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Review article

The use of periodontal membranes in the field of periodontology: spotlight on collagen membranes

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Abstract
Periodontal regenerative techniques are performed to accomplish the restitution of soft and hard teeth-supporting tissues that have been lost due to trauma or inflammatory disease.

Periodontal membranes are used for these techniques to provide support and a framework for cell growth and tissue regeneration. They act as a temporary and selective barrier to cell proliferation. Easy clinical handling, biomechanical specifications, high biocompatibility, cell-occlusivity, and satisfactory bioresorption rate are essential properties a membrane needs to be effective. The creation and maintenance of a secluded space is also a fundamental rule in periodontal regenerative techniques. The use of barrier membranes in the field of restorative dentistry has progressed toward the use of minimally invasive approaches optimizing wound closure and limiting patient morbidity.

This review intends to provide an overview of the major cellular events in the surgical wound and membrane surface. It was also performed to assess, from literature data, the pertinence of using non-resorbable and resorbable membranes for this regenerative purpose. Special attention will be given to collagen membranes.

Keywords: Collagen membrane; Guided bone regeneration; Guided tissue regeneration; Non-resorbable membranes; Resorbable membranes

Highlights:
- Periodontal regenerative techniques (GBR and GTR) are performed to accomplish the restitution of soft and hard teeth-supporting tissues that have been lost due to trauma or inflammatory disease.
- Nowadays, these techniques are used to treat periodontal damage with huge success, and we observe a general increase in the use of membrane-based techniques.
- The use of barrier membranes in this field have progressed toward the use of minimally invasive approaches optimizing wound closure and limiting patient morbidity.
- Resorbable collagen membranes are now being widely used in regenerative dentistry as they ensure a high success rate and cause less postoperative complications.

Introduction

The human periodontium is a complex vital structure. It is composed of the alveolar mucosa, gingiva, periodontal ligament (PDL), root covering cementum, and alveolar bone. A large variety of cell types are present in the functional periodontium, including osteoblasts, cementoblasts, fibroblasts, myofibroblasts, nerve cells, endothelial cells, and epithelial cells, in addition to a population of stem cells. The most important functions of the periodontium are maintaining teeth to jaw bones and providing nutrition to the living structure of the teeth (Fawzy El-Sayed and Dörfer, 2016).

Periodontal damage can be the result of trauma, age-related tissue decay, or secondary periodontal diseases, including tumors, gingivitis, and periodontitis (Iviglia et al., 2019).

Periodontitis is the main pathological condition of the periodontium affecting teeth and their ancillary structures (Bottino and Thomas, 2015). It has been stated that this highly prevalent chronic inflammatory disorder happens when the persistent presence of bacteria-stimulated inflammation of the gingival tissue progressively and irreversibly impairs the periodontium (Bottino et al., 2017; Fawzy El-Sayed and Dörfer, 2016). When the attachment between teeth and gingival tissues is lost, it causes periodontal pocket formation around the tooth (Bottino et al., 2017). If left untreated or not prop-

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erly managed, it can subsequently damage soft tissues, cause alveolar bone loss, and result in tooth loss. In turn, tooth loss causes serious functional and esthetic impairments with possible psychological impact (Bottino and Thomas, 2015).

Periodontitis is frequently associated with major systemic disorders, such as heart disease, rheumatoid arthritis, adverse pregnancy outcomes, gestational diabetes, and diabetes mellitus, which indicate that this disease is of huge interest in the public health sector (Fawzy El-Sayed and Dörfer, 2016).

The National Health and Nutrition Examination Survey (NHANES) evaluated that, in the US, approximately 8% of adults (aged between 20 and 64 years) and 17% of seniors (aged over 64 years) have periodontitis (Bottino et al., 2017). Nearly 50% of the adults in the US are affected by a varying degree of periodontitis (Bottino and Thomas, 2015). About 10% of the global world population is affected by severe forms of periodontitis (Iviglia et al., 2019).

There is an essential need to develop restorative procedures to ensure complete and functional periodontal tissue regeneration (Siaili et al., 2018). Nowadays, oral surgeries are performed with huge success. Dental implants, which are involved in the replacement of lost teeth, have revolutionized restorative dentistry. In fact, in the US more than 300,000 dental implants are surgically placed per annum, and this number is expected to further increase to meet clinical demand (Iviglia et al., 2019).

Based on these considerations, this review is carried out to assess literature data concerning the properties and roles of barrier membranes in the field of periodontics (Fig. 1).

Guided Tissue Regeneration/Guided Bone Regeneration (GTR/GBR)

As mentioned above, periodontal diseases can lead to important damage to the periodontal structures. After the resolution of etiologic factors and controlling inflammatory response, periodontal regeneration is necessary to restore periodontium structure. This regeneration can be achieved clinically through the use of biomaterial, cell signaling molecules, and an adequate blood supply (Iviglia et al., 2019).

Periodontal regenerative techniques are broadly divided into "Guided Tissue Regeneration" (GTR) and "Guided Bone Regeneration" (GBR). GTR and GBR are established techniques in oral maxillofacial reconstructive surgery that use barrier membranes to enable the regeneration of soft and hard tissues. These terms are generally used synonymously, but this is rather inadequate. GTR was introduced in the mid-80s, and it includes procedures used to regenerate lost periodontal tissues and bone. It does so by keeping out epithelial cells from the root surface using a barrier membrane (Dimitriou et al., 2012; Siaili et al., 2018). Meanwhile, the concept of the GBR technique, which evolved from GTR, refers only to the regeneration of bone via the use of barrier membranes. For instance, GBR can be performed to achieve bone augmentation – either before or concomitantly with dental implant placement – to treat bone atrophy (Donos et al., 2015; Sheikh et al., 2017).

Achieving complete periodontal health is the ultimate goal of periodontal therapies, by ensuring the primary and secondary prevention of periodontal diseases. In this way, the health and aesthetics of periodontal tissues is maintained and improved (Siaili et al., 2018).

Membranes for periodontal regeneration

Barrier membranes are used for guided regeneration of periodontal structures as they constitute a biocompatible physical barrier preventing the attraction and ingrowth of undesired competing cells into the wound space. Barrier membranes favor the regeneration of the appropriate periodontal tissues (Sasaki et al., 2121; Sheikh et al., 2017).

