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Barrier Membranes for guided bone regeneration: An Overview

[1]Dr Deepak Kumar Gupta, PG Resident, Department of Prosthodontics, Crown & Bridge and Implantology, Rishiraj College of Dental Sciences & Research Centre, Bhopal Madhya Pradesh, India.

[2]Dr Ambika Shrivastava, Professor Department of Prosthodontics, Crown & Bridge and Implantology, Rishiraj College of Dental Sciences & Research Centre, Bhopal Madhya Pradesh, India.

[3]Dr Siddharth Gupta, Professor Department of Prosthodontics, Crown & Bridge and Implantology, Rishiraj College of Dental Sciences & Research Centre, Bhopal Madhya Pradesh, India.

[4]Dr Chandu G S, Professor & Head, Department of Prosthodontics, Crown & Bridge and Implantology, Rishiraj College of Dental Sciences & Research Centre, Bhopal Madhya Pradesh, India.

[5]Dr Brajendra Singh Tomar, Associate Professor, Department of Prosthodontics, Crown & Bridge and Implantology, Rishiraj College of Dental Sciences & Research Centre, Bhopal Madhya Pradesh, India.

[6]Dr Anushree Khare, PG Resident, Department of Prosthodontics, Crown & Bridge and Implantology, Rishiraj College of Dental Sciences & Research Centre, Bhopal Madhya Pradesh, India.

Corresponding Author: Dr Deepak Kumar Gupta, PG Resident, Department of Prosthodontics, Crown & Bridge and Implantology, Rishiraj College of Dental Sciences & Research Centre, Bhopal Madhya Pradesh, India.

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Abstract

Guided bone regeneration is a surgical procedure that utilises bone grafts with barrier membranes to regenerate enough bone for successful implant placement.

There are two types of barrier membranes resorbable and non- resorbable.

To achieve maximum bone regeneration, barrier membrane should have several characteristics, including (1) biocompatibility (2) proper stiffness for space maintenance (3) prevent epithelial cell migration and (4) appropriate resorption time after proper bone regeneration. Compared to guided tissue regeneration, guided bone regeneration procedures are considered more predictable. This is because osseous regeneration during guided tissue regeneration takes place in a challenging environment. The fundamental principle of guided bone regeneration entails using mechanical barriers to shield blood clots and isolate bone defects

from surrounding environment .This arrangement allows bone forming cells access to a secluded space specially for intended bone regeneration. Not all barrier membranes function the same way, as they differ from their origin and structure, it is important to understand how membranes behave and differ from each-other in order to achieve a predictable treatment.

Thus, the purpose of this review is to summarize advantage, disadvantages, mechanism, and newer trends in barrier membranes to provide a better understanding of the subject and giving predictable outcome for better patient care.

Keywords: Guided Bone Regeneration, Barrier Membrane, Implant, Bone Graft.

Introduction

Adequate bone volume is important for a predictable, long-term prognosis in implant dentistry. But some patients present with insufficient horizontal or vertical bone, which frequently precludes the successful outcome of an ideal implant placement.[1]Although many methods for bone reconstruction exist but established methods are like, distraction osteogenesis,osteoinduction, osteoconductionand guided bone regeneration . [1,2]

Osteoinduction and osteoconduction have an extremely limited clinical application and distraction osteogenesis is still in its development phase often leaving undesirable tissue scarring. This leaves guided bone regeneration and the use of bone grafting materials or combinations of these methods as the only ones commonly applied in clinical practice.[1]

Guided bone regeneration membranes are used to separate the tissues during healing, retard apical migration of the epithelium to the site, maintain the necessary space for bone-in-growth (tenting), and protect the graft material in the defect.[3]

The basic principle of guided bone regeneration involves the placement of mechanical barriers to protect blood clots, isolate the bone defect from the surrounding connective tissue, and providing bone-forming cells with access to a secluded space intended for bone regeneration. The use of a barrier membrane is advantageous to facilitate augmentation of alveolar ridge defects, induce bone regeneration, improve bone-grafting results, and treat failing implants.[1]

