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Review

Various Coated Barrier Membranes for Better Guided Bone Regeneration: A Review

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Abstract: A good barrier membrane is one of the important factors for effective guided bone/tissue regeneration (GBR/GTR) in the case of periodontal bone defects. Several methods are being discussed to overcome and improve the shortcomings of commercially available membranes. One of the methods is to coat the membrane with bioactive materials. In this study, 41 studies related to coated membranes for GBR/GTR published in the last 5 years were reviewed. These studies reported coating the membrane with various bioactive materials through different techniques to improve osteogenesis, antimicrobial properties, and physical/mechanical properties. The reported studies have been classified and discussed based on the purpose of coating. The goal of the most actively studied research on coating or surface modification of membranes is to improve new bone formation. For this purpose, calcium phosphate, bioactive glass, polydopamine, osteoinduced drugs, chitosan, platelet-rich fibrin, enamel matrix derivatives, amelotin, hyaluronic acid, tantalum, and copper were used as membrane coating materials. The paradigm of barrier membranes is changing from only inert (or biocompatible) physical barriers to bioactive osteo-immunomodulatory for effective guided bone and tissue regeneration. However, there is a limitation that there exists only a few clinical studies on humans to date. Efforts are needed to implement the use of coated membranes from the laboratory bench to the dental chair unit. Further clinical studies are needed in the patients' group for long-term follow-up to confirm the effect of various coating materials.

Keywords: anti-bacterial agents; calcium phosphate; guided tissue regeneration; membranes; osteogenesis

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1. Introduction

Many elderly patients with bone loss and tooth loss owed to periodontal disease visit the dentist in an aging society [1]. Sufficient alveolar bone regeneration is essential for successful periodontal treatment or dental implant treatment. However, compared to soft tissue, bone has a relatively low regeneration potential [2]. In guided bone regeneration (GBR) or guided tissue regeneration (GTR) treatment, factors such as barrier membranes, the skillful technique of dentists, healthy patients, and bone materials play an important role. Among them, the membrane used for GTR/GBR prevents invasion of the soft tissue into bone defects due to the fast growth rate of fibroblasts outwards and serves to maintain appropriate space inwards, thereby allowing sufficient time for bone regeneration [2,3]. Therefore, the membrane should have characteristics such as (1) biocompatibility to prevent soft tissue dehiscence and minimize tissue reactions, (2) space maintenance and structural integrity, (3) host tissue integration, and (4) an ease of handling during surgery with no memory [4].

The commercially available membranes that are currently used can be broadly divided into two types: non-resorbable membranes and resorbable membranes. Representative examples of non-resorbable membranes include expanded polytetrafluoroethylene (ePTFE)

and titanium (Ti) mesh. Their advantage is that they have the properties of good intensity and barrier effects. Especially, the Ti membrane could be deformed to suit various forms of bone defect and maintain the extensive space because of their high rigidity and plasticity [5]. However, the disadvantages include poor cellular adhesion, slower cellular growth, bone regeneration, and the need for secondary surgery, which may lead to secondary trauma to the gum [6,7]. Besides, the exposed non-resorbable membranes easily form a biofilm in the oral cavity and may experience failure of bone regeneration due to bacterial infection [8,9]. On the contrary, the resorbable membrane has a great advantage as it does not require secondary surgery for the removal after the regeneration of alveolar bone. In addition, it has advantages such as good biocompatibility, weak immunogenicity, higher cell adhesion, and tissue healing properties [10]. Representative resorbable membranes include collagen membranes made from a bovine or porcine source and biodegradable synthetic polymer membranes [11]. However, collagen membrane has disadvantages such as insufficient mechanical properties and a fast degradation speed that is short to maintain sufficient space for an appropriate time as a barrier [10]. Biodegradable polymer membranes, such as poly(L-lactide) (PLLA), has advanced mechanical properties but are associated with inherent shortcomings such as hydrophobicity, poor cellular affinity, and osteoconductive activity compared to collagen membrane [12].

