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Membranes for Periodontal Regeneration

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Abstract: *Periodontitis is a chronic inflammatory disorder that can lead to the destruction of the periodontal tissues and ultimately tooth loss. Regeneration of the reduced periodontium is the ideal goal in periodontal therapy. To date, regenerative therapy with membranes, bone grafting materials, growth factors and the combination of these procedures have been investigated and employed with distinct levels of clinical success. Barrier membranes prevent epithelial down growth, allow periodontal ligament and alveolar bone cells to repopulate the defect thereby favoring the regeneration of periodontal tissues. This article discusses various membranes used for periodontal regeneration and their impact on the experimental or clinical management of periodontal defects.*

Keywords: *Barrier membranes, Guided tissue regeneration, Regeneration.*

I. Introduction

The periodontium is a functional unit that is composed of gingiva, alveolar bone, periodontal ligament (PDL) and cementum. Periodontitis is an ubiquitous inflammatory condition that leads to progressive destruction of periodontal tissues, and is a major cause of tooth loss in adults. Conventional treatments for periodontitis such as open flap debridement (OFD) are successful in ameliorating the active disease by providing access to root surfaces and establishing improved periodontal form and architecture. However, periodontal defects, if left empty after OFD, fill first with the faster proliferating cells i.e., epithelial cells and fibroblasts which generates a fibro-epithelial tissues that attach to the root surface which does not allow the bone and periodontal ligament (PDL) cells to refill the pocket, and the defect persists. This traditional healing process, known as periodontal 'repair' ultimately prevents orderly and sequential regeneration of true hybrid periodontal tissues.[1,2]

Regeneration of the reduced periodontium is the ideal goal in periodontal therapy. By definition, successful periodontal regeneration is the simultaneous regeneration of cementum, PDL, and alveolar bone, so that the form and function of the lost structures are restored. [3,4]

In 1976 Melcher formulated a hypothesis which suggested that, under physiological conditions, only cells from periodontal ligament can synthesize and secrete cementum to attach newly-synthesised collagen fibres to tooth. [1] This hypothesis was experimentally and histologically verified by Karring et al. The necessity for exclusion of epithelial and connective tissue cells of the gingiva from the wound led to the development and application of Guided Tissue Regenertion (GTR) membranes. [5]

II. Classification Of Barrier Membranes

Membranes used for periodontal regeneration can be classified as

A) 1. Nonresorbable — expanded Poly Tetrafluoroethylene (e-PTFE) Gore-Tex
High density poly tetrafluoroethylene (d-PTFE)
Titanium mesh
Titanium reinforced PTFE

2. Resorbable — Polymeric (vicryl, atrisor, Epiguide) & collagen derived. [6]

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**).** [2]

III. Criteria Essential For Barrier Membrane

1. Biocompatibility: The membrane must be constructed of acceptably biocompatible material. The interaction between the material and tissue should not adversely affect the surrounding tissue, healing result, or the overall safety of patient.
2. The membrane should exhibit suitable occlusive properties to prevent fibrous connective tissue (scar) invasion of the space adjacent to the bone and provide protection from bacterial invasion if the membrane become exposed to the oral environment.
3. Spacemaking: The membrane must be able to provide a suitable space into which osseous regeneration can occur.
4. The membrane should be capable of integrating with or attaching to the surrounding tissue. Tissue integration helps to stabilize the healing wound, helps to create a "seal" between the bone and the material. The membrane must be clinically manageable. [2]

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. On one side of the membrane is an open microstructure collar of 1 mm thick and 90% porous which retards the growth of the epithelium during the early wound healing phase; on the other side, a 0.15 mm thick and 30% porous membrane which provides space for new bone growth and acts to prevent fibrous ingrowth.[6-7]. The efficacy of this membrane to preserve and regenerate bone around implants placed in fresh extraction sockets were validated in several studies.[6]

Drawbacks

Exposure to oral cavity because of high porosity

Removal of membrane is difficult- extensive releasing incisions needed. [6]

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. [(6)] These are considered to be the gold standard membranes available currently on the market. [1]

The increased efficacy of d-PTFE membranes in guided tissue regeneration has been proven with animal and human studies [6-8]

Disadvantage: Tendency for collapse of membrane towards defect.