The membranes must satisfy the following main criteria to ensure barrier function and successful regenerative therapy: (1) Clinical manageability: the membranes should be easy to clinically handle and be easy to tailor to the size of the damage. (2) Creation and maintenance of a secluded space: this space-making function must be maintained long enough until regeneration is completed, and the membrane must be strong enough to avoid its collapse. (3) Temporary and selective barrier for undesired cells: the material should have appropriate cell permeability for the intended clinical application. In the case of GBR, as an example, a cell occlusive membrane should achieve selective cell repopulation of the secluded space by keeping out the undesirable and rapidly growing soft tissue cells that originate from the surrounding gingival epithelium and connective tissue. This avoids fibrous tissue formation, which may compromise bone formation. At the same time, GBR membranes, allow the migration of bone-forming cells to the wound space intended for bone regeneration. (4) Ability to ensure tissue integration: the membrane should stabilize the healing tissues and the contours of the adjacent mucosal tissues without interfering with the newly formed tissue. (5) Non-immunogenicity: upon implantation, the membrane should not provoke any inflammatory response. (6) Biocompatibility, i.e. the quality of being well accepted by the body is one of the essential properties of the membranes – Fig. 2 (Siaili et al., 2018). The failure of one or more of these criteria may cause unsatisfactory restorative performance.

Periodontal diseases can result in significant damage to periodontal structures. Regeneration of periodontium structures requires that the used membranes do not interfere with healthy cell signalling and allow adequate blood supply. In this schematic illustration of GBR, a membrane is used to prevent faster-growing epithelial cells from occupying the wound, while allowing osseous cells to populate, differentiate and fill the surgical site, thus resulting in bone restitution.

Membranes' classification depends on their resorption behavior, and we can identify 2 classes: non-resorbable and resorbable.

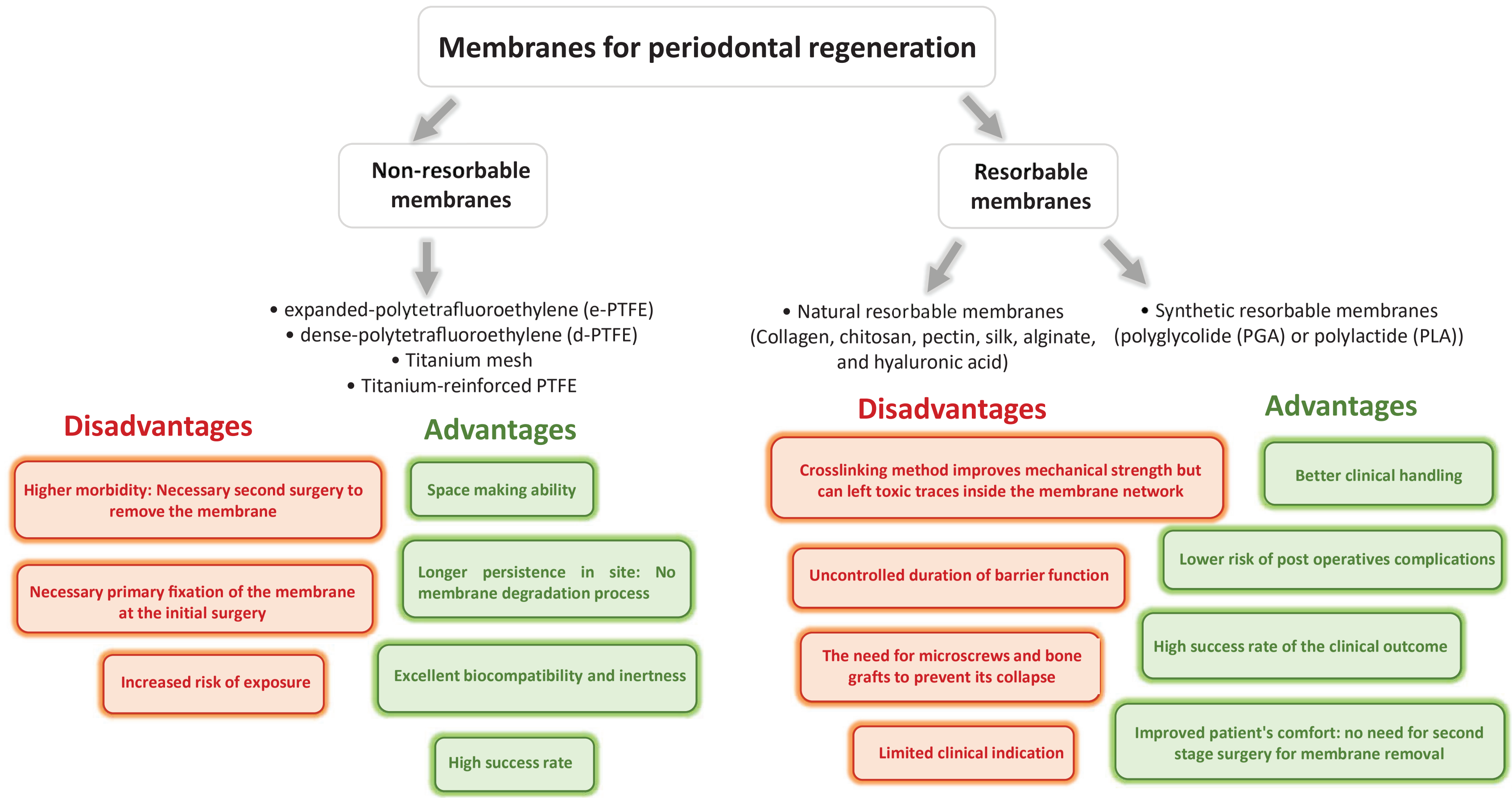
Autogenous periosteal barrier membranes

The use of the host's palate tissue as a source of autogenous barrier membranes is considered an attractive technique for use in periodontal therapy and an effective alternative to existing barrier membranes. Some studies have shown better bone gain levels and less postoperative marginal tissue recession in comparison with open flap debridement alone (Paolantonio et al., 2010; Siaili et al., 2018). However, using this autogenous periosteal membrane as a barrier requires an ancillary surgical graft site, causing patient trauma, bleeding, and discomfort (Sheikh et al., 2017).