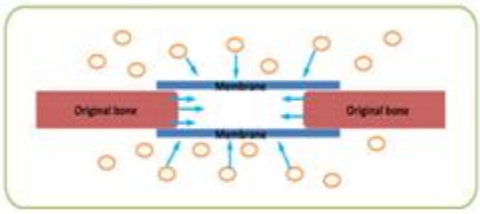

Figure 1: The principle of guided bone regeneration using mechanical barriers (membranes) to seal off the bone defect from the surrounding soft connective tissue into a secluded space by which cells only from the surrounding bone can migrate.

The barrier membrane creates a space and facilitates the proliferation of angiogenic & osteogenic cells from the marrow space into that defect without interferences by fibroblasts.[4] Nowadaysguided bone regeneration (GBR) isan essential procedure in implant dentistry.

Need of barrier membrane

Treatment of large bone defects represents a great challenge, as bone regeneration is required in large quantity and may be beyond the potential for self-healing. Although many methods for bone reconstruction exist, they all have specific indications and limitations. Established methods are distraction osteogenesis and bone transport, or bone grafting, including autologous bone grafts, bone marrow aspirate, allografts, bone substitutes or growth factors . Furthermore, the concept of an induced-membrane represents another strategy for bone regeneration and

particularly in cases of large bone defects secondary to trauma, infection or tumor excision. This method involves a two-stage procedure, where a 'biological' membrane is induced as a foreign body response after application of a cement spacer at the first stage, acting as a 'chamber' for the insertion of autologous bone-graft at the second stage .

Guided Bone Regeneration (GBR), is the concept of using a resorbable or non-resorbable membrane that acts as a barrier to prevent soft-tissue invasion into the defect and forms a 'chamber' to 'guide' the bone regeneration process is also used for bone reconstruction.[5]

Mechanism of guided bone regeneration

A lack of horizontal and/or vertical bone in implant sites may cause major clinical problems and needs to be corrected prior to implant placement. To regenerate enough bone for successful implant placement, a ridge augmentation technique is often required.

One technique of ridge augmentation is guided bone regeneration. It uses barrier membranes with or without particulate bone grafts or/and bone substitutes. Osseous regeneration by guided bone regeneration depends on the migration of pluripotential and osteogenic cells to the bone defect site and exclusion of cells impeding bone formation (e.g. epithelial cells and fibroblasts). To accomplish the regeneration of a bone defect, the rate of osteogenesis extending inward from the adjacent boney margins must exceed the rate of fibro genesis growing in from the surrounding soft tissue. Toensure successful bone regeneration, four principles need to be met:

1. Exclusion of epithelium and connective tissue
2. Space maintenance
3. Stability of the fibrin clot
4. Primary wound closure.

After guided bone regeneration procedures, bone regeneration follows a specific sequence of events. Within the first 24 hours after a bone graft, the graft material/barrier created space is filled with the blood clot which releases growth factors (e.g., platelet derived growth factor) and cytokines (e.g., IL-8) to attract neutrophils and macrophages. The clot is absorbed and replaced with granulation tissue which is rich in newly formed blood vessels. Through these blood vessels, nutrients and mesenchymal stem cells capable of osteogenic differentiation can be transported and contribute to osteoid formation. Mineralization of osteoid forms woven bone, which later serves as a template for the apposition of lamellar bone. This transformation of primary sponge work would eventually constitute both compact and reticular bone with mature bone marrow. These events occur 3 to 4 months post surgery .[6]

Classification of membranes[7]

A. 1. Nonresorbable 2. Resorbable

expanded Poly Tetrafluoroethylene (e-PTFE) Gore-Tex

Polymeric (vicryl, atrisor, Epiguide) &

High density poly tetrafluoroethylene (d-PTFE)collagen derived.

