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Review

Finding the Perfect Membrane: Current Knowledge on Barrier Membranes in Regenerative Procedures: A Descriptive Review

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Abstract: Guided tissue regeneration (GTR) and guided bone regeneration (GBR) became common procedures in the corrective phase of periodontal treatment. In order to obtain good quality tissue neo-formation, most techniques require the use of a membrane that will act as a barrier, having as a main purpose the blocking of cell invasion from the gingival epithelium and connective tissue into the newly formed bone structure. Different techniques and materials have been developed, aiming to obtain the perfect barrier membrane. The membranes can be divided according to the biodegradability of the base material into absorbable membranes and non-absorbable membranes. The use of absorbable membranes is extremely widespread due to their advantages, but in clinical situations of significant tissue loss, the use of non-absorbable membranes is often still preferred. This descriptive review presents a synthesis of the types of barrier membranes available and their characteristics, as well as future trends in the development of barrier membranes along with some allergological aspects of membrane use.

Keywords: guided tissue regeneration; guided bone regeneration; barrier membranes; allergology

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1. Introduction

Periodontitis is an infectious disease, often of multifactorial etiology, in which the perio-pathogenic bacterial biofilm plays an important role. The disease is characterized by an inflammatory reaction of the host to the bacterial aggression, reactions on which both local and systemic risk factors can be grafted. In the evolution of periodontitis, through the aggressive action of bacterial factors in the context of hyper-inflammatory status, there is a gradual destruction of the supporting periodontal tissues: periodontal ligaments, cementum and alveolar bone. To address this issue, periodontal therapy has evolved over time through regenerative therapy surgical methods that include guided tissue regeneration (GTR) and bone regeneration (GBR) techniques. Such guided techniques involve isolating the bone defect with the help of barrier membranes, allowing the regeneration of lost and damaged tissues [1]. The use of a barrier membrane, at the interface with the gingival/epithelial connective tissue and with periodontal ligaments and alveolar bone to promote the regeneration of periodontal tissues is called GTR, and the restoration of alveolar bone sites is called GBR.

The association of barrier membranes and biomaterials of infrabony periodontal lesions investigated in various clinical studies generated significantly better results in

terms of attachment gain and reduction of probing depths than the open flap debridement alone [2–4].

In guided tissue regeneration, there is a number of four essential biological principles under the PASS acronym: (a) Primary closure of the surgical wound to allow uninterrupted healing; (b) Angiogenesis for adequate blood supply (supply of nutrients, as well as cell types that facilitate healing); (c) maintaining the Space for bone neo-formation, while blocking the proliferation of soft tissues and (d) wound Stability to allow blood clots to form [5].

The idea that the repopulation of cells on the root surface after periodontal surgery determines the nature of the attachment that will form is generally accepted. After the periodontal debridement, with or without open flap procedure, the root surface will be repopulated by the fastest cells, which were epithelial cells [6]. Barrier membranes placed over areas of tissue defect have as their main purpose the blocking of cell invasion from the gingival epithelium and connective tissue [7]. Barrier membranes require full in situ functionality for 4–6 weeks for periodontal tissue regeneration and 16–24 weeks for bone growth [8].

There are a number of mandatory requirements for a barrier membrane to be used successfully in guided regenerative therapies; these requirements include (a) good mechanical isolation, occlusion and blocking capabilities; (b) to be biologically active; (c) to be biocompatible; (d) to exhibit tolerance to exposure and (e) to be biodegradable [9]. Moreover, barrier membranes should have adequate porosity to prevent the excessive penetration of oral keratinocytes into the bone defect on one side but also to allow neovascularization and bone formation in the connective tissue part of the membrane [10]. It should also be easy to manipulate the membrane, to stabilize it at the site without damaging it [11].

To date, there is no commercially available membrane that meets all these parameters at optimum capacity, but recent developments in membrane production technology are trying, through various innovative forms, to meet as wide a range of characteristics as necessary to achieve predictable surgical results.

To meet some of these requirements, various techniques and materials have been developed to generate tissue neo-formation. They can be divided according to the biodegradability of the base material into absorbable membranes and non-absorbable membranes [12] (Figure 1). The use of absorbable membranes is extremely widespread due to their advantages, but in clinical situations of significant tissue loss, the use of non-absorbable membranes is often still preferred [13].

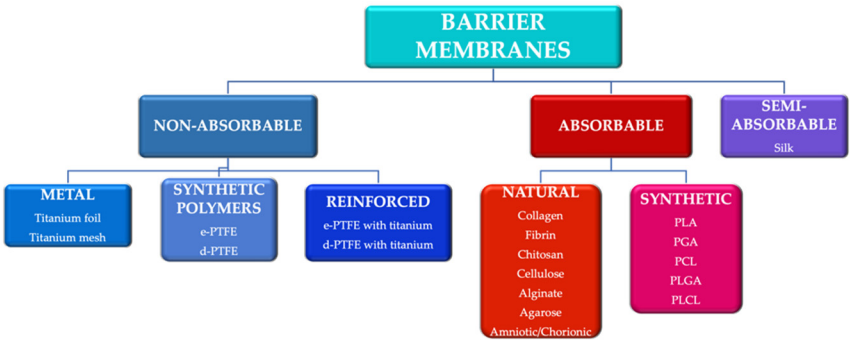

Figure 1. Main categories of barrier membranes used in guided tissue regeneration. e-PTFE: expanded polytetrafluoroethylene; d-PTFE: high density polytetrafluoroethylene; PLA: polylactic acid; PGA: polyglactic acid; PCL: polycaprolactone; PLGA: poly-lactic-co-glycolic acid PLCL: poly-lactic-co-caprolactone acid.