Non-resorbable membranes

There are four main types of non-resorbable membranes used in dentistry for periodontal regeneration procedures (Soldatos et al., 2017). These include:

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



1. Periodontal membranes are used for these techniques to provide support and framework for cell growth and tissue regeneration. They act as a temporary and selective barrier for cell proliferation.
2. This review collected literature data concerning several membrane types. It intends to provide an overview on the major cellular events in the surgical wound and membrane surface.

Fig. 1. Graphical abstract

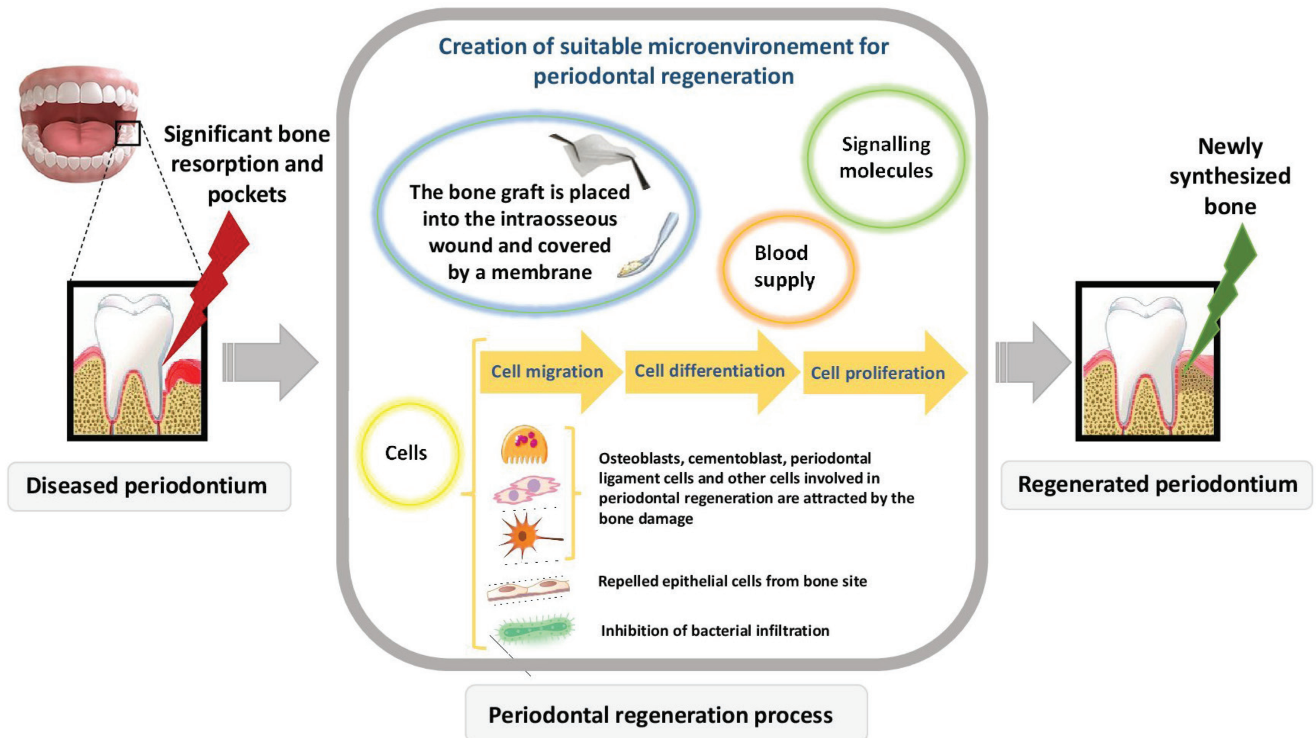


Fig. 2. Schematic illustration of the principal parameters involved in the periodontal regeneration using barrier membrane

- *Benefits of the non-resorbable membranes*

Biocompatibility and inertness are the main characteristics of these non-resorbable membranes (Bottino and Thomas, 2015; Elgali et al., 2017).

These membranes are rigid and characterized by high biomechanical stability and the capability of retaining their shape (Iviglia et al., 2019). These membranes have greater stiffness which guarantees a longer barrier effect that lasts until membrane removal. For this reason, these membranes are preferentially used for the correction of more severe alveolar bone damages (Chiapasco and Casentini, 2018; Ghavimi et al., 2020).

It is important to keep in mind that, the ideal membrane should be rigid enough to withstand the compression of the overlying soft tissue. On the other hand, membranes should also have a certain degree of plasticity to be easily handled and molded into the shape of the surgical site. Biomechanical properties encompass stiffness and plasticity. A balance between these two criteria is important to achieve adequate space-making capacity. On one hand, the rigidity prevents membrane collapse and provides space maintenance. On the other, its plasticity permits bending, contouring, and adaptation to the periodontal damage, thus creating a tent-like effect over the wound site. For example, titanium reinforced membranes have excellent biomechanical performance and are used to better control the created space as they are more resistant to collapse than nonreinforced ones (Elgali et al., 2017).

The above-mentioned space maintenance capacity is important for enabling cell proliferation and repopulation. In fact, if the membrane is subject to collapse into the wound site, the volume for periodontal regeneration is reduced and the optimal clinical outcome would not be reached (Elgali et al., 2017; Siaili et al., 2018).

Non-resorbable membranes have a porous structure, and during the manufacturing process the size of the pores can be tailored to ensure selective migration of the appropriate cell type. Membranes used for GBR are osteoconductive so that they can stimulate the attraction and growth of osseous cells (bone-producing cells), stabilize the bone graft (if used), and minimize the risk of its disintegration. To ensure clinical evidence of newly formed bone, this type of GBR membrane should at the same time, in a selective way, prevent the penetrating of soft tissues into the wound site during the healing process (Allan et al., 2021; Dimitriou et al., 2012).

These porous membranes should be able to promote the growth and attachment of the intended cell tissue. They also promote vascularization of the healing wound, as they facilitate the flow of biological fluids such as nutritive vascular supply, and consequently improve clinical outcomes (Soldatos et al., 2017).

A non-resorbable membrane should not attach to the regenerated tissue, hence, its removal can be performed without traumatizing the regenerated tissues and the mucosal tissue. As an example, due to its reduced pore size and reduction of tissue attachment, the removal of d-PTFE membrane is greatly simplified using minimally invasive surgery (Soldatos et al., 2017). In addition, the reduced pore size of d-PTFE membranes prevents bacterial infiltration into the wound (Soldatos et al., 2017).

