How to Cite:
Bhojak, A., Arora, S. A., Kalsi, R., Barman, C., Peku, H., & Singh, K. S. (2022). Bioengineered membranes-past, present and future in tissue regeneration. *International Journal of Health Sciences*, *6*(S2), 2336–2355. https://doi.org/10.53730/ijhs.v6nS2.5537

Bioengineered membranes-past, present and future in tissue regeneration

Ankita Bhojak
Post Graduate student, Department of Periodontics, ITS Dental College, Hospital and Research Center, Greater Noida, Uttar Pradesh
Email: ankitaijdr@gmail.com

Sachit Anand Arora
Senior Professor and Principal, Department of Periodontics, ITS Dental College, Hospital and Research Center, Greater Noida, Uttar Pradesh
Email: Prin.dntl.gn@its.edu.in

Rupali Kalsi
Professor and Head of Department, Department of Periodontics, ITS Dental College, Hospital and Research Center, Greater Noida, Uttar Pradesh
Email: rupalikalsimathur@gmail.com

Chikku Barman
Post Graduate student, Department of Periodontics, ITS Dental College, Hospital and Research Center, Greater Noida, Uttar Pradesh
Email: Chikku_mds19_22_gn@its.edu.in

Hiba Peku
Post Graduate student, Department of Periodontics, ITS Dental College, Hospital and Research Center, Greater Noida, Uttar Pradesh
Email: Hibap2020@its.edu.in

Kumar Saurav Singh
Reader, Department of Periodontics, ITS Dental College, Hospital and Research Center, Greater Noida, Uttar Pradesh
Email: dr.kumarsauravsingh@its.edu.in

***Abstract*---**Regeneration of soft and hard tissue defects, although not impossible, is not always a predictable outcome. Tissue Engineering has shown to be successful in regenerating such defects with the objective of development of a new functional tissue structure which is either scaffold-based or not. Currently, the barrier membranes are being used as a physical barrier for the growth of unwanted epithelial and connective tissue cells while promoting the growth of desired cells

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
***Corresponding author**: Bhojak, A.; Email: ankitaijdr@gmail.com*
Manuscript submitted: 27 Jan 2022, Manuscript revised: 18 Feb 2022, Accepted for publication: 09 March 2022

like those of periodontal ligament and bone cells, which is quite appreciable. But due to the various drawbacks of the conventional membranes, TE has led to the development of functionally enhanced membranes processed by a variety of techniques and materials which overcome the demerits of the currently used barrier membranes. The objectives of this review are to compare the resorbable and non-resorbable barrier membranes used in tissue regeneration, their properties, applications, merits and demerits and future advances.

Keywords---guided tissue regeneration, resorbable membrane, periodontal regeneration, tissue engineering.

Introduction

Tissue Engineering (TE) is an interdisciplinary field involving engineering, material science, biology, chemistry, physics, and medicine, which involves the utilisation of the principles and methods of engineering and medical sciences to help in the initiation of biological alternatives in restoring, maintaining or improving the activity of lost tissues and organs. TE includes three essential components- cells, scaffolds, and factors that induce growth or biomolecules to induce regeneration of lost tissues (Figure 1), proposed by Langer and Vacanti in 1993.(Langer & Vacanti, 1993) The basic objective behind TE is the appearance of latest functional tissue structure which is either scaffold-based or not and can be arranged like tissue engineered products (TEPs) or tissue engineered constructs (TECs).

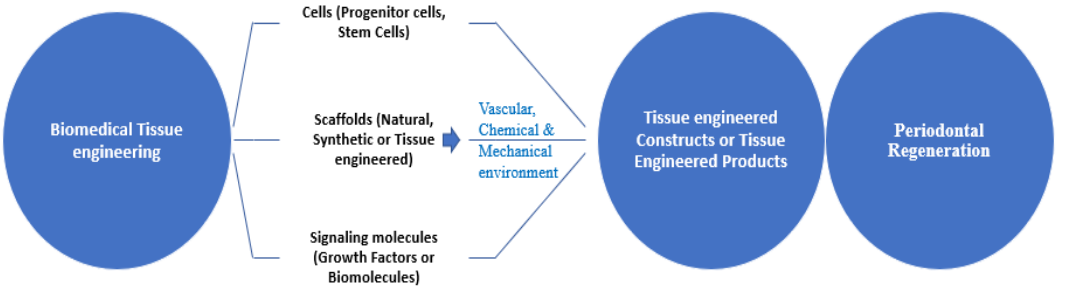

Figure 1: Three essential components of biomedical tissue engineering- cells, scaffolds, and signalling molecules

The scaffold performs via a 3D substructure which colonize cells, which should be able to proliferate, differentiate, form a pattern and operatively useful tissue with convenient outline.

The major roles of 3D substructure are:

1. It should provide physical support, to avoid the disintegration of local tissue to the trauma site, or act as a backbone which maintains the form of the defect or deformity.

2. To produce extracellular matrix, adhesion, migration, multiplication of cells, acting as a 3D substratum.
3. It should act as a wall to selectively restrict unwanted drifting of the tissues to the deficient space.
4. It should potentially act as a medium for releasing growth factors.

The purpose of scaffolds in periodontal regenerative therapy has been suggested with the notion of "Guided Tissue Regeneration (GTR)" which is a procedure attempted to regenerate lost periodontal structures through differential tissue responses as defined in "1996 World Workshop in Periodontics".(Melcher, 1976) There are various bioengineered membranes that have been evolved and studied as part of these two procedures to prevent the unwanted epithelial and connective tissue cells from occupying the deformities, while allowing desired tooth supporting cells to selectively invade into the deficient space. (Figure 2)

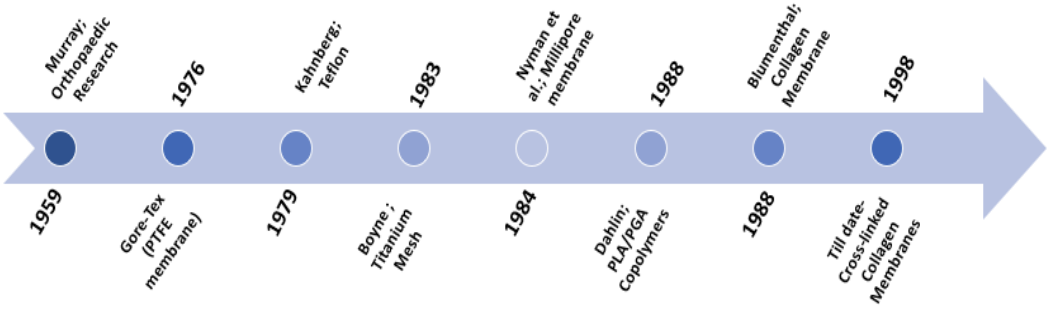

Figure 2: Historical Aspect of Barrier Membranes

The first membrane had been accounted by Younger (Dental Cosmos of 1904), which was made of Japanese paper immersed in liquid cellulose utilized to frame an ensuring divider over the roots and the edge of the gingiva. Prichard (Prichard, 1957) further expressed that the cells very crucial for regenerating tooth supporting structures are accessible in the zone that outskirt the bony deformity. This prompted Melcher in 1976 who arranged the four tissue composes which will invade the root plane. Further examinations in the 1970's and 80's bolstered Melcher's idea.