Another classification of barrier membranes includes the first generation of membranes (non-absorbable), second generation (absorbable) and third generation (membranes as a product of tissue engineering) [14].

We believe that a better understanding of the various types of membranes available and their properties is absolutely necessary in making clinical decisions. Thus, this review proposes a synthesis of the types of barrier membranes available and their characteristics; in addition, this paper presents future trends in the development of the field of barrier membranes, as well as some allergological aspects of membrane usage.

2. Non-Absorbable Membranes

Barrier membranes made of non-absorbable material are characterized by mechanical stability over time so that the by-products of degradation of the basic materials are not a cause for concern, and the period of fixation in place is easy to control [15]. Their setting to the anatomical substrate is usually done with the help of pins or mini-screws [16].

The major disadvantage of these membranes is the need for a second surgical time, removal from the site, after the completion of tissue neo-formation. This extra surgical time increases the risk of complications, such as infectious processes or healing disorders [12]. Moreover, non-absorbable membranes may present a higher risk of complications related to membrane exposure that include bacterial contamination or wound dehiscence [17,18]. Different types of non-absorbable membranes, with their advantages and disadvantages, are presented in Table 1.

Table 1. Types of non-absorbable membranes.

Composition		Commercial Variants	Observations
Titanium		Osteo-Mesh TM-300® Frios BoneShields	Very good mechanical properties Bio-inert High risk of oral exposure Requires setting pins Requires second surgical time
Silicone			Low cost Bio-inert Very low micro-porosity Requires second surgical time
Polytetrafluoroethylene (PTFE)	Expanded (e-PTFE)	Gore-Tex®	Good mechanical properties Good micro-porosity Bio-inert High risk of oral exposure, with bacterial loading
	High density (d-PTFE)	High density Gore-Tex® Cytoplast TXT-200® Cytoplast Regentex GBR-200®	Good mechanical properties Good micro-porosity Smooth surface (low risk of bacterial loading) Can be left partially exposed in the oral cavity High risk of oral exposure
	e-PTFE with titanium	Gore-Tex® Reinforced	Very good mechanical properties Bio-inert High risk of oral exposure
	d-PTFE with titanium	Cytoplast Regentex Ti-250®	

2.1. Non-Absorbable Metal Membranes

Titanium is the material of choice in making non-absorbable metal membranes. It is an inert, stable material with good mechanical strength; in addition, it has a high degree of biocompatibility [19,20]. These qualities of titanium make it usable in high-amplitude tissue defects, where it gives a constant shape over time [21]. An economic disadvantage is the high cost of these membranes compared to other common materials [12]. Titanium membranes may be available as all-metal membranes or metal mesh membranes.

In 2003, the Ultra-Ti® GTR titanium barrier membrane was introduced [22]. Ultra-Ti® membrane is a pure titanium membrane with a homogeneous structure, about 10 microns thick; due to its ultra-thin thickness, it is easy to handle and adapt to the receptor site [23]. Moreover, the surface roughness is reduced, which makes it less susceptible to bacterial contamination. In addition, it does not require setting with pins. Because it is radiolucent,

it allows the monitoring of bone formation. As a disadvantage, being a non-porous membrane, it does not allow the perfect integration of tissues, which can lead to periodontal pocket formation [23].

In 1969, titanium mesh membranes were introduced to regenerate bone defects [24]. Titanium mesh has good mechanical properties in stabilizing bone regeneration materials. Its rigidity ensures the maintenance of the space and prevents the collapse of the defect; its elasticity prevents the compression of the mucosa, and its plasticity allows bending, contouring and adaptation to the bone defect [25]. Titanium mesh has been shown to maintain space with a higher degree of predictability, even in cases of extensive bone defects [26].

In general, titanium mesh membranes are characterized by macro-porosity; this quality is considered to play an important role in ensuring blood supply, allowing the diffusion of extracellular nutrients through the membrane [27]. Moreover, soft tissue attachment, favored by high porosity, facilitates the stabilization and restriction of epithelial cell migration [28]. Celletti et al. claimed in their study data that the use of a pore-free titanium membrane resulted in the exposure of all meshes in three weeks [29].

Of course, this type of membrane also has a number of disadvantages; due to its sharp edges, irritation of the soft tissue components can occur, which can lead to membrane exposure and even compromise therapeutic success [30]. However, titanium membranes can tolerate some degree of exposure. The exposure rate of titanium mesh membranes varies between 5.3% and 52% [31].

In a study of 44 patients who underwent titanium mesh-reinforced GTR, membrane exposure occurred in 23 cases, but graft failure occurred in only one patient [32]. In contrast, in another study, membrane exposure generated a bone resorption of 15–25% [33].

From the point of view of the predictability of the amount of newly formed bone, the studies generated discordant results, with growth values in vertical bone defects between 2.56 mm and 6 mm [32,34]. For increases in horizontal defects, the data indicate average values of 4 mm [32,35].

