TISSUE ENGINEERING (TE) EFFECTIVENESS FOR PERIODONTAL TISSUE AND EDENTULOUS RIDGE REGENERATION

LITERATURE REVIEW

A THESIS

Submitted as Partial Fulfillment of the Requirements for the Attainment of the Degree of Bachelor of Dentistry

COMPLETED BY:

NURUL SALSABILA FEBRYNENA

J011 19 10898

DEPARTMENT OF ORAL BIOLOGY

FACULTY OF DENTISTRY

HASANUDDIN UNIVERSITY

MAKASSAR

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KATA PENGANTAR

Segala puji syukur penulis panjatkan kepada Allah SWT yang telah melimpahkan berkat rahmat, taufik dan hidayah-Nya sehingga penulis dapat menyelesaikan penulisan dan penyusunan skripsi dengan judul “TISSUE ENGINEERING (TE) EFFECTIVENESS FOR PERIODONTAL TISSUE AND EDENTULOUS RIDGE REGENERATION”. Shalawat dan salam juga penulis haturkan kepada junjungan nabi besar Rasulullah Muhammad SAW sebagai teladan yang membawa manusia dari jalan yang gelap menuju jalan serba pengetahuan. Penulisan skripsi ini bertujuan sebagai salah satu syarat penyelesain studi dalam mencapai gelar sarjana kedokteran gigi pada Fakultas Kedokteran Gigi Universitas Hasanuddin. Selain itu, skripsi ini diharapkan dapat memberikan manfaat tidak hanya untuk penulis tetapi bagi pembaca dan peneliti lainnya.

Berbagai hambatan penulis alami selama penyusunan skripsi ini, tetapi berkat doa, dukungan, dan bimbingan dari berbagai pihak, skripsi ini dapat terselesaikan dengan tepat waktu. Oleh karena itu, pada kesempatan ini penulis pertama-tama ingin mengucapkan terima kasih serta penghormatan dan penghargaan kepada kedua orang tua penulis yakni, Ayahanda **Ir. Ambi Idris Nohong, M.si.** dan Ibunda **Hernawaty Tualle, A.Md.** Karena doa dan restunyalah sehingga rahmat Allah tercurah, serta kasih sayang dan kesabaranya dalam memberikan dukungan baik material maupun moril sehingga skripsi ini dapat terselesaikan.

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Makassar, 14 Septermber 2022

Penulis

ABSTRAK

"EFEKTIVITAS TISSUE ENGINEERING (TE) UNTUK REGENERASI JARINGAN PERIODONTAL DAN EDENTULOUS RIDGE"

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Latar Belakang: Rekayasa jaringan merupakan teknologi biomedis yang dikembangkan untuk membantu regenerasi jaringan tubuh dalam mengobati cacat yang sulit disembuhkan sehingga dapat diperbaiki sendiri oleh jaringan. Pendekatan rekayasa jaringan untuk regenerasi tulang dan jaringan periodontal yaitu dengan penggabungan tiga elemen kunci untuk meningkatkan regenerasi yaitu scaffold, molekul sinyal dan sel induk/progenitor. **Tujuan**: Untuk mengetahui efektivitas *tissue engineering* (te) untuk regenerasi jaringan periodontal dan edentulous ridge. **Metode:** Metode penelitian ini merupakan observasional deskriptif melalui penelusuran pustaka secara sistematis dan terstruktur berdasarkan kaidah yang berlaku (*Literature review*). Penelitian ini diambil dari penelusuran jurnal-jurnal akademik SCOPUS seperti PubMed, Science Direct, *Google Scholar*. **Kesimpulan:** Rekayasa jaringan *(TE)* memiliki tujuan untuk mengganti jaringan yang hilang, baik yang disebabkan oleh cacat bawaan, trauma, atau pembedahan.

Kata Kunci: *tissue engineering, bone tissue engineering, tissue engineering periodontal disease, edentulous ridge, edentulism*

ABSTRACT

"TISSUE ENGINEERING (TE) EFFECTIVENESS FOR PERIODONTAL TISSUE AND EDENTULOUS RIDGE REGENERATION"

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Background: Tissue engineering is a biomedical technology that was developed to assist the regeneration of body tissue in treating defects that are difficult to cure so that the tissue can repair itself. The tissue engineering approach for bone and periodontal tissue regeneration combines three key elements to enhance regeneration: scaffold, signaling molecules, and stem/progenitor cells. **Purpose:** To determine the effectiveness of tissue engineering (te) for regeneration of periodontal tissue and edentulous ridges. **Methods:** This research method is descriptive observational through a systematic and structured library search based on applicable rules (Literature review). This research was taken from searches for academic journals, reputable international journals or SCOPUS indexed such as PubMed, and Science Direct, as well as unreputed international and national journals taken from Google Scholar. **Conclusion:** Tissue engineering (TE) has the goal of replacing lost tissue, whether caused by congenital defects, trauma, or surgery. Tissue engineering can also be defined as combining cells, materials, bioactives, and environmental factors to create functional biological tissues.

