

10-10-2019

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FARDOUN, Riad (2019) "Barrier membranes used in guided bone regeneration: A review," *International Arab Journal of Dentistry*. Vol. 10: Iss. 2, Article 6.

Available at: <https://digitalcommons.aaru.edu.jo/iajd/vol10/iss2/6>

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BARRIER MEMBRANES USED IN GUIDED BONE REGENERATION: A REVIEW

Riad Fardoun*

Abstract

Barrier membranes can be mainly classified into bio-resorbable and non-resorbable membranes. Each one of them has its own properties; including bio-compatibility, appropriate barrier features (mechanical prevention of soft tissue proliferation), tissue integration, immunologic neutrality, preservation of the space for new alveolar bone, and simplicity of application. Such membrane must hold out against the masticatory forces and tissue tension of the flap and prevent the collapse of soft tissues and wound space reduction. The property of integration into the tissue guarantees wound stabilization and inhibits epithelial migration.

The aim of this review was to compare and evaluate the influence of bio-resorbable barrier membranes and non-resorbable barrier membranes on bone regeneration.

Keywords: Barrier membranes – resorbable membranes – non resorbable membranes – flap – alveolar bone.

IAJD 2019;10(2):87-94.

MEMBRANES - BARRIÈRES UTILISÉES DANS LA RÉGÉNÉRATION OSSEUSE GUIDÉE: REVUE

Résumé

Les membranes barrières peuvent être classées principalement en membranes bio-résorbables et non résorbables. Chacune d'entre elles a ses propres propriétés; notamment la biocompatibilité, la prévention mécanique de la prolifération des tissus mous, l'intégration des tissus, la neutralité immunologique, la préservation de l'espace réservé au nouvel os alvéolaire et la simplicité d'application. Une membrane doit résister aux forces masticatoires et à la tension tissulaire du lambeau, et empêcher l'effondrement des tissus mous et la réduction de l'espace de la plaie. La propriété d'intégration dans le tissu garantit la stabilisation de la plaie et inhibe la migration épithéliale.

Le but de cette revue était de comparer et d'évaluer l'influence des membranes résorbables et des membranes non résorbables sur la régénération osseuse.

Mots-clés: membranes résorbables - membranes non résorbables – lambeau - os alvéolaire.

IAJD 2019;10(2):87-94.

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Introduction

For the long term-success and esthetically acceptable endosseous dental implant a sufficient amount of living bone is required in the jawbone. There is high percentage of implant site, as high as 50%, where there is no enough bone for placing a dental implant. In these situations, bone regeneration is required to ensure safe functional and adequate implant placement.

Bone formation is attained by several mechanisms, including: osteoinduction through growth factors or bone grafts; osteoconduction by bone grafts or substitute materials that acts as a scaffold for new bone formation; differentiation of progenitor cells into osteoblasts or stem cells transfer; distraction osteogenesis and guided bone regeneration (GBR) using barrier membranes. There is always an underlying basic mechanism of bone healing [1].

Guided bone regeneration combined with grafting material is a routine dental procedure. The slow growing bone tissue offers the opportunity for both epithelial cells and fibroblasts to occupy the space available by producing connective tissue quicker than bone growth. As a result, barrier membranes were introduced to serve as a barrier between the osseous defect and the soft gingival tissue. Thus, the biologic mechanism behind GBR is the exclusion of undesirable cells from the wound environment to enable cells from the bone tissue to proliferate into the coagulum-filled space under the barrier membrane.

If the occlusive barrier lasts long enough and if the barrier membrane is not exposed to the oral cavity, optimal conditions exist for stem cells and osteoprogenitor cells to differentiate into osteoblasts, which deposit the bone matrix [1].

In other words, the barrier membrane creates a secluded space that allows bone to use its great, natural healing capacity in an undisturbed and protected manner.

Both resorbable and non-resorbable membranes are available on the market.

As Caballé-Serrano et al. [2] mentioned the ideal barrier membrane for GBR must fulfill the following criteria:

1. Biocompatibility: The interaction between the membrane and the tissues must affect positively the surrounding tissues, leading to the healing of the defect. If the membrane is resorbable, should either degrade or integrate into the host tissues, decreasing the incompatibility that a cross – linking membrane can cause [3, 4].

2. Space maintainer: A membrane must be stable enough and create space to facilitate bone formation.

3. Occlusive to prevent the ingrowth of soft tissues into the regeneration site but at the same time allow oxygen, fluids and bioactive substances for cell growth to reach the defect.

4. Easy – handling: A membrane should not be too stiff because it would not integrate with the tissue or could create dehiscence of the soft tissues; or too malleable making it difficult to work with.