Caton et al(Caton et al., 1982) inspected healing following four distinct modalities of periodontal treatment (scaling and root planing, adjusted Widman fold with debridement alone or in mix of autogenous or synthetic bone graft). The final products exhibited the base of long junctional epithelium between the connective tissue and the surface of root after healing. This finding upheld other comparative investigations that conventional nonsurgical and surgical periodontal treatments ordinarily brought about repair as opposed to regeneration.(Caton et al., 1982; Melcher, 1976; Scantlebury, 1993)

The impacts of epithelial rejection were additionally explored by Nyman in 1980(Nyman et al., 1982). At the point when root was permitted to contact alveolar bone, the roots of the tooth showed ankylosis and resorption. At the point when root was permitted to contact the gingival or mucosal tissue and the root

plane had been denuded of periodontal fiber, the resorption of root was seen. These perceptions proposed that prohibition of gingival epithelium alone does not advance periodontal regeneration. He further studied Millipore filter in 1982 and observed that the tendon cells (PDL) of the periodontal supporting tissues have a sensible potential for rejuvenation of tooth supporting tissues.(Jacob, 2017)

Principles

Long back, Melcher(Melcher, 1976) and Karring(Nyman et al., 1982) gave a hypothesis, that suggests that selected population of cells residing in the periodontium can be regenerated only when the desired bone forming cells are allowed to occupy a periodontal wound first by prohibiting unwanted gingival fibroblasts or epithelial cells to enter the defect site of the lost tissues in the course of healing phase. This requisite has generated a drive for the origin of barriers in the form of barrier layer, for tissue regeneration.

However, to achieve a successful clinical outcome, 4 major principles which should be followed: healing following primary intentions, angiogenesis, space creation/maintenance, and stability of both the preliminary blood clot and implant fixture as given by 2 researchers, Wang and Boyapatti (Wang & Boyapati, 2006), i.e., the PASS principle.

1. PRIMARY CLOSURE: An environment uninterrupted by microbial or mechanical insult is attained by passive wound closure which also results in lesser reepithelialization, collagen formation and remodeling, wound contraction, tissue remodeling.
2. ANGIOGENESIS: New bone composition has an intimate relation with newly developing blood vessels which occurs after the commencement of clot formation.
3. SPACE CREATION/MAINTENANCE: To provide plentiful of space for bone regeneration process is a prerequisite of GBR to allow slow migration of osteoblasts to enter and proliferate in the lacerated wound, resulting in enhanced bone formation.
4. STABILITY: When the preliminary coagulation and retention of wound are achieved, wound healing phase will occur predictably which brings in certain bone production.

Ideal Requisites of Bioengineered Barrier Membranes

For a barrier layer to be acceptable and function effectively, the membrane has to fulfil certain essential measures:

1. Bio-compatibility-The composition of the bioengineered membrane barrier should not initiate an immune response, hypersensitivity or chronic inflammation that can jeopardize healing and present threat to the neighbouring tissues.
2. Cell- occlusiveness -The material should wall off unwanted cells from invading the defect space adjacent to the root surface.
3. Tissue integration- The membrane should maintain immobility and stability to the overlying tissue covering the deformities and help avoiding

active epithelial proliferation to resurface the body of material or protect the material.

4. Space-making- With the purpose to permit the invasion of tissue movement from the desired tooth supporting tissues the barrier medium should be capable of maintaining a space alongside the root plane.
5. Clinical manageability- It should be supplied in a configuration which is easy for the operator to trim and to place. The barrier layer should have capability to stay in its position during the patient-related various kinds of muscular movement during activities.

Classification of Bioengineered barrier membranes

The terms "nonresorbable or non- biodegradable" and "resorbable or self-degradable" are based upon their degradation properties in human trials and will be discussed in this analysis for the comfort of reading (Figure 3).

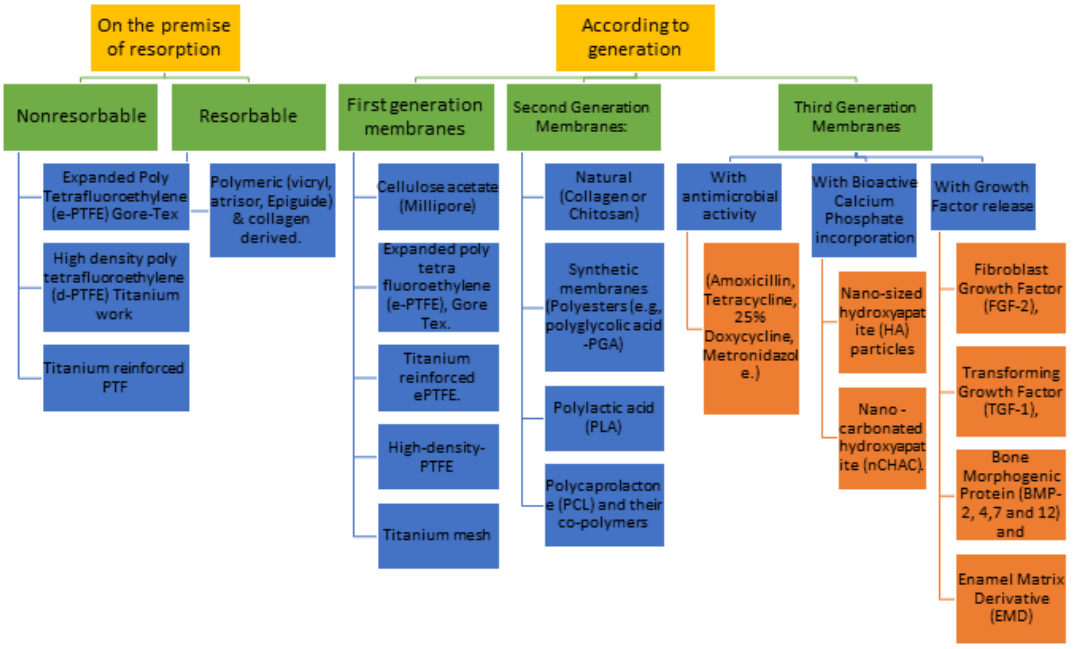

Figure 3: Classification of various barrier membranes

Generally, non-resorbable membranes (Table 1) have superior space maintenance property as opposed to biodegradable membranes. Types of resorbable or biodegradable membrane used for dooming into a barrier are available namely: synthetic (Table 2) and natural biomaterials (Table 3).