Keywords: *tissue engineering, bone tissue engineering, tissue engineering periodontal disease, edentulous ridge, edentulism*

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CHAPTER I

INTRODUCTION

1.1 Background

Tissue engineering is a biomedical technology developed to assist the regeneration of body tissues in treating defects that are difficult to cure so that the tissue can repair itself.[1] Tissue engineering can also be defined as combining cells, materials, bioactive, and environmental factors to create functional biological tissues.[2] Tissue engineering in the 21st century has become a cutting-edge science in the medical field.

In the principle of tissue engineering, one of the main elements after cells is environmental factors. Then signaling molecules are biomaterials that play an important role in the success of functional tissue engineering products. In recent years, significant improvements and advances have been reported in the reconstruction of various human tissue replacements and prostheses, including bone.[3]

The tissue engineering approach for bone and periodontal tissue regeneration is by combining three key elements to enhance regeneration, namely scaffold, signaling molecules and stem/progenitor cells. The main aim of this approach is to bring about the capacity of the periodontal tissue so that the functionally and physiologically active tissues need to respond to mechanical cues.[4,5] Fundamental principles of life sciences and engineering for the development of biological substitutions that then restore, maintain or enhance tissue function.[5] Three key elements are required to reproduce this development. The main aim of this approach is to bring about the capacity of the periodontal tissue to be functionally and physiologically active in response to mechanical cues. Regeneration occurs through recapitulation of key events including cellular migration, proliferation/apoptosis, differentiation, inductive/inhibitory interactions and periodontal tissue morphogenesis.[4]

Periodontal disease is a chronic inflammatory condition that leads to periodontal tissue destruction.[6] Periodontal disease occurs due to various factors including plaque, and calculus and is characterized by inflammation of the periodontal tissue that loses attachment. Periodontal regeneration refers to the complete restoration of the periodontal tissues. Periodontal healing is the most complex process because it occurs in areas contaminated with bacteria so that the occlusal forces on the teeth can affect the healing process.[5]

The goal of periodontal regenerative therapy is to replace bone, cementum, and periodontal ligament on diseased tooth surfaces. Regeneration procedures include soft tissue grafts, bone grafts, root biomodification, guided tissue regeneration, and a combination of the above procedures including restorative surgical procedures related to oral rehabilitation with dental implant placement. At the cellular level, periodontal regeneration is a complex process that requires organized proliferation, differentiation, and development of various cell types to form the periodontal attachment.[7]

Based on the description above and some related literature, it shows that the author is interested in knowing and discussing more about “Tissue Engineering

(TE) Effectiveness for Periodontal Tissue And Edentulous Ridge Regeneration". So the idea arose to compile a literature review.

1.2 Problem Formulation

Based on the background that has been explained, the writer can take the formulation of the problem, namely:

1. What is the effectiveness of tissue engineering (te) for periodontal tissue regeneration?
2. What is the effectiveness of tissue engineering (te) for regenerating edentulous ridge?
3. What are the advantages and disadvantages of tissue engineering (te) regeneration of periodontal tissue and edentulous ridges?

1.3 Writing Purpose

The purpose of the preparation of the background and writing problems aims to:

1. To determine the effectiveness of tissue engineering (te) for periodontal tissue regeneration
2. To determine the effectiveness of tissue engineering (te) for regeneration of edentulous ridge
3. To find out the advantages and disadvantages of tissue engineering (TE) for the regeneration of periodontal tissue and edentulous ridge

1.4 Benefits of Writing

Based on the background of the problem, this literature review is expected to provide a number of benefits, including:

1.4.1 Theoretical Benefits

With this writing, it is hoped that:

1. For the author, it is expected to increase knowledge and insight regarding tissue engineering (te) for the regeneration of periodontal tissue and edentulous ridge
2. For other parties, it is hoped that it can be a reference material for those who want to do further research on related topics and problems

1.4.2 Practical Benefits

1. For institutions, the results of this study can be used to add to the list of new literature related to the effectiveness of tissue engineering (te) for the regeneration of periodontal tissue and edentulous ridge
2. For researchers, it is hoped that they can provide useful information to the public regarding tissue engineering (te) for the regeneration of periodontal tissue and edentulous ridges

CHAPTER II

LITERATURE STUDIES

2.1 Tissue Engineering

2.1.1 Definition of Tissue Engineering

Tissue engineering is a science based on clinical medicine, materials science, genetics, and related life sciences and engineering.[1] Tissue engineering is also the science of fabricating new tissues for the replacement and regeneration of lost or damaged tissues.[4] Tissue engineering (TE) has been considered a third treatment modality that complements medication and surgery. The goal is to replace lost tissue, whether caused by congenital defects, trauma, or surgery.[8] Tissue engineering can also be defined as combining cells, materials, bioactive, and environmental factors to create functional biological tissues.[2]

2.1.2 Principle of Tissue Engineering

The basic principles of tissue engineering can be demonstrated by the way that cells can be isolated from sources (such as allografts, xenografts, and autografts),[9,10] then expanded with a cell culture system/bioreactor (in vitro expansion), the cells are seeded into a matrix which is then given structural support by the addition of media suitable for nutrients and growth factors.[5] The basics of bone regeneration are growth, maturation, and maintenance of bone. Three key elements to enhance regeneration are scaffold, signaling molecules, and stem cells/progenitors. The main aim of this approach is to bring the periodontal tissue capacity so that the functionally and physiologically active tissues need to respond to mechanical cues.[5,8]