Non-resorbable membranes may have some angiogenic properties, but most of the pro-angiogenic effects of these membranes are related to the incorporated pro-angiogenic agents, which are used to enhance the angiogenic activity (Saghiri et al., 2016).

e-PTFE membranes, first GTR membrane used in clinical practice in the '90s, have been considered the gold standard in periodontal regenerative therapies as they provided excellent clinical outcomes (Iviglia et al., 2019). An optimal fill of the periodontal damage was obtained more frequently with a non-resorbable e-PTFE membrane when compared to a poly lactic-co-glycolic acid (PLGA) resorbable membrane (Merli et al., 2016).

• *Limits of non-resorbable membranes*

There are some critical drawbacks regarding membrane stiffness. Too high stiffness of non-resorbable membranes is associated with a higher rate of complications when compared to resorbable membranes (Sheikh et al., 2017).

The major postoperative issue related to non-resorbable membranes is early and spontaneous exposure through the soft tissue, which can decrease treatment efficacy (Elgali et al., 2017). The membrane exposure can also occur at different stages of wound healing. A plausible explanation of this complication is the high tension exerted by the membrane on the soft tissue. In combination with a lack of blood supply, this gives rise to postoperative soft tissue dehiscence and necrosis of gingival tissue in contact with the barrier membrane (Elgali et al., 2017; Sheikh et al., 2017). Once exposed to the oral cavity, there is an elevated risk of bacteria infiltration, leading to the infection of surrounding tissues (Camps-Font et al., 2018). In the case of the GBR technique, this exposure also causes bone graft disintegration (Windisch et al., 2021). If membrane exposure occurs, in many cases, the membrane must be removed before the completion of the healing period, which adversely affects the intended clinical outcomes (Chiapasco and Casentini, 2018). To minimize the risk of such complications, clinicians should assess the amount of keratinized mucosa, vestibular depth, flap flexibility, wound site type, size, and type of membrane used. Each of these factors has been identified as a contributing factor in membrane exposure (Garcia et al., 2018).

Currently, e-PTFE membranes, which were considered the historical gold standard for GBR, have been phased out. 20% of treatments using these resulted in infections and exposures (Sheikh et al., 2017). On the other hand, the use of d-PTFE in the periodontics field is becoming more frequent. Its pore size is smaller than e-PTFE, reducing the risk of bacterial infiltration. Therefore, d-PTFE membranes can be left in the contact with the oral cavity and still prevent surgical wounds from potential risks of bacterial contamination (Soldatos et al., 2017).

Soft tissue is susceptible to growing apically on the outside of the membrane, thus causing inflammation and marginal tissue recession, which in turn can result in unsatisfactory clinical outcomes (Siaili et al., 2018).

It is worth noting that the use of non-resorbable membranes has been decried due to the necessity for a second surgery for removal (between 16 to 24 weeks following the initial procedure), which creates additional pain for the patient and can possibly interfere with the healing process. This drawback is also associated with time-consuming (and thus expensive) medical intervention (Bottino and Thomas, 2015; Camps-Font et al., 2018; Iviglia et al., 2019; Siaili et al., 2018).

Recent research has focused on the development of resorbable membranes that overcome the limitations connected to the use of non-resorbable membranes.

Resorbable membranes

Periodontal tissue regeneration is a growing field of research thanks to the development and use of resorbable GTR/GBR membranes. The term "resorbable" is used to denote membranes that degrade in a biological environment. The membrane remains intact as a physical barrier for a certain time until regeneration is completed. After that, it is hydrolyzed and metabolized gradually. Bioresorption takes place and the membrane is decomposed. The safety of both the membrane and its breakdown products is checked (Bottino and Thomas, 2015).

Bioresorption eliminates the potential risk of complications associated with the long-term presence of foreign material, as well as the need for a second surgery to remove it. The membrane is placed in a single-step procedure and does not need to be removed as it can degrade gradually in parallel with tissue formation. The resorbable membrane thereby reduces a patient's pain, as well as the financial burden associated with second surgery (Camps-Font et al., 2018; Siaili et al., 2018).

Control over the resorption rate is a major feature that needs to be taken into account during the design of a resorbable membrane. The resorption rate should have the same speed as the rate of tissue/bone regeneration, hence the strengths of the newly formed tissue and membrane can be harmonious and avoid membrane collapse (Zhang et al., 2020).

Resorbable membranes are derived from natural sources or produced by synthetic methods (Iviglia et al., 2019).

• *Synthetic resorbable membranes*

Since the early 60s, synthetic resorbable polymers have been used in several biomedical applications. Synthetic resorbable membranes used in periodontics are fully synthetic, so they are not of animal or human origin, and therefore do not bear the risk of disease transmission. Synthetic resorbable membranes may be of great interest in the regeneration of periodontal tissues, as their criteria – such as biomechanical strength, chemical properties, resorption rate, and pore size – can be predefined during the development process to meet clinical needs, which makes the clinical performance more predictable (Hwang et al., 2020).

A wide range of aliphatic polyesters (polyglycolide (PGA) or polylactide (PLA)) and their copolymers have been used in the development of synthetic resorbable membranes. PLA, polyester-based membranes, are the first resorbable barriers to be approved by the Food and Drug Administration (FDA) and are now widely used as GBR membranes (Iviglia et al., 2019).

It has been demonstrated that resorbable membranes can stay physically intact for at least 4 to 6 weeks, which is enough to ensure barrier function and successful regenerative therapy. After that period, the membrane starts to disintegrate and resorb gradually while maintaining a minimum biomechanical strength to support the formation of new tissue (Bottino and Thomas, 2015).

• *Natural resorbable membranes*

Collagen: Collagen membranes are the most common type of resorbable membranes used and they have a similar collagen structure as the periodontal connective tissues. They have the advantage of low antigenicity, high biocompatibility, and excellent cell affinity (Soldatos et al., 2017). Collagen membranes are discussed in detail in the section "Resorbable collagen membranes".