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.[7] 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) [6] The main four main advantages of Ti-mesh membranes over their alternative PTFE membranes: (1) rigidity, which provides extensive space maintenance and prevents contour collapse (2)

elasticity, which prevents mucosal compression (3) stability to prevent graft displacement and (4) plasticity that permits bending, contouring and adaptation to any unique bony defect [7]
Disadvantage: Increased exposure due to their stiffness and also a more complex secondary surgery to remove these membranes. [7]

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. [6]

Jovanovic et al conducted an experimental study in beagle dogs comparing titanium reinforced PTFE to that of standard PTFE and showed that the former were able to maintain a large protected space for blood clot stabilization. [9]
Disadvantages of Non-resorbable Membranes

1. 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.
2. Early exposure of barrier membranes to the oral environment and subsequent bacterial colonization.
3. Wound dehiscence.
4. Due to the rigidity of the non-resorbable membranes, extra stabilization of the membrane with miniscrews and tacks are often required [1,2,6,7]

Resorbable Membranes

To overcome the drawbacks of nonresorbable membranes, resorbable membranes have been developed. Currently there are two kinds of resorbable membranes: polymeric and collagen derived from different animal sources[6]

Polymeric membranes

These are made up of synthetic polyesters, polyglycolides (PGAs), polylactides (PLAs), or copolymers which are completely biodegraded to carbon dioxide and water via the Krebs cycle and by enzymatic activity of infiltrating macrophages and polymorphonuclear leucocytes.[10] Processing techniques by which these membranes are fabricated include melting (i.e., polymer is heated above the glass transition or melting temperature) or Solvent casting/particulate-leaching and phase inversion. [11-13]
Drawbacks:

1. Presence of inflammatory infiltrate around the membrane.
2. Premature membrane exposure to the oral cavity.[6]

Collagen membranes

Collagen is a major constituent of natural extracellular matrix (ECM). [1] Collagen has many auspicious biological 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 render it advantageous for extensive application & as an ideal choice for a bioresorbable GTR or GBR barrier membrane. Most of the commercially available collagen membranes are developed from type I collagen or a combination of type I and type II1. The source of collagen comes from tendon, dermis, skin or pericardium of bovine, porcine or human origin. [6] 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. [1] Studies have shown that cross-linking is associated with prolonged biodegradation, reduced epithelial migration, decreased tissue integration and decreased vascularization. [14,15]
Disadvantages of resorbable membranes

1. Lack of space making ability compared to non resorbable maebranes.
2. Unpredictable degradation profile.
3. Risk of disease transmission. [1,2,6,7]

Considering the drawbacks of both resorbale and non resorbale membranes, quest for alteranate membranes arose. Several research groups investigated the possibility of using membranes with functionally graded, multilayered structures to maintain sufficient mechanical properties, predictable degradation rate, and bioactive properties using calcium phosphate based nanoparticles, electrospinned membranes, growth factors, anctibacterials incorporatd in barrier membranes to inhibit bacterial colonization.[16-19]

Electrospinning (e- spinning) for membranes

Formhals first introduced electrospinning in 1938.[20] Membranes produced by this process are biocompatible, degradable, and resemble the arrangement of native extracellular matrix.[2] 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. [21-22]

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.[23]

Functionally graded multilayered membranes

These were intended to utilize a graded structure with composition and structural gradients that meet the local functional requirements. Functionally graded three layered membrane from PLGA, collagen, nanohydroxyapatite is fabricated by casting method.[2] It is designed with one side constituted by 8% nano carbonated hydroxyapatite/collagen/poly (lactic-co-glycolic) acid porous membrane allowing cell adhesion, and opposite face with a smooth PLGA nonporous film. Functionally graded matrix consisted of a core layer (CL) and two functional surface layers (SL) interfacing bone (nanohydroxyapatite, n-Hap) and epithelial (metronidazole,MET) tissues. The CL comprises a poly (d,l-lactide-co-caprolactone) (PLCL) layer surrounded by two composite layers composed of a gelatin/polymer ternary blend.(PLCL:PLA:GEL). [2]