In general, natural biomaterials show superlative biologically acceptability with binding sites of cells, while having the complication of lower mechanical strength. Nonetheless, synthetic biomaterials hold the properties like controlled rates of constricted destruction and mechanical characteristics, but lack biological acceptance (cellular binding sites). Principally, the degeneration rate should be moderate, for the reason that rapid degeneration would cause early mechanical

loss while retarded degradation prevents novel tissue ingrowth. The objectives of this analysis are to compare the bio-resorbable and non-resorbable barrier membranes edged in tissue engineering, their properties, applications and also the future advances besides the outcomes of periodontal treatments.

Various bioengineered barrier membranes and their properties[7,8]

Table 1: Non- resorbable bioengineered barrier membranes

Membrane	**Commercial Name**	**Manufacture & Nation**	**Properties (Pore size)**	**Composition**	**Advantage**	**Disadvantage**
e-PTFE*	Gore-Tex	W. L. Gore & Associates, Inc., USA	0.1-0.3 µm pores	PLA, poly (DL-lactide) (PLA)	Provide space for new bone growth	Roughness causes bacterial adhesion
	Gore-Tex-TI	W. L. Gore & Associates, Inc., USA		Titanium, PLA, Fluorine	Rigidity	Second surgery is required
	High-density Gore-Tex	W. L. Gore & Associates, Inc., USA	0.1-0.2 µm pores	PLA	No need for primary coverage	Second surgery causes tissue trauma
d-PTFE†	Cytoplast	Osteogenics Biomedical., USA	0.1-0.3 µm pores		Primary closure is not required	Risk of membrane and biomaterial exfoliation
	TefGen FD	Lifecore Biomedical, Inc., USA	0.2–0.3 µm pores		Easy to detach	Require fixation pins for larger defects
	Non-resorbable ACE	Surgical supply, Inc., USA	0.1-0.2 µm pores 0.2 mm thick		Limited cell proliferation	Risk of membrane and biomaterial exfoliation
	Ti-Micromesh ACE	Surgical supply, Inc., USA	1,700 mm pores 0.1 mm thick	Titanium, PLA	Space maintenance	Stiffness

Titanium Mesh	Tocksystem Mesh	Tocksystem, Italy	0.1–6.5 mm pore 0.1 mm thick		Rigidity	Stiffness, more complex surgery required
	Frios BoneShields	Dentsply Friadent, Germany	0.01- 0.03 mm pores 0.1 mm thick		Plasticity	Stiffness, more complex surgery required
	M-TAM		1,700 mm pores 0.1–0.3 mm thick		Space maintenance	Stiffness, more complex surgery required

* e-PTFE- expanded polytetrafluoroethylene , †dPTFE- Dense polytetrafluoroethylene

Table 2: Synthetic resorbable bioengineered barrier membranes

Membrane	**Commercial Name**	**Manufacture & Nation**	**Composition**	**Properties**	**Resorption Period**
Synthetic resorbable membranes	OsseoQuest	W. L. Gore & Associates, Inc., USA	Hydrolyzable polyester	Good tissue integration	16–24 weeks
	Biofix	Bioscience Oy, USA	Poly Glycolic Acid	Isolate the space from cells from soft tissue and bacteria	24–48 weeks
	Vicryl	Johnson & Johnson, USA	Polyglactin 910 Poly Glycolic Acid 9:01	Well adaptable	4–12 weeks
	Atrisorb	Tolmar, Inc., USA	Poly-DLlactide and solvent	Custom fabricated membrane “Barrier Kit”	36–48 weeks
	EpiGuide	Kensey Nash corporation, USA	Poly-DLlactic acid	Self-supporting Support developed blood clot	6–12 weeks

	Resolut	W. L. Gore & Associates, Inc., USA	Poly-DLlactide/ Co-Glycolid	Good tissue integration Separate suture material	10 weeks
	Vivosorb	Polyganics B.V. NL	DL-lactide-ε-caprolactone	Act as a nerve guide	8 weeks

Table 3: Naturally derived resorbable bioengineered barrier membranes

Membrane	**Commercial Name**	**Manufacture & Nation**	**Composition & Source**	**Properties**	**Resorption Period**	**Collagen type**
Natural biodegradable material	Plasma rich in growth factors (PRGFEndoret)	BTI Biotechnology Institute, Vitoria, Spain	Patients' own blood	Abundant growth factors and proteins mediate cell behaviors	8 weeks	-
				Different formulations for various usages		
				Total resorption		
	Bio-Gide	Osteohealth Company, SUI	Porcine I and III	Mechanical strength: 7.5 MPa	24 weeks	Type I & III
	Ossix	OraPharma, Inc., USA		Increase the woven bone	16-24 Weeks	Type I
	Bio-mend	Zimmer, USA	Bovine I	Fibrous network Modulate cell activities	8 weeks	
	Biosorb membrane	3M ESPE, USA		Tissue integration	26–38 weeks	
	Neomem	Citagenix, CAN		Double-layer product	26–38 weeks	
	OsseoGuard	BIOMET 3i, USA		Improve the aesthetics of the final prosthetics	24–32 weeks	

Factors affecting clinical outcomes of biomedical tissue engineering

Regeneration of deformities of mucosa and bony tissues, although not impossible, doesn't always show a predictable outcome. Various agent associated with patient or some local agents may be engaged for the outcomes in respond to GTR. To intensify the predictability and clinical outcome of GTR, condition of the subject, the class of deformities, and the invasive or surgical procedure should be kept in mind during treatment planning. Various reasons have been accountable for the favourable result of regeneration of periodontal lost tissues via tissue engineering involving GTR therapy.

- Plaque Control and Microbial Contamination: Studies has proven that defect sites having barrier membrane are more likely to get accumulated by pathogenic bacteria than those treated without membranes during the active healing period. The adverse nature of plaque accumulation has been determined in longitudinal studies of GTR procedures.
- Defect Morphology and Tooth Anatomy: In some studies, based on factors affecting intraosseous defects' healing, treated by barrier application, the successful outcome of therapy is affected by increased depth of the intrabony portion of the deformity.
- Exposure of the barrier membrane: The postoperative decease of the thin soft tissue flap housing the barrier layer and covering the defect with too thick flap, might lead to soft tissue tension which can result in dehiscence and can subsequently lead to barrier membrane exposure.
- Defect Space Maintenance: Incorporation of bone graft materials such as cortico-cancellous osseous block graft, tenting screws, osseous particulate grafts, and binding agents help in space sustenance part from providing rigidity to the membrane.
- Gingival Flap Thickness: A prerequisite of >1.5 mm gingival tissue thickness is essential to prevent flap degeneration. In the maxillary front teeth region, GTR or GBR performed in main bone defects with delicate or thin mucosal tissue flaps can cause dropping of tissue into the deformity.
- Diabetes: Due to poor regulation of glucose metabolism on the process of inflammation, a delay in process of wound-healing is most likely to happen.
- Smoking: In certain studies, it's been proven that after GTR procedure, in smokers (~10 cigarettes per day) typically less clinical outcome in the periodontal tissue regeneration is achieved in contrast to non-smokers.