Titanium mesh

Titanium reinforced PTFE

B) According to generation

1. First generation membranes

Cellulose acetate (Millipore)

Expanded poly tetra fluoroethylene (e-PTFE),

Gore Tex.

Titanium reinforced ePTFE.

High-density- PTFE Titanium mesh

2. Second generation membranes

Natural - collagen or chitosan.

Synthetic membranes –

Polyesters (e.g. polyglycolic acid -PGA)

Polylactic acid (PLA) Polycaprolactone (PCL) and their co-polymers

3. Third generation membranes

I) Barrier membranes with Antimicrobial activity Amoxicillin, Tetracycline, 25% Doxycycline, Metronidazole.

II) Barrier membranes with Bioactive Calcium Phosphate incorporation Nano-sized hydroxyapatite (HA) particles nano -carbonated hydroxyapatite (nCHAC).

III) Barrier membranes with Growth Factor release.factor (FGF-2), Transforming growth factor (TGF-1), Bone morphogenic protein(BMP-2, 4,7 and 12) and enamel matrix derivative (EMD) .[7]

Criteria essential for barrier membrane:

Barrier membrane should be biocompatible, spacemaking, prevent fibrous connective tissue (scar) invasion of the space adjacent to the bone and provide protection from bacteria and Tissue integration helps to stabilize the healing wound, helps to create a seal between the bone and the material.[7]

Advantages and disadvantages of non -resorbable barriers:

They shows good mechanical properties, remain intact until removal, maintains space between defect and barrier allowing entry of cells PDL and alveolar bone and minimal tissue exposed if membrane not exposed.[5]

Second surgical procedure is needed to remove the membrane which causes discomfort and increased costs for the patients, as well as the risk of losing some of the regenerated bone, because flap elevation results in a certain amount of crestal bone resorption.[7]

Advantages and disadvantages of resorbable barriers:

They eliminate the second stage surgery , tissue friendly and integrated with host tissue, enhance tissue coverage and resist or prevent microbial colonization.[5]By their inherent nature, they offer limited control over the length of application because the disintegration process starts upon placement in the tissues, and the ability of each individual patient to degrade a particular bio-material may vary significantly particularly form materials requiring enzymatic degradation (such as collagen).[5]

Resorbable Membranes

Some absorbable membranes are now commercially available in a variety of materials and structures and have been used to treat angular bony defects, furcation involvements and gingival recessions.

a. Collagen membranes: Collagen is a major constituent of natural extracellular matrix (ECM). Collagen has many activities such as hemostatic ability, attraction and activation of periodontal ligament and ginigival fibroblast cells, augmentation of tissue thickness, biocompatibility, biodegradability, cell affinity. These properties help in making it an ideal choice for a bioresorbable guided tissue regeneration or guided bone regeneration barrier membrane.

Figure 2: collegen membrane

Figure 3: Trimming of membrane to adapt to defects

Most of the commercially available collagen membranes are developed from type I collagen or a combination of type I and type II. The source of collagen comes from tendon, dermis, skin or pericardium of bovine, porcine or human origin. Physical or chemical cross-linking

methods, such as ultraviolet light, hexamethylene diisocyanate (HMDIC), glutaraldehyde (GA), diphenylphosphorylazide (DPPA), formaldehyde (FA) plus irradiation, genipin (Gp), have been used to modify the biomechanical properties, collagen matrix stability of the collagen fibers. Studies have shown that cross-linking is associated with prolonged biodegradation, reduced epithelial migration, decreased tissue integration and decreased vascularization. [7]

b. Polylactic acid and polyglycolic acid polymers: The materials most commonly used are poly (a -hydoxy acids) which includes poly (lactic acid), ploy (glycolic acid) and their co-polymers poly (glycolide-lactide) . Poly (glycolic acid) and poly (lactic acid) barriers are manufactured by catalytic polymerization of monomers of PGA and PLA or mixtures of PLA and PGA. One apparent advantage of poly (a- hydroxy acids) is their degradation by hydrolysis resulting in decomposition products that are mostly metabolized to CO2 and H2O. Through citric acid cycle (Krebs cycle). The degradation rate is dependent on pH, presence of mechanical strain, enzymes, infection, and polymeric composition of the material. Marcato et alin 1996 found that poly (glycolic acid) degrades the fastest and poly (L-lactate) is most stable in vitro.