Membranes with antibacterial properties

Antibacterial substances were incorporated to reduce the bacterial contamination of regenerating wound [2]. 25%wt of metronidozale benzoate incorporated into the layer interfacing with epithelial tissue (PLA:GEL+MET) showed reduced bacterial growth and biofilm formation[1] It was demonstrated that incorporation of amoxicillin or tetracycline into various GTR membranes may enhance the attachment of periodontal ligament cells in the presence of oral pathogens streptococcus mutans and Aggregatibacter Actinomycetemcomitans (A.a).[24] Chou et al compared the antibacterial effects of membrane with and without zinc phosphate and showed a significant decrease in activity of A.a for membranes with zinc phosphate. A recent study revealed higher osteogenic activity with membrane based on silver hydroxyapatite – titania/polyamide nanocomposite when compared to e-PTFE.[25]

Barrier membranes with growth factor release

Growth factors have an essential role in healing process and tissue formation, repair, angiogenesis, chemotaxis and cell proliferation. Several bioactive molecules such as PDGF, TGF-1, BMP-2 EMD have shown positive results in stimulating periodontal regeneration.[2] PDGF-BB loaded PLLA membrane potentially enhanced GTR efficacy in rat calvarial defects.[26]

Platelet rich fibrin (PRF) membrane

Platelet granules are a reservoir of many growth factors that play a role in hard and soft tissue repair mechanisms. Because of its cost effectiveness, relative safety, autologous nature, PRF offers a pleasant alteranative compared to commercially available membranes. Studies by Gassling et al have shown superior results when membranes were used as a scaffold for human periosteal proliferation compared to collagen.[27]

Amniotic membranes (AM)

AM is a thin, tough, transparent, avascular composite membrane composed of three major layers: a single epithelial layer, a thick basement membrane, and an avascular mesenchyme consisting mainly of collagen. The basement membrane of the amnion is very similar to the basement membrane found in the other parts of the body like the conjunctiva, gingival. [28] AM contains many growth factors and exhibit anti inflammatory, anti bacterial properties and has been reported to reduce scarring. [29]

Dan J. Holtzclawies et al in a case series on 64 patients treated with amniotic chorionic membrane (ACM) combined with GTR therapy revealed an average probing depth reduction of 5.06 – 1.37 mm and clinical attachment level improvement after 12 months of follow-up. All patients were treated by thorough degranulation of intrabony periodontal defects and placement of bone allograft covered by ACM. The results of this retrospective observational report are promising and warrant additional controlled, long-term studies to further evaluate the effectiveness of ACM for combination GTR treatment of periodontal intrabony defects.[30]

IV. Summary And Conclusion

This paper reviews the various membranes used in GTR and GBR. Significant advancement has been made since the original e-PTFE membranes, and improvements are continuously being made regarding their

mechanical properties and degradation rates. GTR procedure has been, and still is widely employed in periodontal practice and established as a basic technique in periodontal regenerative medicine. Although the indications of GTR membrane in periodontal regeneration are limited to three wall and class II furcation defects, research efforts are pushing the limits to include more advanced periodontal defects with a predictable outcome. It seems likely that a combination of several techniques (such as GTR in association with bone grafts) may offer more chances for a beneficial outcome, although substantial evidence is still lacking. The next generation of membranes is expected to combine more functional biomolecules projected to increase the success of GBR therapy. Third generation barrier membranes with additional antimicrobial action and calcium phosphate incorporation or as a source of growth factors offers exciting possibilities to the overall usefulness to the membrane. It is clear that the "ideal" membrane for use in periodontal regenerative therapy has yet to be developed. Based on a graded-biomaterials approach, it is hypothesized that a biologically active and spatially designed and functionally graded nanofibrous material that mimics closely the native ECM could succeed as the next-generation of GTR/GBR membranes for periodontal tissue regeneration.

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