Chitosan: Chitosan is a hydrophilic biopolymer obtained from chitin. Its primary natural source is the crustacean carapace (Fernandes et al., 2020). The chitosan-based biomaterials are extensively used because of their attractive characteristics, including bioresorption, biocompatibility, non-immunogenicity, antibacterial activity, and the ability to promote cell attraction, proliferation, and differentiation. The chitosan membranes are easy to manipulate, have a porous structure, and have bacteriostatic properties. They are known for reducing gingival inflammation in case of periodontitis due to their antimicrobial properties. All these properties make it a promising material in many medical indications (Elgali et al., 2017; Iviglia et al., 2019). However, other studies concluded that the chitosan membranes are rigid, degrade slowly, and are not well integrated with the surrounding soft tissue, indicating that this membrane is not adapted to be used as a barrier membrane (Fernandes et al., 2020).

A wide variety of other natural polymers, with interesting composition and promising potential, are used for resorbable biomaterials syntheses, such as pectin, silk, alginate, and hyaluronic acid (Iviglia et al., 2019).

Membranes with therapeutic properties: The introduction of nanotechnology has improved the properties of various types of biomaterials. In particular, electro-spinning, a technique of tissue engineering, has recently been introduced as a novel strategy in the development of nanoscale biomimetic scaffolds. This allows the incorporation of agents with therapeutic properties into the nanofiber meshes during the manufacturing process (Fernandes et al., 2020; Ghavimi et al., 2020).

Both bone and tissue restitution benefit from the promising advances in restorative dentistry. Many cases of membranes with therapeutic functions were synthesized. New biomaterials included antimicrobials (e.g., Metronidazole), inorganic particles (e.g., Calcium Phosphates), and biomolecules (e.g., Growth Factors) (Bottino et al., 2017). For example, metronidazole, widely used to treat periodontitis, was added during manufacturing steps into the membrane to bring antimicrobial activity and prevent bacterial colonization and subsequent inflammation. Nanoparticles of hydroxyapatite were also added to membranes to enhance bone formation (Bottino and Thomas, 2015).

Benefits of the resorbable membranes: Significant attention has been devoted to resorbable membranes. In fact, they are highly biocompatible and potentially bioactive (Iviglia et al., 2019). In addition, this type of barrier usually entails less postoperative morbidity because there is no need for re-entry surgery for membrane removal. They were developed to eliminate the pain and discomfort (as well as the financial burden) associated with a second-stage surgical procedure.

Unlike non-resorbable membranes, which are too stiff and incapable of molding to the shape of the wound site, resorbable membranes have the advantage of being easy to clinically handle (Soldatos et al., 2017). In fact, for resorbable membranes, the crosslinking technique – which is a chemical modification – is used to improve biomechanical strength and reduce resorption rate. In general, too malleable membranes can be uncomfortable for clinical use and cannot be reproducibly used in a clinical practice, thus reducing the success of the regenerative process. Crosslinked resorbable membranes are appropriately malleable and optimal for reconstruction. They are also sufficiently stiff to withstand the pressure exerted by external forces, such as mastication (Sheikh et al., 2017; Soldatos et al., 2017).

As they have a longer resorption time, the crosslinked membranes provide more time for slowly migrating osteoprogenitor cells to repopulate the regenerative site. Considering that bone regeneration occurs at a slower rate than that of soft tissue, the crosslinked membranes facilitate the re-establishment of osteoblasts in damaged sites (Soldatos et al., 2017). These membranes are associated with promising improvement in outcomes of the surgical procedure of GBR. A high success rate, represented by the amount of bone fill, was obtained with the resorbable membrane (as compared to non-resorbable membranes e-PTFE, known to be the gold standard) with the additional benefit of less complications such as dehiscence and re-entry surgery (Khojasteh et al., 2017; Sheikh et al., 2017).

Limits of the resorbable membranes: Unfortunately, resorbable membranes have some contraindications. Simple periodontal damage regeneration can be managed easily with a resorbable membrane. On the other hand, treatment of more advanced damage (e.g., Bone damage class 3) can be performed with resorbable membranes but it needs more advanced surgical skills. However, vertical bone reconstruction is very challenging, and resorbable membranes are not indicated for such complex damages that present a vertical component (e.g., Bone damage class 4). Non-resorbable membranes are more suited to such severe alveolar bone damage (Chiapasco and Casentini, 2018; Sanz-Sánchez et al., 2018).

Another aspect to be considered is the fact that resorbable membranes typically have poor biomechanical properties. Resorbable membranes are not sufficiently rigid and may tend to collapse. Even if the membranes are initially able to keep their intended shape, they generally lose strength and collapse into the wound (Iviglia et al., 2019). Crosslinking method is used to improve their biomechanical properties. In addition, this lack of rigidity means that additional support is required, and these membranes need immobilization at the surgery site with screws. This technique is mandatory to support the membrane, maintain the space, and avoid membrane collapse, which has a detrimental influence on the regenerative outcome and can lead to a failed reconstruction (Chiapasco and Casentini, 2018; Soldatos et al., 2017).

Each type of resorbable membrane has its typical resorption range which needs to be slow enough to enable successful tissue/bone regeneration (Soldatos et al., 2017). Ideally, the membrane should have predictable bioresorption kinetics, which should match the rate of new tissue growth with no residual materials left on the surgical site. A sufficiently long duration is crucial to allow enough time to regenerate newly formed soft tissues and bones (Garcia et al., 2018; Jiménez Garcia et al., 2017). Too early resorption of membranes prevents or delays periodontal regeneration. It is important to note that native resorbable membranes tend to biodegrade rapidly *in vivo* and have an uncontrollable resorption rate, which can vary from 4 to 24 weeks (Dimitriou et al., 2012; Khojasteh et al., 2017). Crosslinking method is used with resorbable membrane to effectively extend the durability time for up to 16 to 24 weeks and to make their bioresorption kinetics more predictable (Iviglia et al., 2019; Soldatos et al., 2017). In contrast, synthetic resorbable materials show a more predictable duration of the barrier function as their resorption and biomechanical properties can be tuned during the design by modulating their composition (Iviglia et al., 2019).

The crosslinking technique is frequently associated with higher cytotoxicity because of the possible presence of toxic crosslinking traces inside the membrane matrix (Iviglia et al., 2019). Among the chemical crosslinking agents, glutaraldehyde is the most widely used, but it has been reported to be cytotoxic. The use of ribose, a natural and non-toxic crosslinking agent, effectively extends resorption time for up to 16 to 24 weeks, while resulting in a sufficient permeability to allow progenitor cells' migration (Soldatos et al., 2017).