Therefore, to compensate for these shortcomings and increase bone regeneration, research on the development of coating or the surface treatment of membranes have been conducted continuously. The technology of coating continues to develop, especially in membrane application. Coating of the membrane with various materials can be applied for GTR applications as bioactive and anti-bacterial purposes [13]. However, there exists only a few review papers focusing on the coating or surface treatment of barrier membranes. In this study, we have reviewed barrier membrane coating-related papers published in the last 5 years, investigated the research conducted to date, and seek the direction of development of coated membranes in the future.

2. Materials and Methods

A literature search was performed in electronic databases, including PubMed, Medline, OVID, and Web of Science, by using the following keywords: "membranes", "guided bone regeneration", "guided tissue regeneration", "coated", and "coating" from 2017 January to 2022 June. Documents written in English were selected. Sixty-two papers were found and among them, a total of 41 papers were included in this study, excluding 21 papers not related to coated membranes or review papers (Figure 1). Based on the selected 41 papers, we would like to briefly review the membrane coating materials studied so far (Table 1).

Table 1. Summary of included studies on coated barrier membranes.

Improved Property	Coated Materials	Resorbable Membrane			Non-Resorbable Membrane		
		Collagen	Synthetic Polymer	SA, Chitosan	Mg Mesh	Ti Mesh	PTFE, PP, Nylon
Osteogenesis	CaP, HA, TCP	Chu et al. [14], Dau et al. [15], Dubus et al. [16], Yang et al. [17]	Higuchi et al. [18], Van et al. [19], Torres-Lagares et al. [20], Torres-Lagares et al. [21]	-	Byun et al. [22]	Nguyen et al. [23]	-
	Bioactive glass, SiO_2	Chen et al. [2], Dau et al. [15]	Shi et al. [24], Torres-Lagares et al. [21], Terzopoulou et al. [25], Lian et al. [26], Castillo-Dalí et al. [27]	-	-	-	-
	Polydopamine	-	Chen et al. [12], Lee et al. [28], Hasani-Sadrabadi et al. [29], Wang et al. [30], Shi et al. [24], Liu et al. [31]	Xu et al. [32]	-	-	Ejeian et al. [33]

Table 1. *Cont.*

Improved Property	Coated Materials	Resorbable Membrane			Non-Resorbable Membrane		
		Collagen	Synthetic Polymer	SA, Chitosan	Mg Mesh	Ti Mesh	PTFE, PP, Nylon
	Drugs	van Oirschot et al. [34], van de Ven et al. [35]	Terzopoulou et al. [25], Lian et al. [26]	-	-	-	-
	Chitosan	Dubus et al. [16],	Porrelli et al. [36]	-	Guo et al. [37]	-	-
	PRF, EMD, AMTN	Kapa et al. [38], Miron et al. [9], Ikeda et al. [39]	Ikeda et al. [39]	-	-	-	-
	HyA	Dubus et al. [16], Silva et al. [40]	Van et al. [19]	-	-	-	-
	Tantalum	-	Hwang et al. [41]	-	-	-	-
	Lactoferrin	-	Lee et al. [28]	-	-	-	-
	Cuprous oxide	-	-	Xu et al. [32]	-	-	-
	Strontium	Yang et al. [17]	-	-	-	Nguyen et al. [23]	-
Antimicrobial property	Silver nanoparticles	Chen et al. [42]	Porrelli et al. [36], Wang et al. [30]	-	-	-	-
	Antibiotic drugs	-	Shi et al. [24], Lian et al. [26]	-	-	Zhao et al. [43]	-
	CHX, AMPs	-	-	Boda et al. [44]	-	-	-
	Cuprous oxide	-	-	Xu et al. [32]	-	-	-
Physical/ mechanical property	FN-silk, pectin	-	-	Boda et al. [44]	-	-	Tasiopoulos et al. [45]
	Ti, Mg	Choy et al. [46]	Zhang et al. [47]	-	-	-	-
	Graphene oxide	De Marco et al. [48]	-	-	-	-	-
	EGCG	Chu et al. [14]	-	-	-	-	-
	Chitosan	-	-	-	Guo et al. [37]	Zhao et al. [43]	Fernandes et al. [49]
	Polydopamine	-	Chen et al. [12]	-	-	-	-
	AMTN	Ikeda et al. [39]	Ikeda et al. [39]	-	-	-	-
No significant difference	HA	-	-	-	Byun et al. [22]	-	-
	II and PVD (Mg)	-	-	-	Steigmann et al. [50]	-	-
	APP (Ti)	-	-	-	-	Toyama et al. [51]	-