2.2. Non-Absorbable Membranes of Synthetic Polymers

From the category of synthetic polymers, polytetrafluoroethylene (PTFE) is an example of a material used in non-absorbable membranes. According to its structure, PTFE can be divided into two types: expanded PTFE (e-PTFE) and high density PTFE (d-PTFE) [24].

e-PTFE was developed in 1969 and became a standard material in the 1990s. Its structure is bi-layered, with pores between 5 and 20 microns in size. One side presents an open microstructure of 1 mm thickness, with 90% porosity, which delays epithelial growth, and on the other side there is a 0.15 mm thick membrane with 30% porosity, which generates space for new bone [36]. The main disadvantages of the e-PTFE membrane are the higher exposure rate and, of course, the need for a second surgical time to remove it from the site, a feature common to all non-absorbable membranes. Subsequently, in 1993, a high-density PTFE membrane (d-PTFE) was developed with pores smaller than 0.2 microns in diameter [36]. Research focused on d-PTFE has shown that surgical removal was easier for the d-PTFE membrane than for e-PTFE analogues, which could lead to fewer disruptions to the underlying tissue [12]. Due to its high density and micro-porosity, bacterial infiltration is much reduced [24]. Barber et al. reported that d-PTFE completely blocks the penetration of food and bacteria; thus, even if the membrane becomes exposed in the oral cavity, it maintains its functionality [37].

As both e-PTFE and d-PTFE had reduced mechanical stiffness, titanium mesh was introduced into their structure; this mesh or reinforcement is malleable for good adaptation to the receiving site [7]. Titanium-reinforced e-PTFE membranes have demonstrated higher space holding capacity and better stability than plain e-PTFE [38]. The Gore-Tex membrane (W.L. Gore & Associates, Flagstaff, AZ, USA), which is made of e-PTFE, has been widely used in clinical treatment and has become a first choice-material for GTR and GBR. It is also widely used for general surgery, neurosurgery and cardiovascular surgery [39].

2.3. Non-Absorbable Silk Membranes

Silk is a material produced by the *Bombyx mori* silkworm (*B. mori*). It is a natural biopolymer, composed mainly of fibroin and sericin [40]. Silk fibroin was used as a biomaterial after the removal of sericin [41]; it is a compound characterized by high capacity for biocompatibility and tissue integration [42]. Silk fibroin membranes can generate a favorable adhesion of osteogenic cells, favoring bone neo-formation [43]. The major disadvantage of these membranes is the difficult handling as well as the low mechanical properties [44,45].

An alternative to simple silk membranes is given by the silk pad; it is produced from the cocoon of silkworms by a simple peeling method [46]. The silk pad has a number of benefits; it has a higher tensile strength in wet conditions than collagen and/or d-PTFE membranes [47]. Moreover, the obtaining procedure is a simple one, and at a low cost [48]. In addition, the silk pad has a high amount of sericin, which promotes bone neoformation [49,50]; Ha et al. demonstrated, in an animal model study, a similar level of bone regeneration for the silk pad compared to collagen or d-PTFE membranes [47].

3. Absorbable Membranes

Absorbable (or second-generation) membranes were developed with the primary goal of avoiding the need for a second surgical time of guided regeneration for the barrier membrane removal from the site. Depending on the material from which the absorbable membrane is made, they can be of natural or synthetic origin (Table 2). In addition, absorbable membranes are characterized by lower costs than non-absorbable membranes, as well as reduced risks of complications [51,52]. Mechanical instability of absorbable membranes is a major disadvantage. Creating and maintaining the space needed for bone formation may be compromised; thus, it is recommended to associate the membranes with bone replacement material to fill the bone defect [12]. Moreover, membrane degradation products can affect the process of tissue regeneration [53]; in addition, there is a risk of cross-infection in membranes of animal origin [54].

3.1. Absorbable Membranes Made of Natural Polymers

The most commonly used natural polymers for barrier membranes are type I collagen and type III collagen. BioMend Membrane (Zimmer Biomet Dental, Warsaw, IN, USA) was the first collagen-based membrane produced for guided tissue and bone regeneration application. Natural collagen is obtained by a decellularization process followed by steps of removal of any antigenic components [55].

Sources for collagen include human skin (Alloderm®, LifeCell, Branchburg, NJ, USA), porcine skin (Bio-Gide®, Geistlich, Shirley, NY, USA), porcine peritoneum (MemGuide®, Ace, Boston, MA, USA) or Achilles' tendon (Cytoplast® RTM Collagen, Franklin Lakes, NJ, USA) [14,56]. After harvesting from the primary source, the product is subjected to decellularization, crosslinking and sterilization processes. The crosslinking treatment aims to increase the resistance of the membrane and can be achieved by different methods: UV irradiation or chemical processing. Glutaraldehyde, carbodiimide, hexamethylene diisocyanate, diphenyl-phosphoryl azide, formaldehyde or genipine can be used in chemical crosslinking [12,57]; other studies have also shown that crosslinking promoted prolonged biodegradation, reduced epithelial migration, decreased tissue integration and decreased vascularization [14,58].

The main concern related to the use of chemical agents is given by the potential toxic and inflammatory reactions produced in the recipient organism [59]. To overcome these disadvantages, other cross-linking agents with low cytotoxicity have been developed, such as (a) diphenylphosphorylazide, with biocompatibility and good handling characteristics, without cytotoxic effects [60]; (b) 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, with high resistance and low cytotoxicity [61] and (c) epigallocatechin-3-gallate, with better mechanical properties and anti-inflammatory effects [62].

Table 2. Types of absorbable barrier membranes.