Types of PLA Membranes

(i). Guidoris a hydrophobic barrier material made from PLA, combined with a citric acid ester softening agent. The barrier is bilayered , an external layer facing the gingival tissue with large rectangular perforations (400 to 500/cm) and outer spacers to allow tissue integration, internal spacers between external and internal layers to create space for tissue growth and an internal layer with smaller circular perforation and outer spacers to ensure space between barrier and root surface. The barrier is made with an absorbable suture attached and continued with the collar region. Histological animal studies suggest that this device completely absorbed by 6-12 months post-implantation and maintains its barrier function for at least 6 weeks post- implantation.[8]

(ii). Resolutis a copolymer of PGA and PLA. It is a composite consisting of non occlusive membrane of glycolide and lactide co-polymer serving cell exclusion function and a web structure of bonded polyglycolide fiber serving the tissue integration function. It is supplied with a suture to be secured to the tooth. Histologicalstudies indicate that this device retains its structure for 4 weeks and absorbs completely within 5-6 months post-implantation.[9]

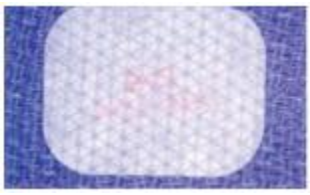

Figure 4: Resolute membrane

(iii).Vicryl periodontal mesh(polyglactin 910) is a synthetic material composed glycolide and lactide in 9: 1 ratio. It is available as a woven or knitted, mesh. Vicryl barrier is thought to degrade over a period of 3-12 weeks.[10]

(iv).Atrisorb (liquid membrane)consists of a polymer of lactic acid, poly (D.L.-lactide), dissolved in N. methyl-2-pyrolidone (NMD). Atrisorb is prepared as a solution that coagulates or sets to a firm consistency on contact with water or other aqueous solutions. This principle is used in forming a barrier that is then to be trimmed to the desired dimensions. The resulting 600-750 um thick device has modest adhesion. Histologic observation suggests that the device is completely absorbed by 6-12 months.

(v)EPI-GUIDEis a hydrophilic membrane formed from PLA (D.L. forms). This barrier contains a flexible open cell structure and internal void spaces .[11]

c. Freeze dried duramater allograft : Duramater consists of irregular network collagen fibers, is obtained from cadavers, processed to eliminate antigenic and pyrogenic activity, then lyophilized and sterilized. Duramater has low immunogenicity. Most of the material resorbs within 6 weeks of surgery. Use of cadaveric duramater may represent a risk to acquire Creutz-Feldt-Jacob Disease not only for the recipient, but for the operator as well .[12]

d. Oxidized cellulose :Oxidized cellulose (Surgicel) is a commercially available absorbable haemostatic dressing in the form of a knitted fibrous mesh. When placed in contact with blood, it converts into gelatinous mass which has been reported to potentiate osseous and sott tissue regeneration cleft reconstructive surgery. Oxidized cellulose can completely resorb within 4 weeks of implantation . Oxidised cellulose (surgical) and cellulose (Gelfoam) have been proposed and used as biodegradable barriers in regenerative treatment of furcation areas and infrabony defects.[13] Histologically studies indicate that oxidized cellulose well tolerated in soft tissue, while it may delay healing in bone tissue. The acidic nature may account for this other adverse effects. Alkali cellulose (Gengiflex) is a similar material that has been used in filling extraction socket after immediate implants. [14]

e. Laminar bone (Lambone DFDBA pacifie coast tissue bank): Sheets or strips of demineralised laminar or cortical bone have also been used as barrier membranes around implants and periodontal defectsand require hydration for approximately 10 min before clinical usage.