Box 1: Indications of bioengineered membranes:

- Larger bone defects (>5mm) with minimum 2 or 3 bone wall support.
- Cul-de-sac type defects in multi-rooted teeth
- When the residual intra-osseous defect is larger than diameter of the implant or a parallel defect is present with a stable implant placement, barrier membranes can help achieve both, bone fill up and bone augmentation.
- Fenestrations

Box 2: Contraindications of bioengineered membranes:

- In cases where soft tissue vascularity is compromised
- Minimal remaining tooth supporting structures
- Horizontal bone defects
- Mucosal perforation

Box 3: Advantages of bioengineered membranes:
There are three observable functions served by membrane barrier in GTR therapy

a) Firstly, they prevent the invasion of unwanted epithelial cells and fibroblasts of connective tissue from overlying tissue, thereby allowing formation of new blood vessels and new bone.
b) Secondly, the membrane stabilizes the graft material to augment bone and blood clot which allows better adaptation and space maintenance.
c) Thirdly, the membrane act as a graft preservation device which reduces the graft resorption.

Box 4: Disadvantages of bioengineered membranes

a) For surgical removal of non-resorbable membrane a second stage surgery is needed.

b) No definitive time has been standardized for taking off non-degradable membrane post operatively.

c) There is no role of non-resorbable membranes in soft tissue closure as they decrease collagen synthesis and Glycosaminoglycan (GAG) accumulation contributing in delayed healing.

d) Removal of Titanium-based meshes has proven to be detrimental as they have the potency for gingival tissue perforation.

e) Membrane-lead post-operative infection and inflammation are occasionally observed in regeneration therapy.

f) The degradable membranes have no certainty in terms of resorption period and amount. Early resorption can cause gradual loss of strength allows unwanted tissue invasion, which leads to delay bone regeneration.

Discussion & Related Studies

In a retrospective meta-analysis performed by Lim and colleagues(Lim et al., 2018), various membranes were compared on the basis of wound-healing

complications and they inferred that statistically there was no significant difference between degradable or non-degradable membrane.

Clinical Trials

Furcation involvement (Grade II) according to Glickman's Classification

Few comparative studies on self-degradable and non-degradable membranes used in the treatment of multirooted tooth's root furcation deformity revealed that on intragroup comparison, both resorbable and nondegradable membrane groups showed significant improvement in soft and hard tissue parameters. (Caffesse and colleagues,(Caffesse et al., 1997) (1997), Scott and colleagues (Scott et al., 1997), Eickholz and colleagues (P Eickholz et al., 1997), and Karapataki and colleagues (Karapataki et al., 1999). In a randomized multicenter study of 38 patients done in 1995 by Hugoson and colleagues (Hugoson et al., 1995) it was found that clinical attachment level in both horizontal and vertical direction in the resorbable membrane group showed statistically significant results, whereas, clinical attachment in nonresorbable membrane group showed improvement in the vertical direction only. Also, gingival recession was significantly higher in the nonresorbable membrane group. In a 10-year study, Eickholz and colleagues (Eickholz et al., 2006) concluded that on intergroup comparison between both the types of membranes for the treatment of Grade II furcation, gain in the horizontal attachment was achieved but it was not statistically significant. Jalaluddin et al. (Jalaluddin et al., 2019) observed a positive correlation between both the treatment therapies of furcation involvement, however, the biodegradable barrier membrane showed better results as far as horizontal bone augmentation was concerned. A study done by Kaushal et al. (Kaushal et al., 2016) displayed similar results. Another study done by Mehrotra et al. (Mehrotra et al., 2019), demonstrated successful clinical results with hydroxyapatite and collagen fibers, used together with PGA and PLA copolymer. It is seen that Glickman Class III through-and-through furcation defects respond poorly to GTR techniques. (P Eickholz et al., 1998)

Intrabony periodontal deformity

In the treatment of intrabony periodontal defects, many clinical trials have failed to obtain statistically significant differences in reduction in probing depth, gain in clinical attachment level, and bone fill on comparing resorbable and nonresorbable barrier membranes.(Christgau et al., 1997; Corinaldesi et al., 2011; P Eickholz et al., 1997). Pretzl and colleagues (Pretzl et al., 2008), conducted a 10- year study where there was gain in stable vertical attachment while using both self-degradable and non-degradable membranes in the treatment of bone loss below alveolar crest but the clinical results were statistically non-significant. Improvement in the clinical results were observed by Kothiwale S. et al (Kothiwale & Ajbani, 2018) during implementation of fetal embryonic sac- chorionic membrane in gingival surgery showing an additional anti-inflammatory effect in long term prognosis. Insignificant difference between the two treatment groups were observed by Srivastava S et al. (Srivastava et al., 2015) involving the resultant efficacy of both graft and membrane.

Ridge preservation procedures

As for cases involving the employment of both the membranes to preserve the resorption of the alveolar ridge no difference was observed statistically in any direction by Arbab and colleagues (Arbab et al., 2016), in their study. Clinically and histological evaluation revealed that there was no histological role of any membrane in alveolar ridge preservation.

Site of Implant development

In a 6- year study by Merli et al. (Merli et al., 2014), employed to check the efficacy of self-degradable and non-degradable membrane along with dental implant placement for replacement of lost tooth, it was concluded that statistically the gain in vertical bone component was same for both the treatment groups.

Maxillary sinus augmentation

When involved in the treatment for maxillary sinus augmentation the comparison between degradable and non-degradable GTR membrane showed uninterrupted healing and successful closure of lateral walls of sinus was observed in both the groups comprising of degradable and non-degradable GTR membrane. However, an excess of fibrous connective tissue growth was observed microscopically in the bone samples obtain from the self-degradable membrane group. (Avera et al., 1997)

Peri-implant bony defects

Treatment modality of bone deformity involving dental implant showed statistically insignificant difference when concerned with clinical parameter, while drawing comparative outcomes of self-degradable and non-degradable membranes correlating particulate bone grafts. (Carpio et al., 2000; Zitzmann et al., 1997)

Root Coverage Procedures in Soft Tissue Defects

According to the results of a study undertaken by Pelekos et al. (Pelekos et al., 2019), esthetic procedure involving soft tissue advancement over the denuded root using collagen membrane, yielded better results in terms of gingival tissue contour and texture. Mahajan et al. (Mahajan et al., 2018) in an independent study inferred that the differences between recession of gingiva and level of attachment of tooth supporting tissues were insignificant after employing healiguide membrane. There was increase in soft tissue thickness in the group that employed healiguide membrane in their treatment. However, a statistically significant increase ($P < 0.05$) in soft tissue thickness was observed in the treatment group using Healiguide membrane when compared with control group. Kapare K. et al. (Kapare et al., 2016) found that there was a greater reduction of gingival RD with the efficacy of collagen membrane as compared to the control group.