Type			Commercial Variants	Absorption Time	Observations
Natural	Proteins	Collagen	BioGide®	24 weeks	From porcine dermis Composition: type I and III collagen
			Periogen®	4–8 weeks	
			RCM	26–38 weeks	From bovine tendon Composition: 100% type I collagen
			BioMend®	6–8 weeks	
			BioMend-Extend®	18 weeks	
			OSSIX®	6 months	
			Paroguide®	4–8 weeks	From calfskin Composition: 96% type I collagen, 4% chondroitin-4-sulfate
			Alloderm®	8–10 weeks	From human cadaver Composition: type I collagen
		Fibrin	Autologous	7–11 days	
			Etik-Patch®	4–6 weeks	Elastin and bovine fibrin with a polyglactin mesh
	Polysaccharides	Chitosan		16–20 weeks	
		Cellulose	Nanoskin®		
		Alginate			
		Agarose			
Synthetic	PGA/TMC		Resolut Adapt X®	16–24 weeks	
			Resolut Adapt LT®		
	PLA	Polylactic acid	Guidor®	10–12 weeks	
			Epi-guide®		
	PLA/PGA/TMC		Resolut Adapt®	8–10 weeks	

PGA: polyglactic acid; PLA: polylactic acid; TMC: trimethyl chitosan

Moreover, although crosslinked collagen membranes have prolonged degradation times, they also have significantly higher membrane exposure rates of up to 70.5% [63,64]. As already mentioned, premature exposure of membranes is often associated with bacterial invasion, as demonstrated by Becker [65].

Collagen membranes can perform hemostatic functions, allowing and stimulating the attachment and proliferation of fibroblasts and osteoblasts due to the presence of arginine-glycine-aspartic acid (Arg-Gly-Asp) and GFOGER sequences (glycine-phenylalanine-hydroxyproline-glycine-glycine) integrin-specific [66]; data suggest that cellular activity begins 3–5 days postoperatively [67]. At the same time, the membrane allows the signals from the cells associated with the membrane to be transferred to the cells in the bone defect, thus creating a favorable environment for bone neo-formation [68]. They can also be easily integrated with soft tissues and are permeable, so nutrient diffusion can be conducted easily [69,70].

There are data on the performance of non-crosslinked type I collagen membranes with non-absorbable PTFE membrane that claim that non-crosslinked collagen membranes promote a high rate of vascularization at two months postoperatively [71]. Other studies have compared the rate of bone formation of collagen membranes with e-PTFE membrane, both of which show similar results [26,72–74]; stromal cells attached to the collagen membrane promoted the production of fibroblast growth factor (FGF-2) and bone morphogenetic protein (BMP-2), stimulating bone regeneration. The influence of the use of collagen membrane in the regeneration of calvarial defects on Wistar rats was investigated; defects that were covered with collagen membranes demonstrated better bone regeneration than defects without membrane [75].

The resorption time differs for each membrane, from 8 to 38 weeks [76,77]. Accelerated resorption of the barrier membrane can compromise the success of surgery. In a study

that looked at the degradation of uncoated collagen membranes, it was found that some membranes begin the resorption process in the first 8 h post-surgery [78].

Natural materials for making absorbable membranes include alginate and chitosan. Alginate is a dimeric polysaccharide with a structure composed of β-D-mannuronate and α-L-guluronate blocks. It is found in the walls of brown algae cells and in some bacterial capsules [79]. Alginate is biocompatible, non-toxic and does not cause inflammatory reactions, but has poor mechanical strength and adhesion. This material remains widely used in dentistry in impression techniques [80].

Chitosan is a copolymer of glucosamine and N-acetyl-D-glucosamine, produced from crustacean chitin [81]. Like alginate, it is a biocompatible and flexible material, the degree of resorption of which depends on its molecular weight [82]; membranes made of chitosan have demonstrated bacteriostatic properties [14] but, due to their fragility, are difficult to handle and to apply [83].

3.2. Absorbable Membranes of Synthetic Polymers

A stage in the development of membrane technologies was the artificial design of absorbable materials. These materials include biodegradable aliphatic polyesters: (a) polylactic acid (PLA); (b) polyglycolic acid (PGA) and (c) polycaprolactone (PCL) and their copolymers: poly-lactic-co-glycolic acid (PLGA) or poly-lactic-co-caprolactone acid (PLCL) [84,85]. PLA can be used alone or copolymerized with PGA. Polyester degradation is determined by hydrolysis and dependent on the hydrophobicity of the polymer [86]; PLA being more hydrophobic than PGA, degradation time is, thus, prolonged.

Aliphatic polyester membranes are bio-absorbable; the resorption of these membranes depends on the polyester types and ratio [87]. They also have good workability and maneuverability. Major disadvantages include lack of rigidity, stability but also concerns about the interactions of their degradation products with the recipient organism [88]; inflammatory reactions due to macrophages and leukocytes around the membrane were observed during absorption [89].

Improving mechanical properties using only biodegradable polyester can be difficult, which is why their main clinical indication is for small vertical bone defects, with the association of bone regeneration materials [12]. A combination of different porosity layers was proposed: the less porous side could act as a barrier, preventing epithelial cell infiltration, and the other side in contact with bone defect would allow tissue integration. Such techniques have been used in the Guidor Matrix Barrier (Sunstar Americas Inc., Schaumburg, IL, USA) and Resolut (W.L. Gore and Associates, Newark, DE, USA). Woven fibers technique (Vicryl Periodontal Mesh; Ethicon Inc., Cornelia, GA, USA), or polymer solution dissolved during the surgical procedure and molded in a cassette to form the Atrisorb membrane (Atrix Laboratories, Fort Collins, CO, USA) have also been adopted [55].