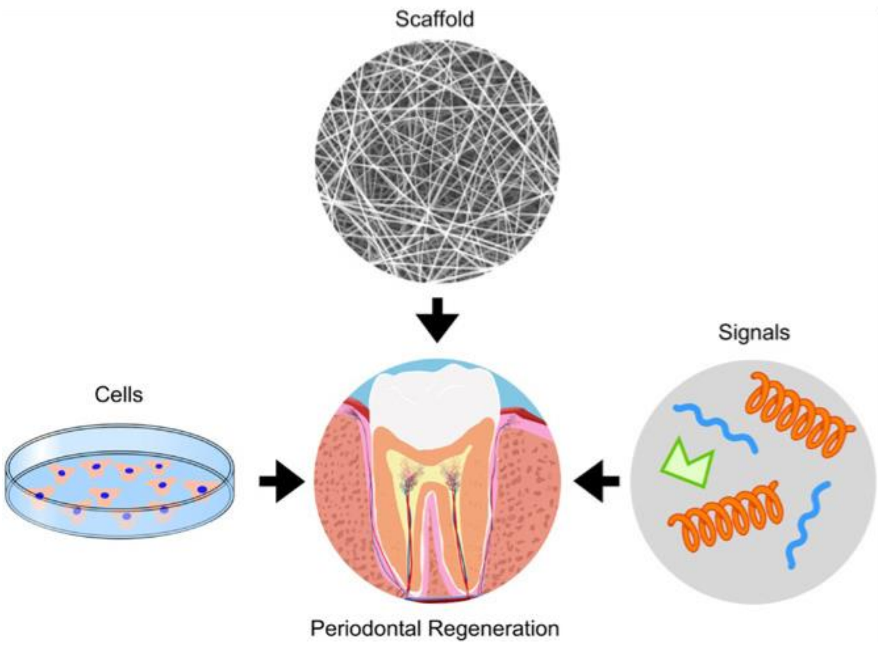

Figure 1. Schematic Drawing of The Three Main Components of Periodontal Regeneration

(Source: Cahaya C and Masulili SLC, "Perkembangan Terkini Membran Guided Tissue Regeneration/Guided Bone Regeneration Sebagai Terapi Regenerasi Jaringan Periodontal", Maj Ked Gi Ind. Vol. 1, (1), pp 1, 2015)

Stem cells or stem cells are cells that have the ability to produce copies of themselves (renew themselves) or differentiate into specialized cell types, where these stem cells facilitate the formation of the required tissue. From the point of view of human cells, several types of assembled cells are called stem cells: (1) human embryonic stem cells (hESCs), (2) anthropogenic pluripotent stem cells (hiP-SCs), mainly in reprogramming somatic cells, and (3) adult stem cells, including various types of cells of hematopoietic and mesenchymal origin.[8] Adult stem cells have potential uses in tissue engineering applications. In the field of periodontal tissue regeneration, autogenous stem cell transplantation is one of the most promising therapeutic concepts being developed.

The scaffold is a framework that supports the attachment and proliferation of cells in the area of damage, stabilizes blood clotting to prevent failure of tissue formation, and is a starting point for the regeneration process. Scaffold also acts as a carrier for osteoinductive growth factors.[1] Scaffold design criteria for tissue engineering must meet several things, namely:

a. The surface can be a site of cell adhesion, stimulate cell growth, and become the retention of differentiated cells,
b. The scaffold must be biocompatible, where the material is safe and does not cause tissue damage.[9,11]
c. Scaffold must be biodegradable or decompose naturally and in a fast time
d. The porosity must be high enough to provide sufficient space for cell adhesion, and regeneration of the extracellular matrix, and the pore structure must allow the distribution of cells through the scaffold to facilitate the formation of a homogeneous network.
e. Materials can be made into 3D structures, and have strong mechanical properties.[9]

Several scaffold fabrication techniques are at the forefront of tissue engineering (TE), such as electrospinning, freeze drying, bioprinting, and decellularization. Combined with this fabrication method, a wide variety of materials have been selected for tissue engineering. This selection is generally based on the functional and biological requirements of the tissue, which is a composite material consisting of organic and natural inorganic components, arranged in a very hierarchical manner. There are several scaffold materials that can be used in tissue engineering, namely:

a. Natural Polymer: Alginate, Chitosan, Collagen, Gelatin
b. Polymer Synthetic: Polyethylene glycol (PEG), Nilon, Silikon, Polytetrafluoroethylene (PTFE), Polyethylene (HDPE, UHMWPE), Polymethyl methacrylate (PMMA), Polyvinyl alcohol (PVA), Polyglycolic Acid (PGA), Polyvinylpyrrolidone (PVP)
c. Biodegradable Polymer: Polylactic acid (PLA), Poly-L-Lactic Acid/Poly Lactic- co-Glycolic Acid (PLLA/PLGA), Polycaprolactone (PCL)[4]

Molecular signaling is one of the growth factors that plays a role in modulating cellular activity and stimulating cells to differentiate and produce matrices for tissue development.[7]