Abbreviation: SA, sodium alginate hydrogel composite; Mg, magnesium; Ti, titanium; PTFE, polytetrafluoroethylene; PP, polypropylene; CaP, calcium phosphate; HA, hydroxyapatite; TCP, β-tricalcium phosphate; SiO_2, silicon dioxide; PRF, platelet-rich fibrin; EMD, enamel matrix derivative; AMTN, amelotin; HyA, hyaluronic acid; CHX, chlorhexidine; AMPs, antimicrobial peptides; FN-silk, recombinant spider silk protein functionalized with a cell-binding motif from fibronectin; EGCG, epigallocatechin-3-gallate; II, ion implantation; PVD, physical vaper deposition; APP, atmospheric pressure plasma treatment.

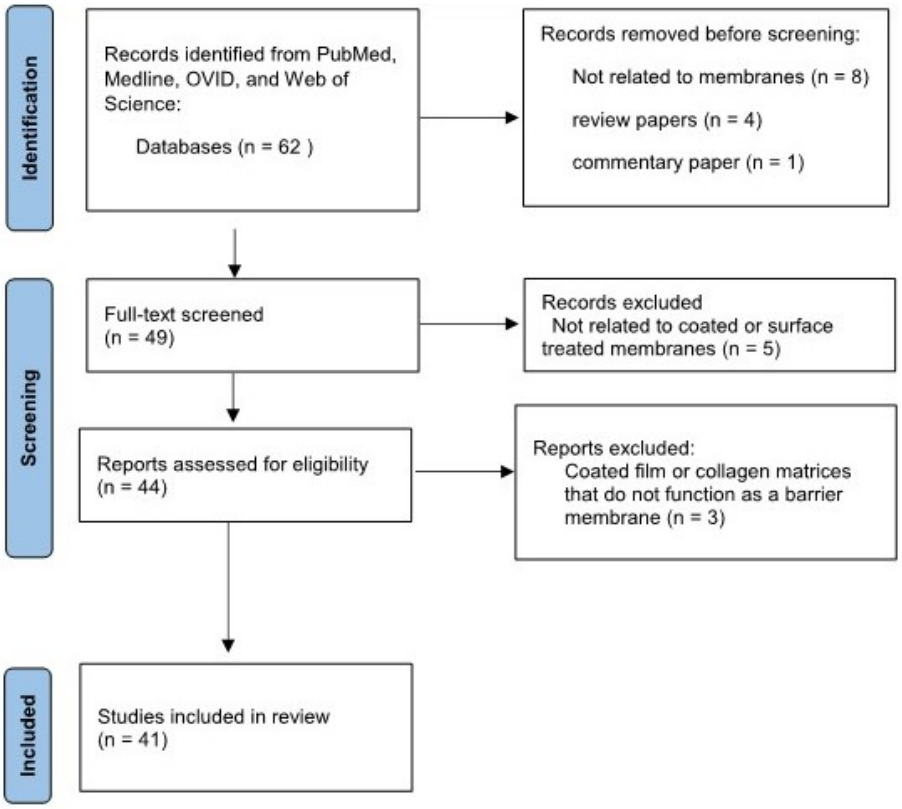

Figure 1. This is the flow chart of this study.

