauma may lead to the replacement of muscle tissue with undesirable connective tissue. Currently, muscle transfers are required to rehabilitate a paralyzed mouth, restore eye movement, and improve masticatory function. To address the need for skeletal muscle replacement, researchers are exploring the use of inductive signaling [26]. Skeletal myoblasts, when seeded on biomaterials or within collagen disks, can differentiate into myotubes and secrete extracellular matrix in vitro. Additionally, the application of external mechanical forces has been used to promote the differentiation of skeletal myoblasts, facilitating the formation of three-dimensional skeletal muscle [15].Gene therapy has been integrated with cell transplantation, where recombinant human growth hormone is produced at high levels by myoblasts both before and after their fusion into multinucleated myofibers. This approach holds the potential for delivering genes that enhance the production of proteins beneficial for the growth and development of bioartificial muscle [18]. PRP therapy is employed to treat muscle and ligament injuries without the need for surgery. The procedure involves extracting concentrated platelets and white blood cells from the patient's blood using a closed platelet separator system, then mixing the PRP with activating agents before re-injecting it into the injured tissue. The injection triggers the body's repair response within the injured tissue. This process starts with the formation of a local blood clot in the muscle, tendon, ligament, or bone, followed by the breakdown of the implanted platelets. As the platelets dissolve, they release growth factors that stimulate the formation of fibrous scar tissue, ultimately replacing the damaged tissue with healthy tissue. Since the materials used in the treatment are sourced from the patient's own body, the risk of adverse reactions is eliminated, ensuring the process is completely safe [26].

2.4 *Tissue engineering of salivary glands:*

The current treatment for xerostomia caused by radiation therapy and diabetes primarily relies on saliva substitutes, which offer only temporary relief and must be used frequently [27-29]. These medications may also cause intolerable systemic side effects. Given the unsatisfactory nature of current treatments, there is a pressing need to develop new options. Alongside the in vitro development of functional salivary gland constructs using tissue engineering techniques, efforts are being made to restore salivary gland function through genetic therapies and stem cell seeding [20]. Tissue engineering offers the opportunity for the restoration of both structure and function to the salivary glands. The creation of implantable, functional salivary gland tissue from autologous glandular cells would provide a physiological solution to this problem. Salivary gland cells were grown, expanded, and seeded on biodegradable polymer scaffolds; the cells were implanted. Salivary gland epithelial cells retained their phenotypic and functional characteristics at all culture stages. Histologically, the formation of acinar gland-like structures was observed within the engineered tissue after implantation, as well as the production of human alpha-amylase over time using a biochemical amylase detection system was demonstrated in tissues [26]. Tissue engineering of salivary glands involves two novel approaches. The first approach uses inductive BMP, which is administered either intraductal or systemic to enhance fluid secretion from damaged or malfunctioning salivary glands. The second approach focuses on cell transplantation to engineer functional salivary tissue. Salivary epithelial cells have been successfully cultured in vitro on two-dimensional biodegradable polymer films coated with specific proteins. These cells growing on two-dimensional scaffolds represent an initial step toward developing salivary gland tissue replacements for patients with impaired salivary flow [31]. Autologous platelet-rich plasma (PRP) has been proven to be very effective in healing salivary gland diseases. Patients with

symptomatic dry eye and mouth were treated with topical PRP and followed up for 1 month. Disappearance of symptoms, increase in best corrected visual acuity, tear meniscus, tear breakup time, and decrease in inflammation of mouth was recorded It was concluded that the treatment of patients suffering from significant dryness of mouth and eye with autologous PR proved to be very effective, improving both patient symptoms and major clinical signs [32].

2.5 *Tissue engineering of peripheral nerves:*

Damage to the peripheral nerves in the head and neck, including the inferior alveolar, lingual, facial, and hypoglossal nerves, can occur through several causes including maxillofacial trauma, orthognathic surgery, neoplastic growth, and dentoalveolar surgery, particularly surgical removal of the lower 3rd molar, implant placement, and injection of local anesthesia. Various non-surgical and pharmacologic treatments are available for patients with nerve injury. Many techniques for repairing peripheral nerves were available, including micro-suturing, gluing (such as fibrin and cyanoacrylate glues), tabulation, grafting, and laser welding. A study evaluating the potentiality of platelet-rich plasma (PRP) in promoting peripheral nerve regeneration after cyanoacrylate anastomosis. The results showed a significant increase in the number of regenerating sciatic nerve fibers in the PRP-treated group compared to the non-treated group, suggesting that PRP may have a neurotrophic effect on regenerating peripheral nerve fibers [17]. Neural stem cells (NSCs) are self-renewing, multipotent cells responsible for generating the primary phenotypes of the nervous system. In vivo, epidermal and fibroblast growth factors act as mitogens for NSCs, while other internal factors produced by the neural stem cells in culture are essential for their proliferation [32-33].