Poly-lactic-co-glycolic acid (PLGA) can be prepared in different copolymer forms depending on the ratio between PLA and PGA; its advantages include biocompatibility and biodegradability, and it is also easy to process [90]. Hoornaert et al. [91] developed a bi-layered PLGA membrane, composed of a dense, thin film that prevents the growth of epithelial cells and a thick, microfiber layer in order to stabilize the blood clot and promote cell colonization; the absorption rate was similar to the monolayer membrane of PLGA, but the rate of bone neo-formation was higher compared to the PLGA membrane [92]. Similar results were obtained by Abe et al. [93] with a bi-layered membrane from PLCL. The authors also observed that the two-layer PLCL membrane reduced bacterial adhesion and prevented bacterial invasion inside the membrane.

4. Enhanced Barrier Membranes

No polymer, natural or synthetic, seems to be sufficient alone. Therefore, the trends were either to combine materials or to enhance them with additives. New membranes have been developed, with additional functions such as the release of beneficial agents: antibiotics, growth factors and adhesion factors.

4.1. Membranes with Inorganic Compounds

In order to enhance the osteoconductive and osteoinductive effects, research has focused on the introduction into the structure of the barrier membrane of synthetic calcium phosphates (hydroxyapatite or β-tricalcium phosphate), single or combined in biphasic calcium phosphates. Such products allow vascular penetration, cell infiltration and attachment, cartilage formation and calcified tissue deposition [94,95]. Phipps et al. [95] showed that the membrane made of a mixture of particles of PCL, collagen and hydroxyapatite generated a rapid cell spread and a significant cell proliferation. Baek et al. [96] evaluated the effects of collagen membrane and a membrane of chitosan, fibroin and hydroxyapatite on calvarial defect in rats; the results were similar for both types of membranes, with the absence of inflammatory reactions [96].

Won et al. [97] compared the collagen membrane with a membrane made of PCL, PLGA and β-tricalcium phosphate; even if both membranes showed similar results in histological and histomorphometric analyses, the membrane made of PCL, PLGA and β-tricalcium phosphate generated a larger area of bone neo-formation [97].

Other studies have looked into potential effects of including zinc, magnesium, iron or strontium in the composition of the membrane. Zinc is an absolutely necessary mineral for skeletal growth and development [98], important in many physiological and metabolic processes [99]. The addition of ZnO in the structure of barrier membranes has generated improvements in the proliferation of osteoblasts, with an accelerated regenerative mechanism [100]; the use of zinc membranes has also demonstrated a faster healing process [101], as well as inhibiting the formation of bacterial biofilm [102,103]. In addition, Oh et al. [104] observed that PLA-Zn-bioactive glass membranes showed tensile strength, elongation and flexibility similar to those of zinc-free membranes [104].

Similar to zinc, magnesium is an important factor in bone metabolism, with both proliferative effects for osteoblasts and anti-osteoclastic effects [105]. The strength of the Mg alloy is higher than that of absorbable polymers, such as PLA; therefore, magnesium alloy can improve the mechanical properties of membranes. However, the rate of the degradation of magnesium alloy is too fast [106]. An in vitro study found that hydrofluoric acid coating can delay the corrosion of magnesium alloys [107]. Xin et al. [108] designed a barrier membrane made of PLA reinforced with a Mg alloy core, with a better loading capacity compared to membranes without Mg reinforcement; when fluorine-coated magnesium alloy was used, it showed better resistance to corrosion. The proliferation of fibroblasts and osteoblasts has also been easily achieved [109].

Strontium is involved in bone mineral metabolism by inducing osteogenesis, stimulating markers of differentiation and proliferation, and reducing apoptosis levels [109]. Kitayama et al. [110] studied the effect of covering rabbit calvarial defects with a collagen membrane with strontium and hydroxyapatite; after 24 weeks, they observed increased levels of newly mineralized bone and less residual grafting material compared to an unmodified collagen membrane [110].

Thus, membranes enhanced with inorganic compounds could offer a favorable alternative in GTR and GBR, but additional data are needed to optimize the protocols for the use of these membranes.

4.2. Membranes with Antimicrobial Factors

The inclusion of several antimicrobial substances, such as antibiotics or silver ions, has been investigated in the structure of barrier membranes. Metronidazole benzoate can be added to the layer in contact with the epithelial tissue, preventing bacterial adhesion and proliferation [111]. Favorable results of metronidazole supplementation were also obtained by Shi et al. [112] and Wang et al. [113]. Other studies have investigated the use of azithromycin [114], tetracyclines [115,116] or silver ions [117].

Techniques for loading silk fibroin with 4-hexylresorcinol have been developed; 4-hexylresorcinol is a natural phenolic compound, with antimicrobial, antioxidant and antimutagenic abilities [118]. Moreover, 4-hexylresorcinol has been shown to inhibit the

pathways of nuclear factor-κB (NF-κB) [119], a molecule involved in osteoclast differentiation, with a resorptive role. Favorable results have been obtained in vivo and in other studies [120,121]. One of the obstacles to the practical applicability of these membranes is represented by their poor mechanical properties [45].