f.Calcium sulfate (capset lifecore biomedical):Calcium sulfate (plaster of paris, eg. Capset) has been used in conjunction with demineralised freeze-dried bone allograft .This mixture is proposed to have advantages like excellent tissue response, low incidence of infection if exposed , good adaptation and adherence to root surface,shorter chair time and no need of suture.[15]

Non Resorbable membrane

a.Titanium mesh (Ti): These were introduced because of their advanced mechanical support which allows a larger space for bone and tissue regrowth. The exceptional properties of rigidity, elasticity, stability and plasticity make Ti mesh an ideal alternative for e-PTFE products as non-resorbable membranes. Due to the presence of holes within the mesh, it does not interfere with the blood supply directly from the periosteum to the underlying tissues and bone grafting material. It is also completely biocompatible to oral tissues. Ti mesh can be used before placing dental implants (staged approach) to gain bone volume or in conjunction with dental implant placement (non-staged approach).

Disadvantage: Increased exposure due to their stiffness and also a more complex secondary surgery to remove these membranes.

b.Titanium-reinforced PTFE: The e-PTFE membrane and d-PTFE membrane are also available as titanium-reinforced e-PTFE or d-PTFE. The embedded titanium framework allows the membrane to be shaped to fit a variety of defects without rebounding and provides additional stability in large, non-space maintaining osseous defects.

Figure 5: Titanium – reinforced

Figure 6: Titanium-reinforced ePTFE membranes preserve volume and help protect the space into which bony regeneration occurs

c. **Non-absorbable membranes of synthetic polymers**: Polytetrafluoroethylene (PTFE) is an example of a material used in non-absorbable membranes. According to its structure, PTFE can be divided into two types: expanded PTFE (e-PTFE) and high density PTFE (d-PTFE) .

(i)Expanded polytetrafluoroethylene (e-PTFE): Developed in 1969 and it became the standard for bone regeneration in the early 1990s. It is sintered with pores between 5 to 20 microns in the structure of the material. It is manufactured when PTFE is subjected to high tensile stress. The efficacy of this membrane to preserve and regenerate bone around implants placed in fresh extraction sockets were validated in several studies.

Drawbacks: Exposure to oral cavity because of high porosity and removal of membrane is difficult- extensive releasing incisions needed.

(ii) High-density polytetrafluoroethylene (d-PTFE): To overcome the problems with e-PTFE a high density PTFE membrane (d-PTFE) with pore size of less than 0.3microns was developed in 1993. Even when the membrane is exposed to the oral cavity, microorganisms are excluded by the membrane while oxygen diffusion and transfusion of small molecules across the membrane is still possible. Thus, the d-PTFE membranes results in good bone regeneration even after exposure. Removal of d-PTFE is simple since there is no tissue ingrowth into the surface structure.

Use of d-PTFE is particularly useful when primary closure is impossible without tension, such as alveolar ridge preservation, large bone defects, and the placement of implants immediately after extraction. In those cases, d-PTFE membranes can be left exposed and thus preserve soft tissue and the position of the mucogingival junction. It enhances healing, since there is no need for extensive releasing incisions to obtain primary closure. These are considered to be the gold standard membranes available currently on the market. The increased efficacy of d-PTFE membranes in guided tissue regeneration has been proven with animal and human studies.

Disadvantage: Tendency for collapse of membrane towards defect.