Advances in biomaterials, stem cells, growth and differentiation factors, to biomimetic environments have created opportunities in tissue formation from a combination of scaffolds, cells, and signaling molecules.[12] Biomaterials derived from decellularized extracellular matrix have also been applied in BTE scaffolds. Decellularized bone extracellular matrix (ECM) maintains the original matrix structure, growth factors, and cytokines, thereby increasing cell viability and growth for tissue repair and regeneration.[13]

2.1.3 Mechanism of Tissue Engineering

Factors that influence the success of periodontal tissue regeneration have been described by the World Workshop in Periodontics in 1996, namely factors that have a relationship or show a detrimental effect on periodontal regeneration therapy, namely poor plaque control, smoking, dental bone defect factors, and surgical management.[18] Tissue engineering has the capacity to produce an artificial progressive immunological organ supply that can be integrated into the patient. Tissue engineering can be a solution for organ or tissue damage without additional therapy so that the costs incurred are more effective.[1]

Structures in oral or dental tissues require a combination of various scaffold fabrication techniques to meet anisotropic pore sizes while adapting spatial physicochemical and mechanical features. Combinatorial scaffold fabrication techniques must be utilized to precisely match the design criteria of the scaffold itself. The application of scaffold use in tissue engineering involves a variety of materials. The biomaterials used are divided into natural and synthetic, such as ceramics, polymers, metals, and proteins which are modified with additives including particles and enzymes to make them suitable for application to teeth.[2] Scaffold provides structural support and guidance for exogenous or endogenous cells.[12]

Clinically, in periodontal tissue repair, a materials-based guided tissue regeneration (GTR) approach has been developed. Furthermore, a biocompatible or bioinert scaffold is used to activate the connective tissue and bone regeneration of the local tissue population. Alveolar bone augmentation approaches, such as guided bone regeneration (GBR), utilize bioactive ingredients, such as calcium phosphate (CaP)-based biomaterials and collagen-based grafts. While these materials are bioactive and osteoconductive, they are not osteoinductive; hence, scaffolds are being developed, which incorporate bone formation promoting growth factors.[14]

Signal molecules are proteins that act systematically to influence cell growth and function in various ways. Growth factors and morphogens act by changing the cell phenotype by causing the differentiation of stem cells into bone-forming cells, a process commonly known as osteoinduction. Growth factors are biologically active polypeptide hormones that affect immune function as well as cell differentiation of epithelium, bone, and connective tissue. In periodontal tissue engineering, the most important are PDGF (platelet-derived growth factor), IGF (insulin-like growth factor), FGF (Fibroblast growth factor), and TGF-B (Transforming growth factor beta) which regulates epithelial-mesenchymal interactions involved in the formation of early teeth. PDGF and IGF-1 promote regeneration when combined. TGF-B is chemotactic for fibroblasts and cementoblasts and promotes fibroblast accumulation and fibrosis in the healing process.[4]

Platelet-rich plasma (PRP) is an autologous whole blood component isolated after plasma centrifugation. PRP acts as a source of growth factors including PDGF and TGF-B which both appear to be important growth factors involved in periodontal regeneration. PRP stimulates the proliferation of human osteogenic cells and periodontal ligament cells. The easy clinical application of platelet-rich plasma and its possible favorable outcomes, including bleeding reduction, rapid soft tissue healing, and bone regeneration promises new treatment approaches.[4]

The first approach uses peptides, which are preparations of proteins and growth factors to regenerate tissue, such as using an enamel matrix, or platelet rich plasma. The second approach is to use growth differentiation factors to promote periodontal regeneration.[11]

In periodontal surgery it has been used in mucogingival operations such as gingival grafting, crown lengthening and periodontal regeneration and implants. PRP has subsequently been used in distraction osteogenesis and for bone-forming activity at extra-skeletal sites. The proposed benefit of PRP in clinical use (sinus graft as a model). PRP is proposed to improve the handling of particulate grafts, facilitate graft placement and stability, increase the speed and quality of vascular growth, promote bone regeneration, promote soft tissue healing, and exert a mitogenic effect on the required cells. It is an inexpensive and readily available source of growth factors and natural biological sealants without the risk of disease transmission.[15]

Bone morphogenic protein (BMP) was identified in bone matrix extract with its capacity to induce endochondral bone differentiation at heterotopic sites. This protein is known to have the unique ability to induce cartilage and bone formation. They play a role in the formation of blood vessels. The hallmark of BMP is the differentiation factor in which undifferentiated mesenchymal cells become osteoblasts.[4]

Stem cells or progenitor cells are cells that have not been able to renew themselves, and multi-lineage differentiation through asymmetric mitosis process produces two daughter cells, one identical to the parent cell and the other capable of differentiation into more mature cells/progenitors. different physical manipulations, mechanical means, and chemical stimulation to mimic the actual physiological situation to regulate the tissue format. The bioreactor approach is divided into two main categories. One category of tissue engineering bioreactors is that they can accelerate cell viability and similarity by regulating the cellular microenvironment and introducing physiological, mechanical, and electrical stimuli, by providing a means to enhance cell equalization, increase mass/gas transfer rates, and control pH and temperature. As for the other category, namely tissue engineering bioreactors improving monitoring of physiological parameters and optimizing process variables, these bioreactors are useful for investigating the effect of different parameters such as oxygen flow, temperature changes, etc on cell proliferation.[4]

The factors that can influence the choice of surgical technique are the estimated duration of the surgical procedure, its complexity, cost, the total estimated length of the procedure until the final rehabilitation can be installed, and the experience of the surgeon. The procedures that can be carried out are:[16]

a. Guided Tissue Regeneration (GTR) and Guided Bone Regeneration (GBR) Procedure

One surgical approach that is often used and has proven successful in increasing tissue regeneration is guided tissue engineering (GTR), dan guided bone regeneration (GBR).