Future Focus

Tissue Engineering has made it possible to make newer barrier membranes by a variety of techniques and by combining various kind of biomimetic substances. There are a number of methods of fabrication of scaffolds, like, 3-D Printing, Electrospinning etc, which are out of scope of this review. Recently the advancements of GTR barrier membranes concentrates on the maximization of properties like mechanical strength, resorption and affiliates new functions of GTR membranes which have been achieved by preparing membranes from composites with addition of different biomaterials.(J. Wang et al., 2016) Moreover, the composites of natural and synthetic polymers consolidated the bioactive recognition of natural materials and improved mechanical strength of synthetic membranes (He et al., 2017; Masoudi Rad et al., 2017; J. Wang et al., 2016). GTR membranes as drug delivery agents have shown to be beneficial in tissue regeneration (Caballé-Serrano et al., 2019; Lee et al., 2016). Anti-bacterial drugs can be integrated into barrier membranes to impedes local contamination and inflammation, therefore, facilitating periodontal tissue formation (Caballé-Serrano et al., 2019). Multi-layered GTR membranes have also shown to enhance tissue regeneration with different functions in each layer. Recently, many complex biologic materials have recently been used to function like barrier membranes. Such a commercially obtainable membrane, BioXclude, derived from human placenta, which contains growth factors and interleukins necessary for blood vessel formation has shown positive influence the healing outcome (Chi et al., 2015).

Hybrid and multiphasic Scaffolds: To overcome the rapid resorption rate before true tissue formation and/or remodeling of the currently obtainable biodegradable membranes various 3D Bio-printed membranes are being processed.

Bioengineered Multiphasic Scaffolds: These are designed in layers, with incorporation of molecules or factors which aid in growth which modulate the mechanical, in order provide a suitable membrane for a particular tissue types, such as, Transforming Growth Factor-β loaded PLA and alginate hybrid combination membrane, which provide a medium long- term release of growth factor. To attain better mechanical stabilization of defect wound and accelerated wound healing, bioactive agents loaded onto a degradable Allogenic membrane is being developed (Bubalo et al., 2012).
A triphasic scaffold consisting of collagen sandwiched between nano-carbonated hydroxyapatite and PLA membrane is currently under investigation. A commercially available product by the name of Atrisorb, (Atrix Laboratories Inc.,) has been successfully used as a hydrogel (Kim et al., 2011).

Bioengineered Membranes Incorporated with Antibacterial Agents

For around fifty years, various antimicrobials which are selectively bactericidal properties like Metronidazole (MNZ) and N-methylpyrrolidone (NMP) have been in regular use. Xue et al.(Xue et al., 2014) stated that the membranes incorporated with > 5% MNZ prevents bacterial growth while acting as a carrier for drug delivery locally. Tetracycline hydrochloride and MET have been incorporated by other investigators into various membranes.

Bioengineered Membranes Incorporating Growth Factors

Various studies have put forth a positive outcome in regeneration of lost tooth-supporting structures by the application of membranes containing platelet-derived growth factors (PDGF) and Bone Morphogenetic Proteins (BMPs)(Bottino & Thomas, 2015). It has also been cited in studies, that Enamel Matrix Derivative (EMD; Emdogain, Straumann AG, Basel, Switzerland) along with various scaffolds has shown an increase in the regeneration of lost tooth-supporting tissues.

Human Placental Embryonic Bioengineered Membranes

More recently, biologically derived tissues from the human placental amnion chorion have emerged as resorbable allograft (BioXclude; Snoasis Medical, Golden, CO, USA). They possess minimal risk of rejection by the recipient's body due to their thorough preparation by a sequence of substances under optimal temperatures and conditions. When compared e-PTFE membrane, facia lata, the Pericardium membrane resulted in better bone regeneration (Oates et al., 1993).

Conclusion

Various advancements in increments, have taken place in the era of biomedical tissue engineering. Non resorbable membranes have enough strength to allow space preservation and stop collapse of its contour along with restraining the mucosal compression. It is indicated to use the aforementioned membrane where vertical growth regeneration is desired. The biggest drawback of non- degradable membranes are early exposure, contamination, and risk of displacement of the graft during second surgery required to take off the membrane barrier from the treated site.

The biggest benefit of degradable membranes is in causing less tissue damage and lesser pain and discomfort. But the timing and degree of resorption of these membranes are unpredictable. There may be loss of membrane integrity and space collapse due to its early resorption. This review attempts to highlight various studies which have shown results in demonstrating the efficacy and practical utilization of both the membranes in lost tissue regeneration. It is evident that single type of barrier will not fit all clinical requisites with their considerable drawbacks, and further research on this valuable clinical technique is mandated.

References

1. Arbab, H., Greenwell, H., Hill, M., Morton, D., Vidal, R., Shumway, B., & Allan, N. D. (2016). Ridge Preservation Comparing a Nonresorbable PTFE Membrane to a Resorbable Collagen Membrane: A Clinical and Histologic Study in Humans. *Implant Dentistry*, *25*(1), 128–134. https://doi.org/10.1097/ID.0000000000000370
2. Avera, S. P., Stampley, W. A., & McAllister, B. S. (1997). Histologic and clinical observations of resorbable and nonresorbable barrier membranes used in maxillary sinus graft containment. *The International Journal of Oral & Maxillofacial Implants*, *12*(1), 88–94.