The Gore-Tex membrane (W.L. Gore & Associates, Flagstaff, AZ, USA), which is made of e-PTFE, has been widely used in clinical treatment and has become a first choice-material for GTR and GBR. It is also widely used for general surgery, neurosurgery and cardiovascular surgery .[7]

Figure 7: Gore – Tex , ePTFE

d. Non-absorbable silk membranes: Silk is a material produced by the Bombyx mori silkworm.It is a natural biopolymer, composed mainly of fibroin and sericin . Silk fibroin was used as a biomaterial after the removal of sericin. it is a compound characterized by high capacity for biocompatibility and tissue integration . Silk fibroin membranes can generate a favorable adhesion of osteogenic cells, favoring bone neo-formation. The

major disadvantage of these membranes is the difficult handling as well as the low mechanical properties . An alternative to simple silk membranes is given by the silk pad; it is produced from the cocoon of silkworms by a simple peeling method. The silk pad has a number of benefits; it has a higher tensile strength in wet conditions than collagen and/or d-PTFE membranes. The obtaining procedure is a simple one, and at a low cost. In addition, the silk pad has a high amount of sericin, which promotes bone neoformation.

Enhanced barrier membranes : New membranes have been developed, with additional functions such as the release of beneficial agents: antibiotics, growth factors and adhesion factors. Membranes with Inorganic Compounds in order to enhance the osteoconductive and osteoinductive effects, research has focused on the introduction into the structure of the barrier membrane of synthetic calcium phosphates (hydroxyapatite or β-tricalcium phosphate), single or combined in biphasic calcium phosphates. Such products allow vascular penetration, cell infiltration and attachment, cartilage formation and calcified tissue deposition. Phipps et al. showed that the membrane made of a mixture of particles of PCL, collagen and hydroxyapatite generated a rapid cell spread and a significant cell proliferation**.**

Won et al. compared the collagen membrane with a membrane made of PCL, PLGA and β-tricalcium phosphate; even if both membranes showed similar results in histological and histomorphometric analyses, the membrane made of PCL, PLGA and β-tricalcium phosphate generated a larger area of bone neo-formation.

a. Zinc, magnesium, iron or strontium in the composition of the membrane : The addition of ZnO in the structure of barrier membranes has generated improvements in the proliferation of osteoblasts, with an accelerated regenerative mechanism and faster healing process as well as inhibiting the formation of bacterial biofilm .

In addition,Oh et al. observed that PLA-Zn-bioactive glass membranes showed tensile strength, elongation and flexibility similar to those of zinc-free membranes. Similar to zinc, magnesium is an important factor in bone metabolism, with both proliferative effects for osteoblasts and anti-osteoclastic effects. The strength of the Mg alloy is higher than that of absorbable polymers, such as PLA; therefore, magnesium alloy can improve the mechanical properties of membranes. However, the rate of the degradation of magnesium alloy is too fast. An in vitro study found that hydrofluoric acid coating can delay the corrosion of magnesium alloys.

Xin et al. designed a barrier membrane made of PLA reinforced with a Mg alloy core, with a better loading capacity compared to membranes without Mg reinforcement; when fluorine-coated magnesium alloy was used, it showed better resistance to corrosion. The proliferation of fibroblasts and osteoblasts has also been easily achieved.

b. Membranes with antimicrobial factors: Metronidazole benzoate can be added to the layer in contact with the epithelial tissue, preventing bacterial adhesion and proliferation . Techniques for loading silk fibroin with 4-hexylresorcinol have shown antimicrobial, antioxidant and antimutagenic abilities .The disadvantages observed were that they have a short release time of the drug; moreover, some periodontal tissue infections often occur after a relatively long period of time after surgery.[16]

c. Membranes with growth factors: These factors include the group of bone morphogenetic proteins (BMP), stromal cell derived factor 1 alpha (SDF-1α), transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), growth factor rich in

platelets (PRGF) or fibroblast growth factor-2 (FGF-2) . Bone morphogenetic proteins are among the most powerful osteoinductive proteins; they have modulatory effects on the differentiation and functionality of cells involved in bone formation.[16]Major disadvantages of growth factors supplementation in the structure of barrier membranes include the high production cost, but also the fact that the doses are usually over-physiological, with potential adverse effects.[16]