In this method, a membrane barrier composed of biocompatible materials is used, where the requirements for a GTR and GBR membrane barrier are biocompatibility, cell exclusion, and able to maintain space. network integration and easy to use. Recent approaches in periodontal regeneration focus on two main areas, using biologics to increase the cell population in periodontal wounds/defects.[11]

b. Periodontal Regeneration by Application of Enamel Matrix Derivatives (EMD)

EMD is a method to promote the regeneration of cementum, periodontal ligament, and alveolar bone. Where its use requires the establishment of a regenerative environment that reproduces the biological conditions that occur in the embryonic development of periodontal tissues. One of the properties of EMD is the prevention of down growth of the epithelium along the root surface after surgical procedures. This can be achieved by the formation of a mechanical barrier such as a barrier membrane in the GTR tissue regeneration procedure. EMD can also promote the proliferation of PDL cells, cementoblasts, and osteoblasts by enabling the re-establishment of normal periodontal architecture.[17]

2.2 Effectiveness of Using Tissue Engineering for Periodontal Tissue Regeneration

Periodontal regeneration is a complex process that requires organized proliferation, differentiation, and development of various cell types to form the periodontal attachment.[7,9] Regeneration of periodontal tissue is a physiological process that goes on continuously. Periodontal regeneration requires the formation of new repair inserts and periodontal support as a result of the disease.[19] The purpose of regenerative techniques is to reshape tissue lost due to disease, restore the function of these structures, to regenerate the supporting tissues of the teeth, which include alveolar bone, cementum, and periodontal ligament.[2] Regeneration also occurs during the destructive process of periodontal disease.[7]

2.2.1 Supporting Structure of Teeth in Periodontal

Periodontal tissue is a complex organ consisting of two tissues. Soft connective tissue is the gingival and periodontal ligament and hard connective tissue is cementum and alveolar bone. Periodontal tissue is a tissue structure that functions as a support for the teeth. The components contained in the periodontal tissue are: gingiva, periodontal ligament, cementum and alveolar bone.[20]

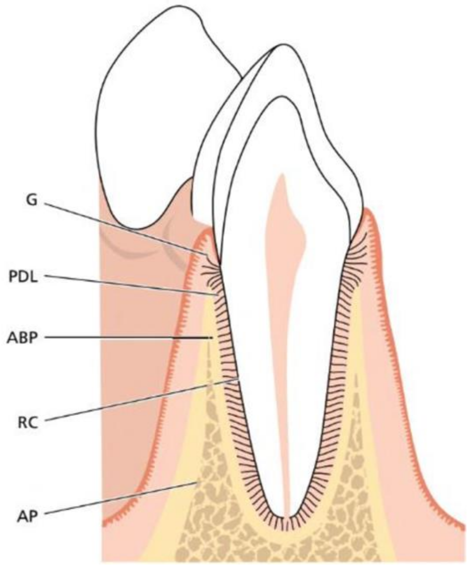

Figure 2. Periodontal Tissue Regeneration

(Source: Bosshardt DD, Lindhe J, Lang NP, Araujo M. Lindhe's Clinical Periodontology and Implant Dentistry. 7th ed. Wiley Blackwell. Vol 1. 2021)

a. Gingiva (G): is the part of the oral mucosa that covers the alveolar processes of the jaws that surround the neck of the teeth
b. Periodontal Ligament (PDL): is a fibrous connective tissue that is specifically located between the cementum covering the root of the tooth, and the bone that forms the wall of the socket.
c. Alveolar Bone (ABP): It is the alveolar process, which is firmly attached to the basal bone of the jaw. Alveolar bone consists of inner and outer components. And it is perforated by many foramina that transmit nerves and blood vessels.
d. Cementum (RC): is a bone-like vascular connective tissue that lines the root of a tooth and is tightly interlocked to the dentin of the root.[21]

2.2.2 Biomaterials in Periodontal Tissue Regeneration and Edentulous Ridge

Several decades of research related to the development of concepts and biomaterials for the regeneration of periodontal tissue and edentulous ridges are classified as barriers, bone fillers, and biologics. Implants in periodontal tissue engineering restore proper alveolar bone, provide adequate regeneration, and stability of teeth or soft and hard tissues surrounding teeth and implants in clinical and esthetic terms.