The disadvantages observed in the membranes with antimicrobial agents were the fact that most of them generally have a short release time of the drug; moreover, some periodontal tissue infections often occur after a relatively long period of time after surgery [112]. A number of studies have shown that the highest concentration of antibacterial substance is released in the first 3 days postoperatively, decreasing progressively in the following days and often becoming insufficient in situations of need [122–124]. Thus, the research focused on the development of techniques for making enriched membranes with slow and adequate release of microbial agent in order to prevent the so-called "waste" of the agent in unnecessary situations. Xue et al. [125] managed to extend the release time of the antimicrobial agent to 15 days, using fibers with encapsulated nanotubes that were loaded with metronidazole.

Trying to obtain the "release as needed" of metronidazole incorporated into the barrier membrane, Shi et al. [112] investigated the effects of esterified and grafted metronidazole on the surface of PCL nanofiber pads modified by ester bonds as a barrier membrane; ester bonds can be selectively hydrolyzed by cholesterol esterase. Cholesterol esterase is an enzyme secreted by macrophages accumulated at the site of infection, the concentration of which is positively related to the severity of the infection. Increased cholesterol esterase results in an increased release of metronidazole from the membrane, with antibacterial action [112].

One of the major problems with the use of membranes with antimicrobial agent is the risk of generating resistant bacterial species [126]; thus, there is an absolute need for clear guidelines and protocols for the use of such membranes.

4.3. Membranes with Growth Factors

Growth factors have been the subject of numerous studies, being included both in bone addition material and in the structure of barrier membranes. These factors include the group of bone morphogenetic proteins (BMP), stromal cell derived factor 1 alpha (SDF-1α), transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), growth factor rich in platelets (PRGF) or fibroblast growth factor-2 (FGF-2) [55].

Bone morphogenetic proteins are among the most powerful osteoinductive proteins; they have modulatory effects on the differentiation and functionality of cells involved in bone formation [127]. Jones et al. [128] and Hsu et al. [129] investigated the treatment of ePTFE and titanium membranes, respectively, with BMP-2, both studies providing favorable data on new bone formation. One study reported beneficial results of BMP-9 incorporation into the collagen barrier membrane; BMP-9 stimulated alkaline phosphatase activity as well as osteoblastic gene expression [130].

A number of studies have shown that BMP-6 induces bone neo-formation, favoring bone augmentation procedures [8,131]. Gümüşderelioğlu et al. [127] developed a biodegradable chitosan membrane whose porous surface that comes in contact with the bone surface was enriched with hydroxyapatite and BMP-6; in order to improve the resistance of chitosan, the membrane was treated with glycerol solution. The authors concluded that this membrane demonstrated osteogenic activity and prevented the migration of epithelial cells [127]. In another study, Soran et al. [132] showed that the application of BMP-6 improved the osteoblastic differentiation of mesenchymal stem cells derived from bone marrow in vivo. A polymeric membrane loaded with BMP-6 on the hydroxyapatite coated membrane surface was patented (WO2016186594A1) [133], with the aim of providing memory and osteogenic activity, supporting bone regeneration, preventing epithelial cell migration and eliminating inflammation.

Incorporation of BMP-9 into the collagen membrane in vivo has also generated favorable results for bone neoformation in horizontal defects [134]. Shalumon et al. [135]

demonstrated favorable results regarding the differentiation of osteogenic cells in GTR therapies with chitosan-fibroin-hydroxyapatite membrane in which BMP was incorporated.

PDGF-enriched PLA membranes have been associated with improved regenerative effects [136,137]. Other studies investigating PLA membranes with TGF-β in alginate/nanofiber hybrid mesh have found effective regeneration in bone defects [138]. In another in vivo study, a six-fold increase in bone volume was observed when using a PCL/gelatin membrane enriched with SDF-1α compared to the use of titanium membrane [139].

Major disadvantages of growth factors supplementation in the structure of barrier membranes include the high production cost, but also the fact that the doses are usually over-physiological, with potential adverse effects [55,140].

5. Trends in the Development of Barrier Membranes

5.1. Amniotic and Chorionic Membranes

Amniotic and chorionic membranes are biological membranes, which means that they are bio-absorbable and compatible with tissues. The human placenta is essential in the development and survival of the fetus, ensuring physical and biological protection [141]. The amniotic membrane consists of a thick basal membrane and an avascular stromal matrix; this is the innermost layer of the placenta. Chorion forms the outer end of the sac and is made up of several types of collagen and bioactive components of cell adhesion [142]. Amniotic and chorionic membranes have been used in transplant surgery, proving healing, anti-inflammatory and antibacterial properties [143].

Membrane harvesting is usually done from healthy pregnant patients; caesarean section is preferred because vaginal birth placentas may be contaminated [141]. After harvesting, the collected placenta is placed in a sterile transport medium; to obtain the amniotic membrane, the amnion is separated from the underlying chorion along their natural plane of cleavage. Subsequently, the amniotic membrane is abundantly irrigated with a saline solution containing streptomycin, penicillin, neomycin and amphotericin prior to storage [143]. Methods of preserving the amniotic membrane include cryopreservation, lyophilization or air drying. Cryopreservation results in an improved retention of proteins and growth factors compared to lyophilization [144], but cryopreservation can affect the viability of cells in the amniotic membrane [145]. After lyophilization or air drying, it is necessary to sterilize the membrane with the help of gamma radiation [146] or with peracetic acid [147].

The amniotic membrane contains type IV, V and VI collagen as well as proteins (fibronectin, laminin, proteoglycans, glycosaminoglycans) [148]. The amniotic membrane contains laminin 5, a protein that stimulates the cell adhesion of gingival epithelial cells, collagen types I, II, IV, V and VI, platelet-derived growth factor, fibroblast growth factor and TGF-β [149]. Perlecan found in the amniotic membrane plays an important role in binding growth factors and interacts with various cell adhesion molecules [150].