3. Results

3.1. Improved Osteogenesis

Various interdisciplinary approaches of surface coating have been performed in terms of biomaterials, drug release, and therapeutic effects [52]. The goal of the most actively studied research on coating or the surface modification of membranes is to improve new bone formation. For this purpose, calcium phosphate (CaP), bioactive glass, polydopamine (PDA), osteoinduced drugs, chitosan, platelet-rich fibrin (PRF), enamel matrix derivatives (EMT), amelotin (AMTN), hyaluronic acid (HyA), tantalum (Ta), and copper were used as membrane coating materials.

3.1.1. Calcium Phosphate, Hydroxyapatite, and β-Tricalcium Phosphate

CaP belongs to the family of minerals containing calcium cations (Ca^{2+}) together with inorganic phosphate anions, which are abundant in native human bone and teeth [53]. CaP is a representative bioactive material [53]. The calcium ion induces the proliferation and differentiation of human mesenchymal stem cells (MSCs), stimulates osteoblastic bone synthesis by activating the extracellular signal-regulated kinase 1/2 pathway and phosphatidylinositol 3-kinase/Akt pathways [53–56]. In addition, phosphate regulates the proliferation and differentiation of the osteoblasts and increases the expression of BMPs [53,57,58]. CaP demonstrates osteoconductivity and osteoinductivity characteristics through the above cell signaling pathways as well as good biocompatibility, non-immunogenicity, and non-inflammatory behavior [59]. CaP has been utilized to improve bone regeneration in ways such as increasing osteoconductivity for bone ingrowth, enhancing osteoinductivity for bone mineralization with ion release control, and encapsulating drugs or growth factors [59,60]. Hydroxyapatite (HA, ($Ca_5(PO_4)_3(OH)$)) and β-tricalcium phosphate (TCP, ($Ca_3(PO_4)_2$)) are also included in this family [53]. HA constitutes the largest amount of inorganic components in human bone [61]. Calcium phosphate has been

studied for bone regenerative treatment as a coating material for membrane and dental implants, and also as a raw material [53].

In 2017, Chu et al. studied nanostructured HA (nanoHA)-coated epigallocatechin-3-gallate (EGCG) cross-linked collagen membranes [14]. In this in vivo study, nanoHA-coated and EGCG cross-linked collagen membranes showed the highest bone healing efficacy [14]. Furthermore, due to EGCG, the membrane showed improved mechanical properties, such as elasticity and thermal stability [14]. In 2019, Nguyen et al. studied strontium (Sr)-doped CaP-coated Ti mesh membranes. Both Sr- and CaP-coated Ti mesh presented the highest percentages of bone–mesh contact in the critical bone defect animal model [23]. In 2019, Higuchi et al. used electrospraying or sonocoating methods for nanoHA coating of Poly(D,L-lactic acid), (PDLLA)/Poly(D,L-lactide-co-glycolide) (PLGA) membranes. In this study, nanoHA sonocoated polymer membranes showed better cellular metabolic activity than non-coated control membranes [18].

3.1.2. Bioactive Glass and Silicon Dioxide

The form and application of glass have developed along with the development of human civilization for thousands of years [62]. Since the late 1960s, various combinations of bioactive glasses for regenerative medicine have been developed and improved [62]. Due to the bonding ability of bioactive glasses to both hard and soft tissues, and osteoconductive, osteoinductive, and angiogenesis properties, the material is considered a third-generation biomedical material [62–65]. Numerous pieces of research on the bioactive glass coating on dental implants and membranes are ongoing to enhance bone regeneration and induce fast tissue bonding [2,27,66,67]. Furthermore, for improved physical, functional, and chemical properties, the bioactive glasses are incorporated with different ions (e.g., Sr, Cu, Zn, etc.), osteo-induced drugs (bisphosphonate and dexamethasone), and nanoHA [2,15,21,25,26,68].