5. Bioactivation friendly: This feature of membranes is nowadays not into consideration. However, new strategies for bone regeneration are being developed which bring the membranes into the next level, not only having a passive role but an active role into the regeneration site [5].

Non-resorbable membranes

Nowadays, four common non-resorbable membranes are being used which include [6, 7]:

- expanded-polytetrafluoroethylene (e-PTFE);
- dense-polytetrafluoroethylene (d-PTFE);
- titanium-reinforced PTFE;
- titanium mesh.

Although there is a need for second surgery when using PTFE and titanium, and due to their surgical handling properties, malleability, structural rigidity in preventing collapse and space maintenance for large ridge defects, surgeons continue their use [8].

E-PTFE membranes

The expanded PTFE membrane (e-PTFE) was the first type of membrane used in implant dentistry [9]. According to Tarnow et al. [10], guided bone regeneration mainly used e-PTFE membranes in the early 1990s to cover dehiscence or fenestration bony defects around implants to preserve and regenerate bone in fresh extraction sockets [11], for vertical and/or horizontal ridge defects [12] and to protect the bony window during sinus lift procedures [13].

E-PTFE membranes have different features at the two sides: one side is approximately 1 mm thick with 90 percent porosity, which impedes the growth of epithelium; and the other side is approximately 0.15 mm thick with 30 percent porosity, which provides space for new bone growth and prevents fibrous tissue ingrowth [4].

As Gutta et al. [13] reported, numerous small pores in e-PTFE membrane promote tissue cell attachment, stabilizing the wound area, but it restricts migration of connective tissue and epithelial cells at the same time. A major disadvantage of the e-PTFE membranes is the risk of bacteria penetration once they become exposed to the oral cavity so that it's mandatory to remove it. Lee JY reported that this membrane needs a second surgery because of its ability to attach to the tissue [14].

Currently, the use of e-PTFE membrane has been discontinued and other non-resorbable membranes are widely used.

Dense-polytetrafluoroethylene (d-PTFE)

d-PTFE membranes have a smaller pore size compared to e-PTFE; that's why their use in dentistry is increasing [2]. According to Lee JY [10], bacterial infiltration is minimized because of small pore size, so that there is lower risk of bacterial contamination and infection if it left exposed to the oral cavity which enhance vertical and/or horizontal bone regeneration and soft tissue healing [9].



Fig. 1: An advantage of high-density PTFE membranes is that they do not require soft-tissue coverage.

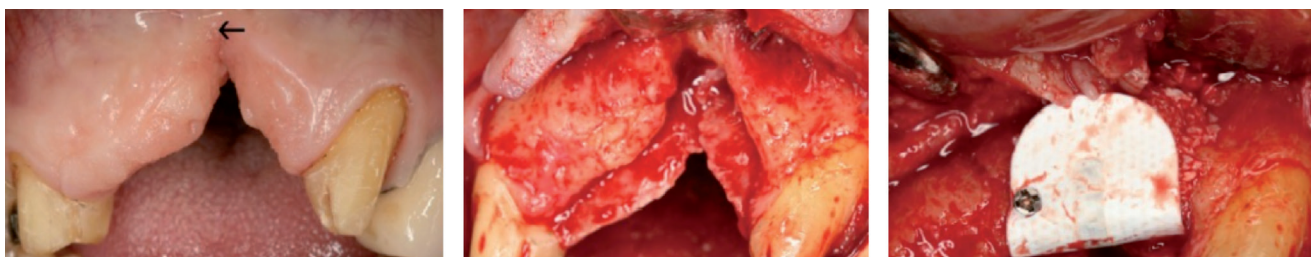


Fig. 2: Patient with class III alveolar defect in the anterior maxillary arch. Horizontal and vertical deficiencies were visualized following a flap reflection. Bone grafting material was placed prior to the fixation of a non-resorbable titanium-reinforced PTFE membranes [16].

A d-PTFE membrane allows sufficient time for bone regeneration because of sufficient space maintaining and wound stabilizing. Also, Lee JY reported that it's possible to remove the membrane through mucosal flap without disturbing or traumatizing the mucosal tissue since the membrane does not attach to the tissue. Successful bone regeneration takes place relying on adequate blood supply from the marrow space through cortical perforations where the blood supply to the area is limited due to the limited porosity of the d-PTFE membranes [14].

However, these membranes do require removal after approximately 30 days.

Titanium-reinforced PTFE membranes

To increase the rigidity of e-PTFE and d-PTFE membranes, titanium was added to the PTFE membranes [12]. According to Jovanovic et al. [15], the

increased structural rigidity allows this membrane to be shaped to fit a variety of defects and provides additional stability in supracrestal bone defects and large dehiscence around dental implants and superior preservation of the regenerated ridge during healing period.