Histologically, the chorionic membrane consists of three layers: reticulate, basal membrane and trophoblastic. Collagen types I, III, IV, V, VI and VII, as well as proteoglycans are found in the crosslinked layer; the basal membrane contains type IV collagen, fibronectin and laminin [151]. Inhibitors of matrix metalloproteinases have been identified in the chorion, factors that can inhibit inflammatory status and stop collagen degradation [152].

Given these aspects, amniotic and chorion structures offer potential for use as barrier membranes in GTR and GBR. Such membranes have antibacterial and antifungal properties, minimize wound inflammation and provide a protein-rich matrix that allows cells to migrate more easily [153]. Moreover, the harvesting technique is relatively simple; by hydration with the blood, the membrane becomes malleable [142]. Major limitations include the risk of cross-contamination, as well as their fragility [151].

Amniotic and chorionic membranes have been shown to be effective in bone neoformation in periodontal defects, on canine [154] and human [155] subjects. Venkatesan et al. used an amniotic membrane in combination with an alloplastic biphasic bone substitute

(60% hydroxyapatite, 40% tricalcium phosphate) to treat infrabony defects; this membrane generated similar results to porcine-derived collagen membrane in terms of postoperative healing and the amount of newly formed bone [155]. Holtzclaw et al. [156] used an amnio-chorionic membrane to treat infrabony defects, observing significant improvements of clinical parameters (probing depth and loss of periodontal clinical attachment) at 12 months [156]. Another study compared the effects of lyophilized amniotic membrane and collagen membrane on newly formed bone density; the bone density of defects treated with amniotic membrane was higher than the sites where no barrier membrane was used and equivalent to the density obtained with collagen membrane ($p < 0.05$) at 3 weeks [157].

The amniotic membrane has also been used successfully in periodontal muco-gingival surgery; the association of the amniotic membrane with repositioned flaps has generated favorable results in covering the gingival recessions and in increasing the thickness of the attached gingiva [158,159].

An amniotic membrane with different potential areas of use was patented (US6326019B1) [160], but its usage was directed mainly in skin and mucosal grafting. Actishield™ (Wright Medical, Memphis, TN, USA) was also developed, but with main indication for orthopedic surgery. Up to date, there is no approved commercial amniotic/chorionic membrane for periodontal tissue regeneration. Nevertheless, in all types of membranes, Quality by Design principles and regulations have been introduced in order to obtain benefits of an integrated and risk-free approach to the industrialization process in membranes manufacturing [55].

5.2. Barrier Membranes from PRF

Platelet concentrates have been a research topic for more than 20 years; platelet-rich plasma, discovered in the late 1990s, was the result of centrifugation of blood harvested on the spot from the patient, offering good advantages in oral and maxillofacial surgery [161]. This procedure, on the other hand, had disadvantages related to the use of anticoagulants that could interfere with the healing process. Subsequently, a new product without anticoagulant was developed, platelet-rich fibrin (PRF). PRF has been shown to significantly increase the potential for tissue regeneration, favoring the slow and gradual release of growth factors trapped in its fibrin matrix [162].

PRP has been used primarily for soft tissue regeneration rather than osteogenesis and requires more blood than PRF. PRP is centrifuged at a higher rate, causing all heavy white blood cells and stem cells to sink to the base of the tube, not being collected in the sample [163]. Further research has found that a higher platelet concentration with the inclusion of white blood cells and stem cells in the sample would be even more therapeutic. The inclusion of white blood cells helped prevent postoperative infection, and the presence of stem cells generated an obvious capacity for regeneration. PRF is centrifuged at a slower rate, which causes a higher concentration of white blood cells, stem cells and platelets to remain in the middle plasma layer. Thus, PRF has a platelet concentration almost double that of blood. Platelets are involved in the release of growth and clotting factors. If the release of the growth factor occurs rapidly in the case of PRP, it is slow for PRF, with an average duration of 7–10 days postoperatively [164].

Lekovic et al. [165] investigated the association of PRF with bovine xenograft in filling periodontal infrabony defects in patients with bilateral defects, evaluating treatment with PRF alone or with PRF combined with bovine bone. Results after 6 months were more favorable when PRF was combined with bovine bone; they noticed a decrease in probing depth and gains in periodontal attachment and bone height. Lekovic et al. concluded that increased efficacy during bone defect regeneration treatment is achieved by the combination of PRF and xenograft, rather than by PRF alone [165]. Mathur et al. [166] compared the efficacy of PRF and autologous bone graft to increase attachment and reduce infrabony defects. Subjects showed infrabony defects that were treated with either an access flap associated with PRF or an access flap supplemented with an autologous bone graft; the third control group followed only the access flap procedure. Plaque index, the gingival

index, the loss of attachment, the gingival recession and the depth of the periodontal pockets were analyzed on the day of surgery and 9 months later. The use of PRF had a more efficient result than the access flap alone, but the combination of the regenerating material allowed for obtaining an even more efficient treatment [166].