1. Barriers

   It is a material to cover periodontal defects and can protect against down growth of the epithelium. Barriers are used to limit and select cells that can regenerate certain tissues, such as bone and the periodontal ligament, reducing the downward growth of epithelial cells in the defect and not allowing the formation of a long connective epithelium.

   a. Resorbable Barriers

      In the last decade, resorbable barriers have increased. Factors considered are reduction of patient discomfort, bioactive properties, and ease of handling. The unfavorable factor is the unexpected pattern of resorption associated with the degradation process and the possible presence of inflammation. Collagen membranes are used not only in periodontal regeneration but also in peri-implant regeneration and, in some cases, regenerative procedures associated with implantoplasty or implant surface decontamination.

b. Non-resorbable Barriers

The main advantages of non-resorbable membranes are high mechanical stability and inhibition of cell migration. some criticisms, such as surgical intervention second possible exposure, and emphasized inflammation in the event of infection. These barriers are not used for the introduction of minimally invasive approaches (minimally invasive surgical techniques, single flap approaches, or modified minimally invasive approaches) that can achieve periodontal regeneration without cell selection but with the use of growth factors within the associated defect with a space-saving minimal flap design. inside it.

2. Bone fillers

It is a scaffold or bone graft to replace the missing portion of the alveolar bone. Used in the preservation or augmentation of height and to restore the volume of lost periodontal defects. This type of graft is divided:

1. Autografts are the gold standard due to their osteogenic, osteoconductive, and osteoinductive potential and the absence of foreign body reactions. Depending on the defect, autografts can be obtained intraorally from the extraction socket, edentulous ridge, symphysis, tuberosity, and buccal plate.
2. Allografts are biological materials of the same species. The advantages of allografts are the elimination of the second surgical site and the availability of tissue. The disadvantage of this material

is the possibility of foreign body reactions and disease transmission. In several studies identified allografts as a reliable source for regenerative procedures and function as osteoinductive or osteoconductive biomaterials preserved from proteins and their matrix.

3. Xenograft is a substitute for bone obtained from other species such as beef or pig grafts, and transplanted into humans. The disadvantage of xenografts is antigenicity, these tissues need to be treated carefully to remove organic components. Advantages are single surgical procedure, availability, and reduced patient morbidity.

3. Biologics

   Is a growth factor, cell therapy, or substance directly administered to the defect. Biological mediators are considered the ultimate innovation in oral regeneration. The most widely used mediators are platelet-rich growth factor (PDGF), bone morphogenetic protein (BMP), and enamel matrix derivatives (EMD).[22]

Currently, many techniques and biomaterials are available to regenerate periodontal soft tissue defects. The importance of manipulating and engineering the composition and morphology of biomaterials, to address the associated regeneration of periodontal soft tissue defects.[2]

2.2.3 Soft Tissue and Hard Tissue Regeneration

a. Soft Tissue Regeneration

1. Oral epithelium

   The mucosal epithelial layer is a stratified squamous epithelium, which is either keratinized or nonkeratinized according to its location in the mouth. The epithelium has four layers which are commonly known as cornified layers in the keratinized oral mucosa namely: basal layer, spinous layer, granular layer, and superficial layer. As for the non-keratinized oral epithelium, the granular layer is replaced by an intermediate layer where the cells do not have keratohyalin granules. Keratinocytes in the basal layer are stem cells that undergo terminal differentiation as they migrate to the surface. Cytokeratins are intermediate filaments found in all types of epithelium and are the most basic marker of epithelial differentiation. The shape of the cytokeratin reflects the cell type and differentiation status in different types and layers of the epithelium.[2]

2. Connective Tissue

   The lamina propria consists of a network of type I collagen fibers having a deeper layer containing type III collagen fibers and elastic fibers that vary depending on their location. There are fibroblasts present but only occasionally macrophages, plasma cells, mast cells, and lymphocytes are found. The lamina propria also contains a vascular component, which can form broad capillary loops in the papillae between the epithelial ridges. Lymphatic vessels, nerves, and nerve endings are also present, as well as salivary gland ducts, the acini usually found in the deeper submucosa. A variable number of sebaceous glands are found in the oral cavity but are not associated with hair follicles.[2]

3. Salivary Gland

   Various conditions such as metabolic, immunological, or latrogenic can affect salivary gland physiology and cause morbidity. for example, xerostomic conditions are currently treated with supportive therapies such as artificial saliva and sialagogue drugs which are often ineffective. so that tissue-engineered glands can provide a better solution for such conditions, however, complex anatomical and histological structures (secretory lumen, ducts). Efforts to regenerate artificial salivary gland tissue using aquaporin-5 aqueduct protein. Three-dimensional salivary gland tissue construction was attempted using a biodegradable polymer scaffold. These tissue-engineered glands are able to maintain tight junctions and secrete the water protein, amylase, and can be used as a treatment modality in patients with impaired salivary gland function.[23]

4. Periodontal Ligament (PDL)

   The periodontal ligament is a fibrous connective tissue that connects the teeth to the alveolar bone, where the PDL contains both nerve and vascular parts, which are lined by the overlying epithelium. Connective tissue is attached to the teeth through the cementum on one side and to the alveolar bone. jaw on the other. Although the

PDL is characterized as highly fibrous, it is a highly cellular structure that has many important functions to allow the masticatory apparatus to function properly. The main function of the PDL is the support system it provides when attaching the teeth to the alveolar bone. The main cells that makeup PDL include synthetic cells, resorptive cells, progenitor cells, epithelial cells, and connective tissue cells. For periodontal tissue regeneration to be successful, four basic criteria must be met: the correct signaling molecules, cells, blood supply, and scaffolding must all be able to reach the area of the defect. When the PDL is damaged, if the four components properly stimulate and coordinate with each other to form a biotechnological process, then the healing process and tissue formation can be successful.[2]

b. Hard Tissue Regeneration

1. Tooth

Dental stem cells are a small population of mesenchymal stem cells. Stem cells can differentiate into dental tissue and are considered as a source of stem cells for tooth regeneration. In tooth regeneration, many cell types are different and it is possible to regenerate dental pulp, dentin, and amelogenesis. In research and application of stem cells are still far from clinical use. Several questions regarding the techniques and mechanisms for stimulation, and the use of cells need to be studied further. If rapid development and genetic modification allow.