In 2018, Chen et al. reported a nanometer-sized bioactive glass $Ca_2ZnSi_2O_7$-coated collagen membrane via a pulsed laser deposition coating technique [2]. This study showed that the expression of osteogenic factors was upregulated and osteogenic differentiation of bone marrow stem cells was enhanced in the coated membrane group, attributable to coated nutrient bioactive glass [2]. In 2020, Dau et al. reported SiO_2-enhanced nanoHA-coated collagen membranes via the spin–spray coating method [15]. In this study, SiO_2-enhanced nanoHA-coated collagen membranes showed the fastest and most pronounced vascularization properties [15]. In 2019, Terzopoulou et al. reported ibandronate-loaded bioactive glasses-coated poly(ε-caprolactone) (PCL) membrane [25]. In the reported study, two different synthesized mesoporous bioactive glasses (SiO_2-CaO-P_2O_5 and SiO_2-SrO-P_2O_5) were loaded with ibandronate and coated on PCL membranes by the spin coating technique. Both the bioactive glasses demonstrated an increase in hydrophilicity and bioactivity, especially in the ibandronate-loaded and Sr-substituted bioactive glass-coated membranes [25].

3.1.3. Polydopamine and Polydopamine Platform with Other Substances

PDA has been known as one of the most efficient universal surface-coating materials due to its ability to strongly attach to almost all kinds of substrates, since its first report in 2007 [69,70]. PDA has been reported to promote cellular adhesion and mineral deposition of hydroxyapatite [29,71,72]. In addition, PDA is a good platform for surface tethering and releasing small molecules for tailoring the functionality of PDA. The target molecules (polymers, proteins, peptides, and drugs) could be readily immobilized on PDA by ad-layer formation or one-pot coating technique [73–75].

In 2019, Hasani-Sadrabadi et al. developed biomimetic PDA-coated PCL membranes via the membrane immersion technique using dopamine hydrochloride to promote adhesion [29]. In this study, the coated PDA layer was identified to accelerate the osteogenic differentiation of MSCs by promoting hydroxyapatite mineralization [29]. In 2019, Chen et al. reported that the PDA-coated PLLA membrane improved hydrophilicity, cytocompatibility, tensile properties, and osteogenic activity [12], and the membrane was soaked in

1.5 times stimulated body fluid for the biomineralization of HA. In this in vitro study, HA immobilization and PDA coating played a synergistic osteoconductive effect [12]. In 2020, Ejeian et al. reported in situ crystallization of zeolitic imidazolate framework-8 (ZIF-8) on the PDA-modified polypropylene (PP) membrane [33]. The ZIF-8/PDA/PP membrane showed significantly increased osteogenic differentiation of dental pulp stem cells, as well as increased physical properties. In 2022, Lee et al. reported that lactoferrin immobilized the PLLA/PCL membrane by using the polydopamine coating technique [28]. Lactoferrin is known to exhibit biological functional activities such as bone regeneration and anti-inflammation [28,76,77]. In this study, the lactoferrin–polydopamine-coated PLLA/PCL membrane showed enhanced osteoinductive and anti-inflammatory activities compared to only the PDL-coated membrane [28].

3.1.4. Drugs for Osteogenesis: Bisphosphonate with or without Testosterone and Dexamethasone

As anti-osteoporotic drugs, the bisphosphonates (e.g., alendronate, ibandronate, and zoledronate, etc.) interfere with the bone turnover process through inactivation of the osteoclast activity, thereby resulting in reduced bone breakdown [1,34]. The bisphosphonates prevent osteoporotic pathologic fractures and improved bone regeneration [34,78]. However, it could also be a causative agent for medication-related osteonecrosis of the jaw [1]. Testosterone is another important osteoanabolic agent in men, that stimulates the proliferation of preosteoblasts and the differentiation of osteoblasts [79]. Currently, bisphosphonate and testosterone combination therapy has been exploited for the synergistic stimulation of bone regeneration [34,35]. As a synthetic glucocorticoid, locally delivered dexamethasone (Dex) showed great osteogenic induction of MSCs [76]. However, the inappropriate systemic delivery of glucocorticoids may cause side effects such as hyperglycemia, immunosuppression, and osteoporosis [76,80].