Recent Trends in the development of barrier membranes

a. Amniotic and chorionic membranes: Amniotic and chorionic membranes are biological membranes, which means that they are bio-absorbable and compatible with tissues. The amniotic membrane consists of a thick basal membrane and an avascular stromal matrix; this is the innermost layer of the placenta. Chorion forms the outer end of the sac and is made up of several types of collagen and bioactive components of cell adhesion . Amniotic and chorionic membranes have been used in transplant surgery, proving healing, anti-inflammatory and antibacterial properties.

b.Barrier membranes from platelet rich – fibrin(PRF): PRF has been shown to significantly increase the potential for tissue regeneration, favoring the slow and gradual release of growth factors trapped in its fibrin matrix .

c.3D Printed membranes- Natural biomaterials used in 3D printing techniques include collagen, agarose, alginate, chitosan, silk, gelatin, cellulose, hyaluronic acid and fibrin and synthetic biomaterials include PLA, PGA, PLGA and PCL .Decellularized matrix components containing both conserved cellular elements and specific signaling factors of high importance in regenerative processes can also be used, because the latter can guide the cells of the resident tissue or provide the host cells with the necessary instructions for tissue regeneration .[16]

d. Electrospinning (e- spinning) for membranes: Formhals first introduced electrospinning in 1938. Membranes produced by this process are biocompatible, degradable, and resemble the arrangement of native extracellular matrix. Three-dimensional(3D) structure of these membranes with high surface area of improved hydrophilicity and wettability endow the structure with mechanical support and regulate cell functions guiding new bone into the defect.

Li et al, have cultured different cells such as fibroblasts, cartilage cells, mesenchymal stem cells, on PLGA and PCL nanofibrous e- spun scaffolds and demonstrated the ability of the nanofiber structure to support cell attachment and proliferation.[7]

e.Functionally graded multilayered membranes :use of multilayered barrier membranes was proposed to utilize a graded-structure with compositional and structural gradients that meet the local functional requirements by enhancing bone growth while preventing the gingival tissue down-growth.

The membrane was designed with one side constituted by 8% nano-carbonated hydroxyapatite/collagen/poly (lactic-co- glycolic) acid porous membrane allowing cell adhesion, and the opposite face with a smooth PLGA nonporous film. A novel functionally graded membrane (FGM) was designed and fabricated via multilayeringe-spinning . The FGM consists of a core-layer (CL) and two functional surface-layers (SL) interfacing bone (nano-hydroxyapatite, n-HAp) and epithelial (metronidazole, MET) tissues. The CL comprises a neat poly(d,l-lactide-co-caprolactone) (PLCL) layer surrounded by two composite layers

composed of a gelatin/ polymer ternary blend (PLCL:PLA:GEL).[17]

Conclusion

The concept of guided bone regeneration (GBR) for the reconstruction of the alveolar ridge defect prior to implant placement has been developed in an effort to optimize treatment strategies. Research from animal and clinical studies in this field is still ongoing in order to establish an ideal membrane for treatment.[1]

Since every membrane offers both advantages and disadvantages, a membrane should be selected based on a thorough understanding of the benefits and limitations inherent to the materials in relation to the functional requirements in the specific clinical application.[1]

To enhance regenerative properties, numerous modifications have been attempted in the membrane properties. To ensure cell specificity during repopulation, adhesion molecules have been incorporated. Recent advances include infusion of antibiotics in GBR membranes. This antibacterial nature of membrane is thought to be of great benefit during early wound healing phases and thus improve regenerative outcome. Addition of growth factors have also been investigated. These factors are expected to aid in cell differentiation and migration to the wound space.Thus, it is important to understand that Guided bone regeneration is not a procedure, rather, it is a promising approach for attempting regeneration of bone tissues and enhancing success rates of implant dentistry.[4]

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