2. Cartilage

   Cartilage is a difficult tissue to engineer because cells tend to differentiate toward bone. Tissue engineering is emerging as a promising option for repairing or replacing diseased tissue in the temporomandibular joint (TMJ). Stimulation in cell growth and differentiation can be accomplished in a bioreactor by applying, for example, hydrostatic pressure, dynamic loading, rotation, or perfusion. In scaffold-free construction, passing costal chondrocytes appear to be the most viable alternative for TMJ. disc reconstruction.

3. Bone

   Bone is the most common hard tissue for tissue engineering. In several studies on tissue-engineered bone, both experimental and clinical. In general, mesenchymal cells and biomaterials can be used in combination with regulatory factors, such as different growth factors. In a recent study dealing with gene therapy combined with - cell therapy.[8]

The development of oral mucosal tissue engineering seems to follow advances in skin technology in terms of scaffold fabrication and engineering strategies. 3D bioprinting technology has been used for skin engineering in recent years and has demonstrated the advantages of being more flexible, reproducible, resembling real skin morphologically and biologically, and allowing for the simultaneous incorporation of multiple cell types. A component in the reconstruction of the oral mucosa and skin is the scaffold that holds the cells together. Selecting the right scaffold with ideal biocompatibility, porosity, biostability, and mechanical properties is an important step in tissue engineering. The scaffolds used in oral mucosa and skin reconstruction are divided into several different categories, namely:

a. Naturally derived scaffolds such as the acellular dermis and amniotic membrane,
b. Fibroblast-filled skin substitute,
c. Collagen-based scaffold,
d. Gelatin-based scaffold,
e. Fibrin-based material,
f. Synthetic scaffolds such as polymers, and
g. Hybrid scaffold, is a combination of natural and synthetic matrices.

Most of the research conducted in bone tissue engineering, relying on conventional methods, a new trend has been directed towards the utilization of microfabrication technology. In a commonly used top-down approach, cells and biomaterials are combined and cultured until the cells grow and form the engineered structure. The bottom up or modular network approach, and vice versa, addresses the concept of biomimetics by designing micro-scale building blocks through various means such as cell aggregation, cell sheets, cell-loaded hydrogels, or tissue imprinting which is then assembled to create macro-scale networks with specific microarchitectures. This approach can be adopted to engineer well-organized and vascularized bone in a precise, reproducible and low-cost manner with the advantage of combining various materials, cells, and biological cues.[2] The factors that can affect periodontal regeneration are quite complex, namely, the right type and number of cells, a favorable microenvironment with biological signals, and an appropriate scaffolding matrix are all important for regeneration. This strategy serves to increase the focus of self-healing directing host cells to target the development of cells in growing new tissue.[24]

2.3 Edentulous Ridge

2.3.1 Definition of Edentulous Ridge

Edentulous or tooth loss is a dental and oral health problem that often arises in the community due to disruption of masticatory, speech, and aesthetic functions.[25] Tooth loss can also affect the oral cavity and other general health that can affect a person's overall quality of life. Tooth loss is a condition in which one or more teeth are removed from their sockets. Loss of teeth will cause a decrease in alveolar bone, migration of neighboring teeth and can affect supporting tissues.[26] Partial or complete tooth loss has been treated using removable partial or complete denture prostheses, or fixed dentures that can retain adjacent teeth.

The engineering of the tissue around dental implants shows great promise for effectively achieving vertical bone augmentation while minimizing complications. The lack of height or width of the remaining alveolar bone after tooth loss is sometimes increased as a consequence of periodontal disease, infection, and trauma. Lack of vertical bone height can be a problem and can cause particular problems in the posterior region of the mandible where the mandibular canal provides a rigid anatomical barrier. This results in insufficient bone height for successful dental implant placement and makes surgical implant placement impossible without a bone augmentation procedure. Without sufficient vertical alveolar bone height, the initial stability and clinical success of the implants that have been placed may be compromised.[27]

2.3.2 Etiology of Edentulous Ridge

According to research, age, gender, systemic diseases such as diabetes mellitus, social and geographical inequality, and attitudes of patients and dentists towards dental and oral health status are the most risk factors for tooth loss.[28] There are several factors that cause tooth loss, namely:

a. Caries

   Dental caries is a disease of hard tissues, where enamel, dentin, and cementum are caused by microorganisms in carbohydrates. At this stage, caries begins with pain when in contact with food and drink, either cold or hot.

b. Periodontal disease

   Periodontal disease is a disease that affects the supporting tissues of the teeth, namely the gingiva, as well as the periodontal tissue, which connects the teeth and the supporting bone, namely the alveolar bone.