One of the most recurrent postoperative complications is membrane exposure to the mucosal cavity. It should be emphasized that membrane exposure has frequently been linked to the use of a more stable form (crosslinked membrane) or non-resorbable membrane (Thoma et al., 2019). In fact, in part because of the longer resorption time, crosslinked membranes have a greater probability to become exposed to the oral environment and developing critical complications such as inflammation, swelling, or wound infection (Garcia et al., 2018; Jiménez Garcia et al., 2017). Spontaneous membrane exposure can significantly alter the regeneration of periodontium (Khojasteh et al., 2017).

A potential disadvantage of using a resorbable membrane is the eventual bacterial contamination. To be precise, the surface of the exposed membrane is prone to be colonized by bacteria. The contamination of the periodontal site by pathogens may cause early membrane bioresorption and compromise the final clinical outcome (Soldatos et al., 2017).

Table 1. Benefits and limits of non-resorbable and resorbable membranes

	Benefits	Limits
Non-resorbable membranes	Mechanical stability of the space under the membrane [1]	Increased risk of exposure [3, 4, 5, 9, 10, 11]
	Excellent biocompatibility and inertness [1, 2, 4]	Increased risk of soft tissue ingrowth [6]
	Stiffness which is suitable for space maintenance, wound stability, and successful bone regeneration [1, 3]	Disadvantage related to membrane stiffness: necessary primary fixation of the membrane at the initial surgery [1, 3, 4, 7]
	Plasticity allows for bending, contouring, and adaptation to any damaged morphology [4]	A necessary second surgery to remove the membrane [1, 2, 6, 10]
	High success rate (e-PTFE membranes are considered a gold standard for GBR) [8]	
Resorbable membranes	Improved patient comfort: no need for second-stage surgery for membrane removal [1]	Uncontrolled duration of barrier function: unpredictable resorption rates [1, 7]
	Simplified surgical procedure (easy to handle and user-friendly) [1, 3]	The need for microscrews and bone grafts to support the membrane and prevent its collapse [3]
	Lower rate of exposure [3]	Limited clinical indication [3]
	Excellent success rate of the clinical outcome and less exposure-related failures [11, 12]	Lack of sufficient mechanical strength [1]. Crosslinking method improves mechanical strength but can leave toxic traces inside the membrane network
	Resorbable membranes can be potentially bioactive with therapeutic properties [1, 2]	

Notes: [1] Iviglia et al. (2019); [2] Bottino and Thomas (2015); [3] Chiapasco and Casentini (2018); [4] Elgali et al. (2017); [5] Garcia et al. (2018); [6] Siaili et al. (2018); [7] Soldatos et al. (2017); [8] Merli et al. (2016); [9] Wessing et al. (2018); [10] Camps-Font et al. (2018); [11] Sheikh et al. (2017); [12] Khojasteh et al. (2017).

- *Resorbable collagen membranes*

Components of resorbable collagen membranes: Collagen, the most abundant extracellular matrix protein, can be obtained from different collagen-rich tissue, such as dermis or tendons of bovine/porcine species (Allan et al., 2021). Type 1 collagen is the main constituent of resorbable collagen membranes. It is a fibrous protein that is extracted by several methods, such as proteolytic treatment that results in the cleavage of collagen links and telopeptides (Sheikh et al., 2017). Collagen from animal origin needs to be chemically purified to eliminate fat, bacterial, and viral contaminants. The antigenicity, biocompatibility, and sterility are also checked. The behaviour of the collagen membranes depends very much on the source of the collagen and the conditions used during their production (Iviglia et al., 2019; Lee et al., 2020).

Properties of resorbable collagen membranes: The resorbable collagen membranes exist in numerous forms and thicknesses depending on the method used to manufacture the membrane, as well as the collagen source and extraction method. There are membranes composed of homogenous collagenous matrix and membranes with bilayer structures, where each layer has different characteristics – such as one being spongy and the second being compact, thus limiting the passage of cells through the membrane. These characteristics may directly influence their biomechanical and space-maintaining properties (Elgali et al., 2017).

Non-crosslinked collagen membranes have a short half-life that ranges between 7 and 28 days. Collagen can be crosslinked, and according to the type of crosslinking process the resorption time varies from 4 to 16 weeks (Iviglia et al., 2019; Soldatos et al., 2017). Crosslinked collagen membranes stay intact sufficiently long to achieve early periodontal wound healing. For instance, crosslinked porcine collagen membranes were found 6 months after GBR (Soldatos et al., 2017).

Benefits of resorbable collagen membranes: As with other resorbable membranes, resorbable collagen membranes are very practical for clinical use. They have low immunogenicity and cytotoxicity. They are also biocompatible and enhance hemostasis (Iviglia et al., 2019).

Collagen membranes and matrices are extensively used in periodontal soft and hard tissue regeneration due to their numerous desirable biological properties. The porous structure of collagen-derived membranes is important to facilitate the diffusion of bioactive substances, oxygen, and nutrients, which are vital for hard and soft tissue regeneration (Elgali et al., 2017; Lee et al., 2020).

Resorbable collagen membranes have pro-angiogenic potential due to the release of prolyl hydroxylase inhibitors. In addition, the synthesized collagen membranes can be enriched with growth factors to enhance their angiogenic properties (Saghiri et al., 2016).

In vivo bioresorption of resorbable collagen membranes are due to the activity of endogenous collagenases (Sheikh et al., 2017; Soldatos et al., 2017).

The resorbable collagen membranes are the preferred material for periodontal regeneration because they appear to mimic the natural composition of the periodontal connective tissues (Iviglia et al., 2019). They have the potential to attract and activate periodontal ligament cells and gingival fibroblast cells. Moreover, it has been observed that these membranes stimulate extra-cellular matrix synthesis. Osteoblasts have higher levels of adherence to the surface of the collagen membrane, especially when compared with other membrane surfaces. In addition, collagen membranes have the special properties to calcify and ossify when placed near to the bone, which can have an impact on GBR clinical outcome improvement (Caballé-Serrano et al., 2019; Sheikh et al., 2017; Soldatos et al., 2017).

The added benefits of collagen membranes over non-resorbable membranes are that there is no need for a second surgical procedure for membrane removal and there is a reduced risk of infections (Elgali et al., 2017; Sheikh et al., 2017). The dehiscence of wound edges at 6-week follow-up was only 9% for the collagen membranes, which is significantly less frequent when compared with non-resorbable e-PTFE (Merli et al., 2016; Sheikh et al., 2017). Besides, when compared to e-PTFE membrane, collagen membranes prevent the apical proliferation of epithelial cells. Such a proliferation causes inflammation and marginal tissue recession, causing unfavorable clinical outcomes (Iviglia et al., 2019).