Titanium mesh

Porous titanium meshes, first used in 1969, are non-resorbable membranes that have been shown to be effective in maintaining space without collapsing [18].

According to Soldatos [17], titanium mesh can provide the perfect rigidity required for the stability of the surgical site, more over it maintains the space for bone regeneration, prevents micromovement, membrane collapse, and graft displacement from external forces. Also, low risk of infection and rare premature removal of the membrane has been reported in case of membrane exposure [18]. Rakhmatia

et al. [7] reported that it can hold high temperatures (e.g. sterilization prior to implantation) and it can resist corrosion. Moreover, its flexibility due to its low density enables the membrane to bend and contour to the shape of bony defect.

Advantages and disadvantages of resorbable membranes

There are two types of titanium mesh materials, microporous and macroporous. In a study by Gutta et al., macroporous titanium mesh showed greater bone formation and regeneration compared to the microporous titanium mesh and resorbable membrane. In addition, macroporous titanium mesh prevented the soft tissue ingrowth in a better way than the two other types of membranes. However, the mineral apposition rate was found to be higher with the resorbable membrane compared to either titanium mesh membranes [8].

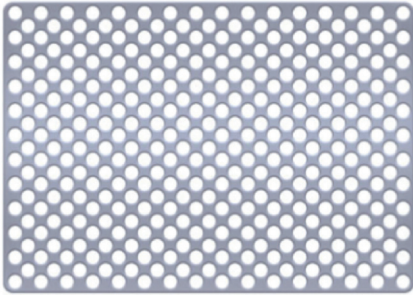


Fig. 3: Titanium mesh membrane.

Advantages	Disadvantages
Decreased patient morbidity	Uncontrolled duration of barrier function
No need for second stage surgery to remove the membrane	The need for tenting screws and bone to support the membrane and to avoid its collapse
Simplified surgical procedure	Remnants of the membrane found in direct contact with dental implants
Lower rate of exposure	Micromovement of the membrane leads to movement of grafting material and disruption of the blood clot
	Memory, especially for the highly cross-linked membranes

Table 1: Advantages and disadvantages of resorbable membranes.

Resorbable synthetic barrier membranes

In an effort to overcome the need for a second operation for membrane removal, barrier membranes are also constructed from biodegradable materials. According to Schneider et al. [18], using resorbable synthetic membranes additionally decreases the need for surgical intervention and inflammation [19].

Advantages of resorbable membranes

As stated by Cochran et al., the need for developing resorbable membranes as an alternative to non-resorbable membranes primarily arose to avoid an additional surgery for removal [20]. Due to their integration within the tissue, these membranes require the addition of biocompatibility while maintaining their shape and material properties for weeks while in the wound site. Currently, clinicians use membranes made of poly-lactic acid (PLA) and poly-glycolic acid (PGA), and various blends of these polymers made commercially available under the names in Table 2. As reported by Sakalloglu et al in clinical trials comparing use of Atrisorb membranes with various debridement methods, the Atrisorb trials showed increases

in clinical attachment level of gingival tissues (3.61 mm vs. 1.64 mm) and also in growth of alveolar bone (2.76 mm vs. 1.42 mm) over the span of a year [21].

Mechanical and chemical properties

Resorbable synthetic membranes have a wide range of tensile strengths that depend on the ratio of polymers used such as PLA and PGA. According to Nagarajan et al., other factors such as the extent of crosslinking can be used to increase tensile strength at the cost of prolonging the degradation timeline, the variation in membrane composition and treatment leads to a wide range of tensile strengths from 40-140 MPa for PLA and PGA scaffolds [21].

A study done by Yamada et al. compared the average tensile strength of non-resorbable synthetic membranes such as e-PTFE; the value was around 100 MPa [22].

Diao et al. reported that natural degradable polymers, such as porcine membranes, have much lower tensile strength, within the range of 4-5 MPa [23].

Biologically resorbable membranes, such as PLA and PGA, are broken down by proteolytic enzymes from the polymorphonuclear (PMN) cells into lactic acid or glycolic acid that is

excreted through the kidney or used in the citric acid cycle as a pyruvate in metabolism. These cells are also key members of the inflammatory response and often generate harmful oxidative species when breaking down synthetic membranes. As stated by Buchmann et al., studies have shown that there is a correlation between material choices and the duration and magnitude of the PMN response [24].

This inflammatory response at the membrane site can cause de-coherence in tissue integration and may even lead to failure of the implant over time. A material of choice that minimizes this inflammatory response involves the use of decellularized bovine bone as a guiding membrane. Stavropoulos et al. [25] announced that these biologically based matrices provide the decrease in immune response necessary to ensure proper tissue healing environments but also may lack the osteoconductivity that synthetic membranes possess.