Periodontal disease is divided into two groups, namely gingivitis and periodontitis. Periodontitis can result in progressive loss of alveolar bone around the teeth, if left untreated it can lead to loosening of the connective tissue attachments and tooth loss.

c. Trauma

Trauma is damage to dental tissue or periodontal tissue due to hard contact with unexpected foreign bodies on the teeth, maxilla and mandible. Trauma can occur directly or indirectly. Direct trauma occurs as a result of the impact of a hard object hitting the teeth, while indirectly, that is, when an impact hits the teeth in the lower jaw hitting the maxillary teeth with great and sudden pressure. This can cause the tooth to fracture and fall out of the socket.[25]

In a population, the decision in patients to be edentulous reflects not only their level of caries and periodontal disease but the effect of several non-disease factors such as behavior, dental history, characteristics of the health care system, and cost issues associated with low socioeconomic status. Some authors suggest that tooth loss has no relationship with the prevalence of the dental disease. Nevertheless, it can be concluded that edentulism is caused by various combinations of dental disease along with determinants such as culture, finance, behavior, and previous dental care.[29]

2.3.3 Relation of Edentulous Ridge to Periodontal Tissue

Periodontal is a complex structure consisting of soft tissue and hard tissue. Periodontal tissue loss is most commonly associated with the bacterial plaque-induced inflammatory condition, periodontitis, but can also occur as a result of other causes, such as mechanical trauma. While full periodontal complex regeneration involves both soft and hard tissue reconstitution, in certain cases, surgical procedures are performed with the sole aim of reconstructing the soft tissues surrounding the teeth. A periodontal ligament is a group of specialized collagen fibers with different diameters ranging from nano to micro which essentially connect the root surface of the tooth with the tooth socket. They break down into smaller fibers, which join with adjacent fibers to produce an interconnecting woven fiber that is oriented between bone and cementum.

Edentulous ridges are a common problem that can range from small periodontal defects to complex and difficult structural defects to treat. In addition, the increasing demand for bone regenerative therapy is expected to increase along with the increase in population and life expectancy. The current conventional approach to the treatment of bone deficiency is the use of various types of bone grafts, guided tissue regeneration, or osteodistraction.[2]

Edentulous ridge and complications are concerns that lead to aesthetics. Missing teeth are replaced by prostheses including fixed partial dentures and removable dentures. Application of this treatment requires appropriate bone and mucosal layers to provide adequate support and stability to the prosthesis. However, at present, it is recommended to preserve the remaining bone and even increase bone mass with augmentation techniques rather than reducing bone disruption. The biggest advantage of this approach is that it improves attachment and provides support for future prostheses. The anatomical repositioning that can be done is:

a. Osteogenesis distraction (gradual repositioning)

   Distraction osteogenesis (DO) is based on bone formation after segmental bone separation at the osteotomy site to correct maxillofacial deformities and has been recommended to correct atrophic alveolar ridges and deficits in vertical and horizontal dimensions without harvesting site morbidity.[2]

b. Inlay bone graft (acute repositioning)

   Rehabilitation of atrophic bone with interposition grafts after segmental osteotomy was first introduced in 1976 for the reconstruction of the anterior mandible and to improve denture retention. Then the “inlay grafting” or “sandwich technique”, which means the placement of the graft material in a 3 to 5 walled cancellous compartment, has been advocated for bone and ridge augmentation prior to denture fabrication or implant insertion.[2]

c. Inferior alveolar nerve lateralization

   A distance of 2 mm is recommended between the alveolar canal and the temporary implant in a severely atrophic mandibular posterior segment, this may not be achieved and inferior alveolar nerve (IAN) encroachment may be a challenge in this case. Several measures have been developed to avoid these sequelae such as nerve lateralization. In this operation, the

IAN is freed from the nerve canal and an implant is placed in the jaw, after which the nerve will be placed on top of the implant.[2]

2.4 Comparison and Tissue Engineering Conventional Techniques

Traditional or conventional standard techniques based on the replacement of lost or damaged tissue with autologous grafts from living or even cadaveric donors are still used in dentistry as well as other medical fields, although they have drawbacks, such as the risk of infection and rejection after transplant procedures. An innovative alternative is provided by regenerative medicine, which aims to regenerate, repair, or replace tissue and ensure restoration of impaired function by combining tissue engineering with human self-healing capabilities.[30]

Tissue engineering is the science of fabricating new tissue with the aim of changing and regenerating lost or damaged tissue.[4] Where tissue engineering aims to replace lost tissue, whether caused by congenital defects, trauma, or surgery.[8] While conventional techniques in periodontal tissue therapy, such as scaling, root planing, and periodontal surgery, are to remove pathogenic bacteria and infected granulation tissue around the teeth. This procedure results in a weak attachment to the epithelial tissue, besides that this procedure cannot restore the periodontal tissue to its original shape, and recession of the gingiva causes aesthetic damage.[31] So that tissue engineering can be used as a further alternative in the success of network reconstruction so that damaged tissue can function again.[32]

Effective tissue engineering is expected to form reattachment of epithelial seals, cementum formation, extrinsic fibers and restore lost alveolar bone. Advances in tissue engineering are promising but further research is needed.[23]