Collagen membranes use reduced peri-implant damage by 92% (Merli et al., 2016; Sheikh et al., 2017). That is why collagen membranes progressively replace e-PTFE membranes, the historical gold standard for GBR (Sheikh et al., 2017).

Thus, collagen membranes have excellent properties needed for clinical manageability, space maintenance, cell occlusivity, cell attachment, cell migration, tissue integration, hemostatic properties, biocompatibility, controllable biodegradability, low antigenicity, non-cytotoxicity, and rapid wound healing. Usage of collagen membranes minimizes postoperative complications such as dehiscence of wound edges, tissue perforations, tissue sloughing, or postoperative infections.

Limits of resorbable collagen membranes: Limited rigidity and low space maintenance are considered as drawbacks of collagen membranes (Iviglia et al., 2019). To compensate for the limited rigidity of collagen membranes, tenting screws or pins, and osseous particles grafts are regularly used to maintain space and avoid membrane collapse (Sheikh et al., 2017).

Native collagen membranes have the major handicap of rapid *in vivo* resorption failing. Crosslinking methods are used to extend their durability and to improve their biomechanical properties, thus providing the structural integrity necessary for tissue and bone regeneration.

However, crosslinked collagen membranes have decreased biocompatibility and tissue integration. They cause more postoperative complications than non-crosslinked collagen membranes (Garcia et al., 2018; Jiménez Garcia et al., 2017). Local toxicity from remnants of crosslinking chemicals (such as glutaraldehyde) has hindered the application of collagen membranes (Allan et al., 2021).

In addition, crosslinked collagen membranes, due to their increased resorption time are more prone to exposure to the oral environment (Garcia et al., 2018; Jiménez Garcia et al., 2017), which in turn may cause wound infections (Sheikh et al., 2017). Exposure rates for crosslinked membranes were 30% higher than for non-crosslinked membranes (Wessing et al., 2018). This observation was confirmed by Elangovan, who demonstrated that the exposure rates were higher for crosslinked membranes (28.62%). Whereas it was about 20.74% for non-crosslinked membranes (Elangovan, 2013; 2018).

In addition, crosslinking can be associated with unfavorable clinical outcomes if performed improperly. It has been demonstrated that highly crosslinked porcine collagen membranes are associated with reduced vascularization and tissue integration. Meanwhile, a greater attachment gain was observed with weakly crosslinked membranes (Sheikh et al., 2017).

Conclusions

Barrier membranes have been introduced into the oral and maxillofacial surgery field to support GBR and GTR plans. This review collected literature data concerning several membrane types. Recent advances in resorbable membranes have been discussed, such as the crosslinking technique which provides longer resorption time and optimal biomechanical properties, especially when compared to membranes from non-crosslinked collagen. Resorbable collagen membranes have drawn much attention, as they ensure a high success rate and cause fewer postoperative complications. Collagen membranes are now widely used in regenerative dentistry. In particular, bioactive collagen membranes are a popular choice in tissue engineering applications (Allan et al., 2021; Lee et al., 2020).

The use of regenerative therapies to treat periodontal damage is now popular. We have observed a general increase in the use of membrane-based techniques. The future of these regenerative therapies is undoubtedly optimistic, due to the ongoing refinement of membrane criteria and the utilization of new technology for their development.

Ethical aspects and conflict of interests
The author has no competing financial interests to declare.

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References

Allan B, Ruan R, Landao-Bassonga E, Gillman N, Wang T, Gao J, et al. (2021). Collagen Membrane for Guided Bone Regeneration in Dental and Orthopedic Applications. Tissue Eng Part A 27(5–6): 372–381. DOI: 10.1089/ten.TEA.2020.0140.

Bottino MC, Thomas V (2015). Membranes for Periodontal Regeneration – A Materials Perspective. Front Oral Biol 17: 90–100. DOI: 10.1159/000381699.

Bottino MC, Pankajakshan D, Nör JE (2017). Advanced Scaffolds for Dental Pulp and Periodontal Regeneration. Dent Clin North Am 61(4): 689–711. DOI: 10.1016/j.cden.2017.06.009.

Caballé-Serrano J, Munar-Frau A, Delgado L, Pérez R, Hernández-Alfaro F (2019). Physicochemical characterization of barrier membranes for bone regeneration. J Mech Behav Biomed Mater 97: 13–20. DOI: 10.1016/j.jmbbm.2019.04.053.

Camps-Font O, Martín-Fatás P, Clé-Ovejero A, Figueiredo R, Gay-Escoda C, Valmaseda-Castellón E (2018). Postoperative infections after dental implant placement: Variables associated with increased risk of failure. J Periodontol 89(10): 1165–1173. DOI: 10.1002/JPER.18-0024.

Chiapasco M, Casentini P (2018). Horizontal bone-augmentation procedures in implant dentistry: prosthetically guided regeneration. Periodontol 2000 77(1): 213–240. DOI: 10.1111/prd.12219.

Dimitriou R, Mataliotakis GI, Calori GM, Giannoudis PV (2012). The role of barrier membranes for guided bone regeneration and restoration of large bone defects: current experimental and clinical evidence. BMC Med 10: 81. DOI: 10.1186/1741-7015-10-81.

Donos N, Dereka X, Mardas N (2015). Experimental models for guided bone regeneration in healthy and medically compromised conditions. Periodontol 2000 68(1): 99–121. DOI: 10.1111/prd.12077.

Elangovan S (2013). Complete regeneration of peri-implantitis-induced bony defects using guided bone regeneration is unpredictable. J Am Dent Assoc 144(7): 823–824. DOI: 10.14219/jada.archive.2013.0193.

Elangovan S (2018). Dental Implants Placed in Alveolar Ridge Augmented Using Guided Bone Regeneration Procedure Performed Using Resorbable Collagen Membranes and Particulate Bone Grafts Using Simultaneous or Staged Approach Exhibit a High Survival Rate. J Evid Based Dent Pract 18(2): 173–175. DOI: 10.1016/j.jebdp.2018.03.010.