Resorbable natural barrier membranes

The majority of natural resorbable membranes are composed of collagen, either bovine or porcine in origin. According to Tal et al. [26], type I collagen is most commonly used

since it is the most prevalent of the collagens comprising about 25% of the body's proteins, 80% of connective tissue proteins, and 90% of mineralized organic bone extracellular matrix [27]. Type I and III collagen membranes are Food and Drug Administration approved (FDA) for their biocompatibility as evident in the number of clinically available membranes on the market.

Types of resorbable membranes:

- Polymeric membranes;
- Collagen membranes;
- Electrospinning (e- spinning) for membranes;
- Functionally graded multi-layered membranes;
- Membranes with antibacterial properties;
- Barrier membranes with growth factor release;
- Platelet rich fibrin (PRF) membrane;
- Amniotic membranes (AM).

Polymeric membranes

These are made up of synthetic polyesters, polyglycolides (PGAs), polylactides (PLAs), or copolymers that are completely biodegraded to carbon dioxide and water via the Krebs cycle and by enzymatic activity of infiltrating macrophages and polymorphonuclear leucocytes. As stated by Hutmacher [28], 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 [29].

However, these membranes present drawbacks:

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

Collagen membranes

Collagen is a major constituent of natural extracellular matrix (ECM). According to Bottino [31], collagen has many auspicious biological activities such as hemostatic ability, attraction and activation of periodontal ligament

and gingival fibroblast cells, augmentation of tissue thickness, biocompatibility, biodegradability, and cell affinity [30].

These properties render it advantageous for extensive application and 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 III. The source of collagen comes from tendon, dermis, skin or pericardium of bovine, porcine or human origin.

Disadvantages of collagen resorbable membranes

1. Lack of space making ability compared to non-resorbable membranes.
2. Unpredictable degradation profile.
3. Risk of disease transmission

Electrospinning (e- spinning) for membranes

Electrospinning was first introduced 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 [32].

Li et al. [32] 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.

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, nano- hydroxyapatite is fabricated by casting method [33].

Membranes with antibacterial properties

Antibacterial substances were incorporated to reduce the bacterial contamination of regenerating wound. It was demonstrated that incorporation of amoxicillin or tetracycline into various GBR membranes may enhance the attachment of periodontal ligament cells in the presence of oral pathogens *Streptococcus mutans* and *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*).

Chou et al. [34] compared the antibacterial effects of membrane with and without zinc phosphate and showed a significant decrease in activity of *A. actinomycetemcomitans* 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 [28].

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. PDGF-BB loaded PLLA membrane potentially enhanced GTR efficacy in rat calvarial defects [34].

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 alternative compared to commercially available membranes.

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

Product (Company)	Material	Resorption Period (months)
Guidor® (Sunstar)	PLA (Polylactic Acid)	1.5 – 2
Resorb X® (KLS Martin)	PDLLA (Poly-DL-Lactic Acid)	1.5 – 2
Cytoflex Resorb® (Unicare Biomedical)	PLGA (Poly-Lactic-Glycolic Acid)	4
Resolute® (Gore®)	PGA-TMC (Polyglycolic Acid Trimethylene Carbonate)	4-6
Epi-Guide® (Curasan, Inc.)	PDLLA (Poly-DL-Lactic Acid)	6 – 12
Atrisorb (Tolmar)	P(DL)LA – NMP (Poly-DL-Lactic Acid)	9 – 12
Inion™ GTR (Inion)	PLDLGA-TMC (Poly-LD-Lactic-Glycolic Acid Trimethylene Carbonate)	12 – 24
Vivosorb® (Polyganics)	PDLLCL (Poly-DL-Caprolactone)	16

Table 2: Summary of commercially available resorbable membrane for guided bone regeneration.

basement membrane of the amnion is very similar to the basement membrane found in other parts of the body like the conjunctiva and the gingiva. AM contains many growth factors and exhibit anti-inflammatory, anti-bacterial properties and has been reported to reduce scarring.

and bioactivation friendly materials are the ones that will fulfill our necessities. The biomechanical barrier produced by those membranes elicited the advantage of guided bone regeneration. The choice of the barrier membrane depends on the bone defect configuration.

Conclusion

In conclusion, from the first development of barrier membranes until today there has been a great progress in membrane sciences. Although nowadays natural collagen membranes are the ones that offer the wider range indications, we must consider that they are not suitable for every procedure, and that the clinician should be able to choose the right membrane.

It has been clearly described that biocompatibility is the most important requirement to take into account when choosing a membrane, but other factors such as space maintaining capacity, cell occlusiveness, easy handling

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