3. Bottino, M. C., & Thomas, V. (2015). Membranes for Periodontal Regeneration--A Materials Perspective. *Frontiers of Oral Biology*, *17*, 90–100. https://doi.org/10.1159/000381699
4. Bubalo, M., Lazić, Z., Matić, S., Tatić, Z., Milović, R., Curcin, A. P., Djurdjević, D., & Loncarević, S. (2012). The impact of thickness of resorbable membrane of human origin on the ossification of bone defects: a pathohistologic study. *Vojnosanitetski Pregled*, *69*(12), 1076–1083.
5. Caballé-Serrano, J., Abdeslam-Mohamed, Y., Munar-Frau, A., Fujioka-Kobayashi, M., Hernández-Alfaro, F., & Miron, R. (2019). Adsorption and release kinetics of growth factors on barrier membranes for guided tissue/bone regeneration: A systematic review. *Archives of Oral Biology*, *100*, 57–68. https://doi.org/10.1016/j.archoralbio.2019.02.006
6. Caballé-Serrano, J., Munar Frau, A., Ortiz-Puigpelat, O., Soto-Peñaloza, D., Penarrocha, M., & Hernández-Alfaro, F. (2018). On the search of the ideal barrier membrane for guided bone regeneration. *Journal of Clinical and Experimental Dentistry*, *10*. https://doi.org/10.4317/jced.54767
7. Caffesse, R. G., Mota, L. F., Quiñones, C. R., & Morrison, E. C. (1997). Clinical comparison of resorbable and non-resorbable barriers for guided periodontal tissue regeneration. *Journal of Clinical Periodontology*, *24*(10), 747–752. https://doi.org/10.1111/j.1600-051x.1997.tb00192.x
8. Caffesse, R. G., Smith, B. A., Castelli, W. A., & Nasjleti, C. E. (1988). New attachment achieved by guided tissue regeneration in beagle dogs. *Journal of Periodontology*, *59*(9), 589–594. https://doi.org/10.1902/jop.1988.59.9.589
9. Carpio, L., Loza, J., Lynch, S., & Genco, R. (2000). Guided bone regeneration around endosseous implants with anorganic bovine bone mineral. A randomized controlled trial comparing bioabsorbable versus non-resorbable barriers. *Journal of Periodontology*, *71*(11), 1743–1749. https://doi.org/10.1902/jop.2000.71.11.1743
10. Caton, J., Proye, M., & Polson, A. (1982). Maintenance of healed periodontal pockets after a single episode of root planing. *Journal of Periodontology*, *53*(7), 420–424. https://doi.org/10.1902/jop.1982.53.7.420
11. Chi, C. S., Andrade, D. B., Kim, S. G., & Solomon, C. S. (2015). Guided tissue regeneration in endodontic surgery by using a bioactive resorbable membrane. *Journal of Endodontics*, *41*(4), 559–562. https://doi.org/10.1016/j.joen.2014.10.018
12. Chopra, A., & Thomas, B. S. (2013). Amniotic membrane: A novel material for regeneration and repair. *J Biomim Biomater Tissue Eng*, *18*(1), 1–8.
13. Christgau, M., Schmalz, G., Wenzel, A., & Hiller, K. A. (1997). Periodontal regeneration of intrabony defects with resorbable and non-resorbable membranes: 30-month results. *Journal of Clinical Periodontology*, *24*(1), 17–27. https://doi.org/10.1111/j.1600-051x.1997.tb01179.x
14. Corinaldesi, G., Lizio, G., Badiali, G., Morselli-Labate, A. M., & Marchetti, C. (2011). Treatment of intrabony defects after impacted mandibular third molar removal with bioabsorbable and non-resorbable membranes. *Journal of Periodontology*, *82*(10), 1404–1413. https://doi.org/10.1902/jop.2011.100466
15. Dahlin, C., Linde, A., Gottlow, J., & Nyman, S. (1988). Healing of bone defects by guided tissue regeneration. *Plastic and Reconstructive Surgery*, *81*(5), 672–676. https://doi.org/10.1097/00006534-198805000-00004

16. Dahlin, C., Sennerby, L., Lekholm, U., Linde, A., & Nyman, S. (1989). Generation of new bone around titanium implants using a membrane technique: an experimental study in rabbits. *The International Journal of Oral & Maxillofacial Implants*, *4*(1), 19–25.
17. Eickholz, P, Kim, T. S., & Holle, R. (1997). Guided tissue regeneration with non-resorbable and biodegradable barriers: 6 months results. *Journal of Clinical Periodontology*, *24*(2), 92–101. https://doi.org/10.1111/j.1600-051x.1997.tb00473.x
18. Eickholz, P, Kim, T. S., & Holle, R. (1998). Regenerative periodontal surgery with non-resorbable and biodegradable barriers: results after 24 months. *Journal of Clinical Periodontology*, *25*(8), 666–676. https://doi.org/10.1111/j.1600-051x.1998.tb02504.x
19. Eickholz, Peter, Pretzl, B., Holle, R., & Kim, T.-S. (2006). Long-term results of guided tissue regeneration therapy with non-resorbable and bioabsorbable barriers. III. Class II furcations after 10 years. *Journal of Periodontology*, *77*(1), 88–94. https://doi.org/10.1902/jop.2006.77.1.88
20. Gottlow, J., Nyman, S., Karring, T., & Lindhe, J. (1984). New attachment formation as the result of controlled tissue regeneration. *Journal of Clinical Periodontology*, *11*(8), 494–503. https://doi.org/10.1111/j.1600-051x.1984.tb00901.x
21. Hämmerle, C. H., Schmid, J., Olah, A. J., & Lang, N. P. (1996). A novel model system for the study of experimental guided bone formation in humans. *Clinical Oral Implants Research*, *7*(1), 38–47. https://doi.org/10.1034/j.1600-0501.1996.070105.x
22. He, Y., Wang, W., Tang, X., & Liu, X. (2017). Osteogenic induction of bone marrow mesenchymal cells on electrospun polycaprolactone/chitosan nanofibrous membrane. *Dental Materials Journal*, *36*(3), 325–332. https://doi.org/10.4012/dmj.2016-203
23. Hugoson, A., Ravald, N., Fornell, J., Johard, G., Teiwik, A., & Gottlow, J. (1995). Treatment of class II furcation involvements in humans with bioresorbable and nonresorbable guided tissue regeneration barriers. A randomized multi-center study. *Journal of Periodontology*, *66*(7), 624–634. https://doi.org/10.1902/jop.1995.66.7.624
24. Ingber, D. E., Mow, V. C., Butler, D., Niklason, L., Huard, J., Mao, J., Yannas, I., Kaplan, D., & Vunjak-Novakovic, G. (2006). Tissue engineering and developmental biology: going biomimetic. *Tissue Engineering*, *12*(12), 3265–3283. https://doi.org/10.1089/ten.2006.12.3265
25. Ivanovski, S., Vaquette, C., Gronthos, S., Hutmacher, D. W., & Bartold, P. M. (2014). Multiphasic scaffolds for periodontal tissue engineering. *Journal of Dental Research*, *93*(12), 1212–1221. https://doi.org/10.1177/0022034514544301
26. Jacob, S. A. (2017). Guided Tissue Regeneration: A Review. *Journal of Dental Health, Oral Disorders & Therapy*, *6*(3), 67–73. https://doi.org/10.15406/jdhodt.2017.06.00197
27. Jalaluddin, M., Patel, R. K., Almalki, S. A., Nagdev, P., Roshan, R., & Varkey, R. R. (2019). Assessment of the Efficacy of Periodontal Tissue Regeneration using Non-resorbable and Bioabsorbable GTR Membrane-A Clinical Comparative Study. *The Journal of Contemporary Dental Practice*, *20*(6), 675–679.
28. Jensen, O. T., Greer, R. O. J., Johnson, L., & Kassebaum, D. (1995).