Elgali I, Omar O, Dahlin C, Thomsen P (2017). Guided bone regeneration: materials and biological mechanisms revisited. Eur J Oral Sci 125(5): 315–337. DOI: 10.1111/eos.12364.

Fawzy El-Sayed KM, Dörfer CE (2016). Gingival Mesenchymal Stem/Progenitor Cells: A Unique Tissue Engineering Gem. Stem Cells Int 2016: 7154327. DOI: 10.1155/2016/7154327.

Fernandes RC, Damasceno MI, Pimentel G, Mendonça JS, Gelfuso MV, da Silva Pereira SRL, Passos VF (2020). Development of a membrane for guided tissue regeneration: An *in vitro* study. Indian J Dent Res 31(5): 763–767. DOI: 10.4103/ijdr.IJDR_244_19.

Garcia J, Dodge A, Luepke P, Wang H-L, Kapila Y, Lin G-H (2018). Effect of membrane exposure on guided bone regeneration: A systematic review and meta-analysis. Clin Oral Implants Res 29(3): 328–338. DOI: 10.1111/clr.13121.

Ghavimi MA, Bani Shahabadi A, Jarolmasjed S, Memar MY, Maleki Dizaj S, Sharifi S (2020). Nanofibrous asymmetric collagen/curcumin membrane containing aspirin-loaded PLGA nanoparticles for guided bone regeneration. Sci Rep 10(1): 18200. DOI: 10.1038/s41598-020-75454-2.

Hwang C, Park S, Kang I-G, Kim H-E, Han C-M (2020). Tantalum-coated polylactic acid fibrous membranes for guided bone regeneration. Mater Sci Eng C Mater Biol Appl 115: 111112. DOI: 10.1016/j.msec.2020.111112.

Iviglia G, Kargozar S, Baino F (2019). Biomaterials, Current Strategies, and Novel Nano-Technological Approaches for Periodontal Regeneration. J Funct Biomater 10(1): 3. DOI: 10.3390/jfb10010003.

Jiménez Garcia J, Berghezan S, Caramês JMM, Dard MM, Marques DNS (2017). Effect of cross-linked vs non-cross-linked collagen membranes on bone: A systematic review. J Periodontal Res 52(6): 955–964. DOI: 10.1111/jre.12470.

Khojasteh A, Kheiri L, Motamedian SR, Khoshkam V (2017). Guided Bone Regeneration for the Reconstruction of Alveolar Bone Defects. Ann Maxillofac Surg 7(2): 263–277. DOI: 10.4103/ams.ams_76_17.

Lee J-S, Mitulović G, Panahipour L, Gruber R (2020). Proteomic Analysis of Porcine-Derived Collagen Membrane and Matrix. Materials (Basel) 13(22): 5187. DOI: 10.3390/ma13225187.

Merli M, Merli I, Raffaelli E, Pagliaro U, Nastri L, Nieri M (2016). Bone augmentation at implant dehiscences and fenestrations. A systematic review of randomised controlled trials. Eur J Oral Implantol 9(1): 11–32.

Paolantonio M, Femminella B, Coppolino E, Sammartino G, D'Arcangelo C, Perfetti G, Perinetti G (2010). Autogenous periosteal barrier membranes and bone grafts in the treatment of periodontal intrabony defects of single-rooted teeth: a 12-month reentry randomized controlled clinical trial. J Periodontol 81(11): 1587–1595. DOI: 10.1902/jop.2010.100094.

Saghiri MA, Asatourian A, Garcia-Godoy F, Sheibani N (2016). Effect of biomaterials on angiogenesis during vital pulp therapy. Dent Mater J 35(5): 701–709. DOI: 10.4012/dmj.2015-332.

Sanz-Sánchez I, Carrillo de Albornoz A, Figuero E, Schwarz F, Jung R, Sanz M, Thoma D (2018). Effects of lateral bone augmentation procedures on peri-implant health or disease: A systematic review and meta-analysis. Clin Oral Implants Res 29 Suppl. 15: 18–31. DOI: 10.1111/clr.13126.

Sasaki J-I, Abe GL, Li A, Thongthai P, Tsuboi R, Kohno T, Imazato S (2021). Barrier membranes for tissue regeneration in dentistry. Biomater Investig Dent 8(1): 54–63. DOI: 10.1080/26415275.2021.1925556.

Sheikh Z, Qureshi J, Alshahrani AM, Nassar H, Ikeda Y, Glogauer M, Ganss B (2017). Collagen based barrier membranes for periodontal guided bone regeneration applications. Odontology 105(1): 1–12. DOI: 10.1007/s10266-016-0267-0.

Siaili M, Chatzopoulou D, Gillam DG (2018). An overview of periodontal regenerative procedures for the general dental practitioner. Saudi Dent J 30(1): 26–37. DOI: 10.1016/j.sdentj.2017.11.001.

Soldatos NK, Stylianou P, Koidou VP, Angelov N, Yukna R, Romanos GE (2017). Limitations and options using resorbable versus nonresorbable membranes for successful guided bone regeneration. Quintessence 48(2): 131–147. DOI: 10.3290/j.qi.a37133.

Thoma DS, Bienz SP, Figuero E, Jung RE, Sanz-Martín I (2019). Efficacy of lateral bone augmentation performed simultaneously with dental implant placement: A systematic review and meta-analysis. J Clin Periodontol 46 Suppl. 21: 257–276. DOI: 10.1111/jcpe.13050.

Wessing B, Lettner S, Zechner W (2018). Guided Bone Regeneration with Collagen Membranes and Particulate Graft Materials: A Systematic Review and Meta-Analysis. Int J Oral Maxillofac Implants 33(1): 87–100. DOI: 10.11607/jomi.5461.

Windisch P, Orban K, Salvi GE, Sculean A, Molnar B (2021). Vertical-guided bone regeneration with a titanium-reinforced d-PTFE membrane utilizing a novel split-thickness flap design: a prospective case series. Clin Oral Investig 25(5): 2969–2980. DOI: 10.1007/s00784-020-03617-6.

Zhang HY, Jiang HB, Kim J-E, Zhang S, Kim K-M, Kwon J-S (2020). Bioresorbable magnesium-reinforced PLA membrane for guided bone/tissue regeneration. J Mech Behav Biomed Mater 112: 104061. DOI: 10.1016/j.jmbbm.2020.104061.