In 2020, van Oirschot et al., and in 2021, van den Ven et al., reported a testosterone and alendronate ultrasonic spray-coated collagen membrane by using PLGA 5004A as a carrier [34,35]. The drug-coated membranes showed superior bone regeneration to the control group with 124% in the minipig bone defect model and 160% in the rat critical-size calvarial defect model [34,35]. In 2019, Lian et al. reported dexamethasone-loaded mesoporous silica nanoparticle-coated PLGA and gelatin composite membranes [26]. In this in vitro experiment, the coated membrane showed an enhanced osteoinductive capacity for rat bone marrow stem cells (BMSCs).

3.1.5. Chitosan

Chitosan derived from the deacetylation of chitin derivatives is one of the most important natural polymers and has been reported to induce osteogenesis and enhanced tissue healing [11,81]. It has biocompatible, self-resorbable, antimicrobial, and economical properties [11]. Though it has poor mechanical properties and a low degradation rate, chitosan plays a role in improving the biological, physical, mechanical, and antimicrobial properties of the membranes either alone or in combination with other functional coating materials [36,37,43,49]. Guo et al. reported a chitosan-coated magnesium (Mg) membrane [37]. In this study, chitosan was used to reduce the degradation rate of the Mg membrane and enhance osteogenic activity. The results showed that the chitosan-coated Mg membrane had a suitable degradation rate and a higher osteogenic potential [37]. However, mechanical properties may not be maintained once degradation begins. In 2021, Porrelli et al. reported that silver nanoparticles (nAgs) stabilized a bioactive lactose-modified chitosan-coated PCL membrane [36]. The nAgs lactose-modified chitosan-coated membrane showed enhanced hydrophilic properties, improved osteoblastic adhesion, proliferation, and discouraged biofilm formation without cytotoxicity [36].

3.1.6. Platelet-Rich Fibrin, Enamel Matrix Derivatives, and Amelotin

PRF, as one of the forms of platelet concentrates, is obtained from the autologous venous blood in the glass-coated tube after centrifugation at 400 g. The PRF contains platelets and their byproducts released during platelet activation. These include numerous growth factors, circulating cytokines, glycoproteins, and fibrin-associated glycan chains that are crucial factors for tissue regeneration [82]. In 2020, Kapa et al. reported the clinical study about the treatment with PRF-coated bones and PRF-coated collagen membranes in sixteen patients with gingival recession due to the loss of alveolar bone and soft gingival tissue [38]. In the study, twelve out of the sixteen patients achieved complete healing of gingival recession, and an increase in gingival thickness was observed in all patients [38].

Like PRF, the extract of porcine embryonic enamel matrix termed 'EMD' has been reported to induce mesenchymal cells to mimic the processes of the development of the tooth and has been broadly used for periodontal regenerative treatment [83]. In 2017, Miron et al. reported the EMD in a liquid carrier system coated with a collagen membrane [9]. The EMD-coated collagen membrane showed increased cell adhesion, osteodifferentiation, and mineralization in an in vitro study.

AMTN, an enamel protein expressed by ameloblasts, is known to play an important role in enamel mineralization [84,85]. Furthermore, the AMTN is known to promote HA mineralization [86]. In 2022, Ikeda et al. reported a collagen hydrogel incorporated with rhAMTN (rhAMTN gel)-coated collagen or polyglactin-woven mesh membranes [39]. The AMTN gel-coated membranes showed accelerated mineralization and adhesion.