2.6 *Tissue engineering of sinus lift grafts:*

In autologous bone graft sinus lifts, approximately 5 cc of PRP is needed for each sinus lift procedure when added to the cancellous marrow graft in a beaker to start the clotting process, the PRP helps hold the graft material together. This process facilitates the direct handling and placement of the graft into the prepared sinus lift. Similarly, PRP can be added to the autogenous bone and "bone graft expanders," such as various available "bone substitute" products. Although sinus lift surgery requires at least 20% of the composite graft to be autologous bone, PRP affects bone progenitor cells and mesenchymal stem cells, promoting bone formation from the autologous component [22].

2.7 *Tissue engineering ridge augmentation grafts:*

PRP can benefit both vertical and horizontal ridge augmentation procedures by being incorporated into and applied to the surface of the graft, whether a cortical-cancellous block or a strictly cancellous marrow graft is used. It has been demonstrated that combining PRP with B-tricalcium phosphate (BTCP) enhances bone formation, exhibiting strong osteogenic properties. This supports the idea of tissue engineering for repairing bone defects. A study was conducted where the maxillary sinus floors of adult rabbits were augmented with BTCP and PRP on the test side, and BTCP alone on the control side. Histological evaluation at 4 weeks showed a significant amount of newly formed bone along the BTCP on both sides, confirming BTCP's osteoconductive properties. However, the bone volume in the augmented area was higher on the test side, while the control side exhibited a lower bone volume than BTCP alone [22].

2.8 *Tissue engineering of distraction osteogenesis:*

Distraction osteogenesis (DO) is a surgical procedure involving osteotomy, where a bone segment is separated to create a gap. This gap stimulates bone regeneration, allowing the alveolar ridge to be gradually lengthened through the application of controlled tensile stress [34]. The regenerated bone consisting of mature lamellar and cancellous bone achieved osseointegration between implant and bone. The effects of bone marrow mesenchymal stem cell transplantation on new bone formation in mandible osteo-distraction have been carried out. Autologous bone marrow stem cells were obtained. Two weeks after cell harvest, following the completion of distraction, stem cells were injected into the distracted gaps. It was concluded that autologous bone marrow stem cell transplantation may serve as a potential method to accelerate bone regeneration in the distraction gap and enhance consolidation [24]. The effect of BMP on callus formation during bone regeneration after mandibular distraction in rats was investigated. Immediately after distraction, autologous bone-forming stem cells modified with BMP were injected into the distraction gaps of the mandible. The results showed enhanced bone formation, early mineralization, and increased callus formation in the distracted area [25]. The author concluded that BMP-7

and MSCs may accelerate callus formation in distraction osteogenesis and facilitate consolidation. A combination of autologous bone graft and platelet-rich plasma in alveolar DO for mandibular reconstruction has been studied. The author concluded that platelet gel, combined with alveolar DO, is an effective and reliable approach for restoring a severely atrophic mandible [35].

2.9 *Tissue engineering of temporomandibular disc:*

Articular cartilage damage is a common joint condition, often exacerbated by the limited regenerative capacity of adult cartilage, leading to pain and disability. Attempts have been made to develop cell-based therapies for cartilage repair, including tissue-engineered constructions using cultured cells on three-dimensional scaffolds [35]. Cartilage tissue replacements resembling the temporomandibular joint disc, nasal septal cartilage, and human ear have been developed in vivo by seeding chondrocytes onto fibrin glue. The combination of chondrocytes and gel is highly appealing for its moldability and injectability, allowing for delivery of the defect through a syringe in a minimally invasive procedure. A major challenge in cartilage tissue engineering is identifying an appropriate cell source. This field aims to regenerate cartilage tissue damaged by disease or injury, as cartilage cannot repair itself. To address this, it is crucial to develop strategies that deliver the right cells, biomaterials, and signaling factors to the site of damage. Autologous chondrocyte transplantation (ACT) has been successfully used to treat both craniofacial and articular cartilage defects [21]. Various cell types, including chondrocytes, fibroblasts, stem cells, and genetically modified cells, have been investigated as potential sources for cartilage repair. Furthermore, these cells can be genetically engineered to promote or enhance chondrogenesis [6].

3. Conclusions

Tissue engineering has demonstrated significant value, contributing not only to maxillofacial surgery but also to the replacement of other vital organs. The survival of stem cells is crucial for achieving clinical success in cell-based bone tissue engineering. Platelet-rich plasma (PRP) combined with β-tricalcium phosphate (B-TCP) has shown a potential to enhance bone formation due to its excellent osteogenic properties. Additionally, the combination of bone morphogenetic proteins (BMP) with polytetrafluoroethylene (PTFE) offers a viable alternative to traditional bone grafts and substitutes for reconstructing bone defects.

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