Vertical guided bone-graft augmentation in a new canine mandibular model. *The International Journal of Oral & Maxillofacial Implants*, *10*(3), 335–344.
29. Kapare, K., Gopalakrishnan, D., Kathariya, R., Tyagi, T., & Bagwe, S. (2016). Evaluation of efficacy of a novel resorbable collagen membrane for root coverage of Miller's Class I and Class II recession in the maxillary anteriors and premolars. *Journal of Indian Society of Periodontology*, *20*(5), 520–524. https://doi.org/10.4103/0972-124X.207051
30. Karapataki, S., Falk, H., Hugoso, A., Olsson, G., & Slotte, C. (1999). Treatment of class II furcation defects using resorbable and non-resorbable GTR barriers. *Swedish Dental Journal*, *23*(5–6), 173–183.
31. Karfeld-Sulzer, L. S., Ghayor, C., Siegenthaler, B., Gjoksi, B., Pohjonen, T. H., & Weber, F. E. (2017). Comparative study of NMP-preloaded and dip-loaded membranes for guided bone regeneration of rabbit cranial defects. *Journal of Tissue Engineering and Regenerative Medicine*, *11*(2), 425–433. https://doi.org/10.1002/term.1926
32. Karring, T. (1995). Guided tissue regeneration. *Advances in Dental Research*, *9*(3 Suppl), 18. https://doi.org/10.1177/08959374950090030S0901
33. Karring, T. (2000). Regenerative periodontal therapy. *Journal of the International Academy of Periodontology*, *2*(4), 101–109.
34. Karring, T., Nyman, S., Gottlow, J., & Laurell, L. (1993). Development of the biological concept of guided tissue regeneration--animal and human studies. *Periodontology 2000*, *1*, 26–35.
35. Kaur, J., & Bathla, S. C. (2018). Regenerative potential of autologous platelet-rich fibrin with and without amnion membrane in the treatment of Grade-II furcation defects: A clinicoradiographic study. *Journal of Indian Society of Periodontology*, *22*(3), 235.
36. Kim, D., Kang, T., Gober, D., & Orlich, C. (2011). A liquid membrane as a barrier membrane for guided bone regeneration. *ISRN Dentistry*, *2011*, 468282. https://doi.org/10.5402/2011/468282
37. Kostopoulos, L., & Karring, T. (1994). Augmentation of the rat mandible using guided tissue regeneration. *Clinical Oral Implants Research*, *5*(2), 75–82. https://doi.org/10.1034/j.1600-0501.1994.050203.x
38. Kothiwale, S., & Ajbani, J. (2018). Evaluation of anti-inflammatory effect of chorion membrane in periodontal pocket therapy: A clinical and biochemical study. *Journal of Indian Society of Periodontology*, *22*(5), 433–437. https://doi.org/10.4103/jisp.jisp_280_18
39. Langer, R., & Vacanti, J. P. (1993). Tissue engineering. *Science (New York, N.Y.), 260*(5110), 920–926. https://doi.org/10.1126/science.8493529
40. Lee, B.-S., Lee, C.-C., Lin, H.-P., Shih, W.-A., Hsieh, W.-L., Lai, C.-H., Takeuchi, Y., & Chen, Y.-W. (2016). A functional chitosan membrane with grafted epigallocatechin-3-gallate and lovastatin enhances periodontal tissue regeneration in dogs. *Carbohydrate Polymers*, *151*, 790–802. https://doi.org/10.1016/j.carbpol.2016.06.026
41. Li, F., Yu, F., Xu, X., Li, C., Huang, D., Zhou, X., Ye, L., & Zheng, L. (2017). Evaluation of Recombinant Human FGF-2 and PDGF-BB in Periodontal Regeneration: A Systematic Review and Meta-Analysis. *Scientific Reports*, *7*(1), 65. https://doi.org/10.1038/s41598-017-00113-y
42. Liao, S., Wang, W., Uo, M., Ohkawa, S., Akasaka, T., Tamura, K., Cui, F., & Watari, F. (2005). A three-layered nano-carbonated

hydroxyapatite/collagen/PLGA composite membrane for guided tissue regeneration. *Biomaterials*, *26*(36), 7564–7571. https://doi.org/10.1016/j.biomaterials.2005.05.050

43. Lim, G., Lin, G.-H., Monje, A., Chan, H.-L., & Wang, H.-L. (2018). Wound Healing Complications Following Guided Bone Regeneration for Ridge Augmentation: A Systematic Review and Meta-Analysis. *The International Journal of Oral & Maxillofacial Implants*, *33*(1), 41–50. https://doi.org/10.11607/jomi.5581
44. Lin, Z., Rios, H. F., & Cochran, D. L. (2015). Emerging regenerative approaches for periodontal reconstruction: a systematic review from the AAP Regeneration Workshop. *Journal of Periodontology*, *86*(2 Suppl), S134-52. https://doi.org/10.1902/jop.2015.130689
45. Locci, P., Calvitti, M., Belcastro, S., Pugliese, M., Guerra, M., Marinucci, L., Staffolani, N., & Becchetti, E. (1997). Phenotype expression of gingival fibroblasts cultured on membranes used in guided tissue regeneration. *Journal of Periodontology*, *68*(9), 857–863. https://doi.org/10.1902/jop.1997.68.9.857
46. Lundgren, D., Sennerby, L., Falk, H., Friberg, B., & Nyman, S. (1994). The use of a new bioresorbable barrier for guided bone regeneration in connection with implant installation. Case reports. *Clinical Oral Implants Research*, *5*(3), 177–184. https://doi.org/10.1034/j.1600-0501.1994.050309.x
47. Mahajan, R., Khinda, P., Shewale, A., Ghotra, K., Bhasin, M. T., & Bhasin, P. (2018). Comparative efficacy of placental membrane and Healiguide™ in treatment of gingival recession using guided tissue regeneration. *Journal of Indian Society of Periodontology*, *22*(6), 513–522. https://doi.org/10.4103/jisp.jisp_88_18
48. Masoudi Rad, M., Nouri Khorasani, S., Ghasemi-Mobarakeh, L., Prabhakaran, M. P., Foroughi, M. R., Kharaziha, M., Saadatkish, N., & Ramakrishna, S. (2017). Fabrication and characterization of two-layered nanofibrous membrane for guided bone and tissue regeneration application. *Materials Science & Engineering. C, Materials for Biological Applications*, *80*, 75–87. https://doi.org/10.1016/j.msec.2017.05.125
49. Mehrotra, S., Chowdhary, Z., & Rastogi, T. (2019). Evaluation and comparison of hydroxyapatite crystals with collagen fibrils bone graft alone and in combination with guided tissue regeneration membrane. *Journal of Indian Society of Periodontology*, *23*(3), 234–241. https://doi.org/10.4103/jisp.jisp_386_18
50. Melcher, A. H. (1976). On the repair potential of periodontal tissues. *Journal of Periodontology*, *47*(5), 256–260.
51. Merli, M., Moscatelli, M., Mariotti, G., Rotundo, R., Bernardelli, F., & Nieri, M. (2014). Bone level variation after vertical ridge augmentation: resorbable barriers versus titanium-reinforced barriers. A 6-year double-blind randomized clinical trial. *The International Journal of Oral & Maxillofacial Implants*, *29*(4), 905–913. https://doi.org/10.11607/jomi.3203
52. Nyman, S., Lindhe, J., Karring, T., & Rylander, H. (1982). New attachment following surgical treatment of human periodontal disease. *Journal of Clinical Periodontology*, *9*(4), 290–296.
53. Oates, T. W., Rouse, C. A., & Cochran, D. L. (1993). Mitogenic effects of growth factors on human periodontal ligament cells in vitro. *Journal of*