PRF has also proven effective in treating gingival recessions. Anilkumar et al. [167] compared PRF and connective tissue grafting with lateral repositioned flap to cover Miller class II recessions. Recession coverage was complete for 91% of patients treated with PRF, compared with 66% for those treated with a connective graft [167]. Jankovic et al. [168], in a treatment of Miller class I or II recessions, compared the results of the use of PRF membranes and connective tissue graft, combined with coronally repositioned flaps and connective tissue graft. The parameters studied were the size of the recession, attachment gain, the height of the keratinized gingiva, the pocket depth, the quality and speed of wound healing and the patient's discomfort; clinical parameters were evaluated at baseline and after 12 months. The results were similar between the use of a PRF membrane and a connective graft. The authors noted that although the amount of acquired keratinized tissue is higher with the connective graft, PRF provided better healing and less discomfort to the patient [168]. Thus, PRF may be an interesting, effective and relatively low-cost option, but further studies are needed on larger study groups in order to establish accurate protocols.

5.3. 3D Printed Membranes

Three-dimensional printing aims to generate an individualized 3D object, according to a design developed by software (computer aided design—CAD), by depositing the chosen material layer by layer. Three-dimensional technology already has applications in various fields, such as the production of anatomical models and surgical guides or regenerative medicine. There are multiple methods of 3D printing, including fusion deposition modeling (FDM), stereolithography (SLA) or selective laser sintering (SLS), but FDM remains the technique of choice for bioprinting [169]. The biomaterials used include hydrogels in combination with living cells and/or growth factors, natural and synthetic bioplastics, proteins, polymer biomolecules and ceramics [170].

Natural biomaterials used in 3D printing techniques include collagen, agarose, alginate, chitosan, silk, gelatin, cellulose, hyaluronic acid and fibrin [171], and synthetic biomaterials include PLA, PGA, PLGA and PCL [172,173]. Decellularized matrix components containing both conserved cellular elements and specific signaling factors of high importance in regenerative processes can also be used, because the latter can guide the cells of the resident tissue or provide the host cells with the necessary instructions for tissue regeneration [174].

Tayebi et al. tested a 3D-printed membrane of sodium elastin/gelatin/hyaluronate in vitro; the membrane has shown good mechanical properties as well as a stimulation of fibroblast proliferation [10]. Bai et al. [175] developed an individualized membrane with 3D-printed titanium mesh; various types of titanium mesh designed with different diameters, and thicknesses were tested based on their mechanical strength by a three-point bending test and FEA. According to the authors, the mechanical properties of the titanium mesh increased when the thickness decreased (0.5 mm to 0.3 mm); by increasing mesh diameter (3 mm to 5 mm), the mechanical properties of the mesh decreased [175].

A time dimension was added to 3D technology, with the appearance of being 4D; 3D printed construction thus changes, resulting in a transition in shape, structure and function [176]. This technology is based on intelligent biomaterials that have the ability to undergo changes as a result of exposure to various stimuli (temperature, pH, humidity, electric or magnetic fields, light, sound or a combination thereof) [177]. Thus, 4D bioprinting offers new directions for the development of tissue reconstruction techniques.

6. Allergological Considerations

The most common allergic reactions to various implants, reported in the literature, were with nickel, cobalt and even titanium, although the latter has a high biocompatibil-

ity [178]. The titanium test was patch-type and was conducted later and not before the implant. Authors who tried a lymphoblastic transformation test (LLT) are cited, but did not have success. However, these reactions are very rare [108].

The implantation of biomembranes can give two types of reactions: type I reactions (non IgE dependent) and IV (delayed type). A type I immune-allergic reaction is manifested by immediate angioedema and type IV by late reactions, which occur after a few days, even weeks, from the implant [179].

Regarding biological biomembranes (platelet concentrate, amniotic and chorionic concentrate) the high risk is rejection, as well as type IV reactions, such as contact dermatitis or mucositis, due to the additives with which they are impregnated, and which have been previously described [180].

Prophylactic testing would not be indicated, as it has no real clinical predictive benefit. Especially in the case of titanium, the time of penetration into the tissues is long. If the patient develops an immediate allergic reaction, which occurs in a few minutes, it would require a prior sensitization of the patient so that he already has cellular memory, with a specific IgE dosage, such as the situation of another implant, and not necessarily in the dental field or for the patient to work in an industry that uses titanium or other metals invoked in biomembranes. Type IV reactions would occur within weeks or even 2 months after membrane insertion.

The only test that would be eloquent is the patch test (with reading at 30 min, 1 h, 24 h, 72 h and 7 days), but only if after the placement of these membranes the suspicion of an allergic reaction arises. Additionally, if the reaction is not severe, such as anaphylactic shock, difficult to control generalized urticaria, or a Stevens Johnson-type reaction, it would be worthwhile to treat the reaction and keep the membrane in place, even if the test is positive.

What is the profile of a risk patient? This is best illustrated by the patient who has had an implant, such as knee, hip, etc., the patient who works in industries that handle these materials and may associate contact dermatitis and, practically, a patient who could have been professionally sensitized prior to a dental implant.

Would immunosuppressive treatment be justified or not, in the case of these delayed type allergic reaction implants? This might depend on the severity of the periodontal disease, the severity of the rejection reaction and the patient's choice (since these implants are not cheap and the immunosuppressive therapy might not be subsidized by the state in this situation).

7. Conclusions

There is a wide range of technologies and materials used in guided tissue regeneration, some of which are still in the in vitro or in vivo testing phase. The use of the barrier membrane associated with bone grafting materials has shown better results than its single use. Further studies are needed to develop treatment algorithms and protocols to obtain predictable, case-specific regenerative results. In order to respond to our aim, it is more than clear that the perfect barrier membrane is not quite here, but the choice of the most appropriate membrane relies on the particular case, as well as on the medical experience of the operator.

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