Periodontology, *64*(2), 142–148. https://doi.org/10.1902/jop.1993.64.2.142

54. Park, Y. J., Lee, Y. M., Park, S. N., Lee, J. Y., Ku, Y., Chung, C. P., & Lee, S. J. (2000). Enhanced guided bone regeneration by controlled tetracycline release from poly(L-lactide) barrier membranes. *Journal of Biomedical Materials Research*, *51*(3), 391–397. https://doi.org/10.1002/1097-4636(20000905)51:3<391::aid-jbm13>3.0.co;2-9
55. Pelekos, G., Lu, J. Z., Ho, D. K. L., Graziani, F., Cairo, F., Cortellini, P., & Tonetti, M. S. (2019). Aesthetic assessment after root coverage of multiple adjacent recessions with coronally advanced flap with adjunctive collagen matrix or connective tissue graft: Randomized clinical trial. *Journal of Clinical Periodontology*, *46*(5), 564–571. https://doi.org/10.1111/jcpe.13103
56. Pretzl, B., Kim, T.-S., Holle, R., & Eickholz, P. (2008). Long-term results of guided tissue regeneration therapy with non-resorbable and bioabsorbable barriers. IV. A case series of infrabony defects after 10 years. *Journal of Periodontology*, *79*(8), 1491–1499. https://doi.org/10.1902/jop.2008.070571
57. Prichard, J. F. (1957). The Infrabony Technique as a Predictable Procedure. *Journal of Periodontology*, *28*, 202–216.
58. Rani, N., Kaushal, S., & Singh, S. (2018). Evaluation of the relative efficacy of autologous platelet-rich fibrin membrane in combination with β-tricalcium phosphate (Septodont-resorbable tissue replacement)™ alloplast versus β-TCP alloplast alone in the treatment of grade II furcation defects. *National Journal of Maxillofacial Surgery*, *9*(2), 196.
59. Reynolds, M. A., Kao, R. T., Camargo, P. M., Caton, J. G., Clem, D. S., Fiorellini, J. P., Geisinger, M. L., Mills, M. P., Nares, S., & Nevins, M. L. (2015). Periodontal regeneration - intrabony defects: a consensus report from the AAP Regeneration Workshop. *Journal of Periodontology*, *86*(2 Suppl), S105-7. https://doi.org/10.1902/jop.2015.140378
60. Sam, G., & Pillai, B. R. M. (2014). Evolution of Barrier Membranes in Periodontal Regeneration-"Are the third Generation Membranes really here?". *Journal of Clinical and Diagnostic Research : JCDR*, *8*(12), ZE14-7. https://doi.org/10.7860/JCDR/2014/9957.5272
61. Scantlebury, T. V. (1993). 1982-1992: a decade of technology development for guided tissue regeneration. *Journal of Periodontology*, *64*(11 Suppl), 1129–1137. https://doi.org/10.1902/jop.1993.64.11s.1129
62. Scott, T. A., Towle, H. J., Assad, D. A., & Nicoll, B. K. (1997). Comparison of bioabsorbable laminar bone membrane and non-resorbable ePTFE membrane in mandibular furcations. *Journal of Periodontology*, *68*(7), 679–686. https://doi.org/10.1902/jop.1997.68.7.679
63. Sheikh, Z., Qureshi, J., Alshahrani, A. M., Nassar, H., Ikeda, Y., Glogauer, M., & Ganss, B. (2017). Collagen based barrier membranes for periodontal guided bone regeneration applications. *Odontology*, *105*(1), 1–12. https://doi.org/10.1007/s10266-016-0267-0
64. Srivastava, S., Tandon, P., Gupta, K. K., Srivastava, A., Kumar, V., & Shrivastava, T. (2015). A comparative clinico-radiographic study of guided tissue regeneration with bioresorbable membrane and a composite synthetic bone graft for the treatment of periodontal osseous defects. *Journal of Indian Society of Periodontology*, *19*(4), 416–423. https://doi.org/10.4103/0972-124X.154544

65. Takayama, S., Murakami, S., Shimabukuro, Y., Kitamura, M., & Okada, H. (2001). Periodontal regeneration by FGF-2 (bFGF) in primate models. *Journal of Dental Research*, *80*(12), 2075–2079. https://doi.org/10.1177/00220345010800121001
66. Tatakis, D. N., Promsudthi, A., & Wikesjö, U. M. (1999). Devices for periodontal regeneration. *Periodontology 2000*, *19*, 59–73. https://doi.org/10.1111/j.1600-0757.1999.tb00147.x
67. Thomaidis, V., Kazakos, K., Lyras, D. N., Dimitrakopoulos, I., Lazaridis, N., Karakasis, D., Botaitis, S., & Agrogiannis, G. (2008). Comparative study of 5 different membranes for guided bone regeneration of rabbit mandibular defects beyond critical size. *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research*, *14*(4), BR67-73.
68. Vert, M. (1989). Bioresorbable polymers for temporary therapeutic applications. *Angewandte Makromolekulare Chemie*, *166*, 155–168.
69. Villar, C. C., & Cochran, D. L. (2010). Regeneration of periodontal tissues: guided tissue regeneration. *Dental Clinics of North America*, *54*(1), 73–92. https://doi.org/10.1016/j.cden.2009.08.011
70. Wang, H.-L., & Boyapati, L. (2006). "PASS" principles for predictable bone regeneration. *Implant Dentistry*, *15*(1), 8–17. https://doi.org/10.1097/01.id.0000204762.39826.0f
71. Wang, J., Wang, L., Zhou, Z., Lai, H., Xu, P., Liao, L., & Wei, J. (2016). Biodegradable Polymer Membranes Applied in Guided Bone/Tissue Regeneration: A Review. *Polymers*, *8*(4). https://doi.org/10.3390/polym8040115
72. Winet, H. (1996). The role of microvasculature in normal and perturbed bone healing as revealed by intravital microscopy. *Bone*, *19*(1 Suppl), 39S-57S. https://doi.org/10.1016/s8756-3282(96)00133-0
73. Xue, J., He, M., Niu, Y., Liu, H., Crawford, A., Coates, P., Chen, D., Shi, R., & Zhang, L. (2014). Preparation and in vivo efficient anti-infection property of GTR/GBR implant made by metronidazole loaded electrospun polycaprolactone nanofiber membrane. *International Journal of Pharmaceutics*, *475*(1–2), 566–577. https://doi.org/10.1016/j.ijpharm.2014.09.026
74. Yang, S., Leong, K. F., Du, Z. H., & Chua, C. K. (2001). The design of scaffolds for use in tissue engineering. Part I. Traditional factors. *Tissue Engineering*, *7 6*, 679–689.
75. Zitzmann, N. U., Naef, R., & Schärer, P. (1997). Resorbable versus nonresorbable membranes in combination with Bio-Oss for guided bone regeneration. *The International Journal of Oral & Maxillofacial Implants*, *12*(6), 844–852.