3.1.7. Hyaluronic Acid

HyA, a natural linear glycosaminoglycan, is one of the components of the extracellular matrix, and its presence has been documented in skin, aorta, cartilage, and brain [87]. The HyA has hygroscopic, viscoelastic, biocompatible, biodegradable, anti-inflammatory, and bacteriostatic properties [88,89]. Furthermore, it has been reported to induce and enhance cell proliferation, migration, adhesion, and angiogenesis [90,91]. For its ideal regeneration properties, HyA has been widely used in the medical field for orthopedic surgery in the form of intraarticular injection into the osteoarthritic joint and in plastic surgery for dermal regeneration and soft tissue augmentation [87]. In dentistry, HyA has been applied for the treatment of osteoarthritic temporomandibular joint disease and periodontitis [40,92,93].

In 2017, Silva et al. reported that a HyA-coated collagen membrane by using the soaking coating technique did not show a significant difference in new bone formation compared to the non-coated collagen membrane group in rats [40]. However, other studies demonstrated that HyA coated with CaP and chitosan into a collagen membrane through a spraying technique or a HyA- and TCP-modified PCL membrane by the spin-coating technique showed significantly different results in in vitro experiments [16,19]. Dubus et al. [16] reported that a HyA-, CaP-, and chitosan-coated collagen membrane enhanced the proliferation of MSCs and the secretion of cytokines and growth factors. However, further in vivo studies are needed to confirm the effective role of HyA in bone regeneration.

3.1.8. Other Coating Materials—Tantalum, Copper

Ta is known to increase osteoconductivity by promoting the formation of CaP surface layers and is also known to have superior biocompatibility and mechanical properties [94–96]. In 2020, Hwang et al. reported a Ta coated-PLA membrane using sputtered Ta ions using a DC magnetron sputterer to enhance the bioactivity of the PLA membrane [41]. In the reported study, the Ta-coated PLA membrane showed more advanced osteoconductivity than the uncoated PLA membrane in both in vitro and in vivo experiments.

Copper has been known to have attractive dual functions in regenerative medicine [32,97]. Cuprous oxide (CuO_2) nanoparticles have a high efficiency and broad-spectrum antibacterial properties [98]. In addition, Cu^{2+} has been reported to induce the osteogenic differentiation of BMSCs [97]. In 2020, Xu et al. reported a sodium alginate hydrogel composite (CTP-SA) doped with cubic CuO_2 and PDA-coated titanium dioxide (TiO_2) nanoparticles

for guided tissue regeneration [32]. In this study, CuO_2 PDA/TiO_2-modified CTP-SA showed improved antibacterial and osteogenic properties according to dual light controls [32].

3.2. Improved Antimicrobial Properties

Besides the previously mentioned CuO_2, nAgs, metronidazole (MNA), doxycycline (Dox), chlorhexidine (CHX), and antimicrobial peptides (AMPs) have been used to improve the antimicrobial properties of the membranes [32].

3.2.1. Silver Nanoparticles

Silver is well known to have broad-spectrum antibacterial properties and has been used in various forms due to its low cytotoxicity [99,100]. Many studies have demonstrated the important activity of Ag nanoparticles (nAgs) against bacterial biofilms [101–104]. There exist studies on the promotion of antimicrobial activity using nAg as a coating material for membranes in the oral cavity [30,36,42]. In 2018, Chen et al. reported nAgs-coated collagen membranes through sonication coating or the sputtering coating technique [42]. The nAgs-coated membranes showed excellent antibacterial effects against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and exhibited advanced anti-inflammatory effects by reducing the expression and release of inflammatory cytokines [42]. In 2020, Wang et al. reported that nAgs immobilized a PDA-coated PLLA membrane that showed advanced antibacterial effects against *S. aureus* and a good biocompatibility due to low cytotoxicity [30].

3.2.2. Antibiotic Drugs

In 2019, Shi et al. reported an infection-responsive membrane that was esterified MNA-grafted PDA functionalized with a siloxane-coated PCL membrane [24]. The ester bonds could be selectively hydrolyzed by cholesterol esterase (CE) secreted by macrophagocytes accumulated at the site of infection. Thus, the membrane was designed in a manner that increases the CE concentration due to severe infection leading to the release of a higher amount of MNA, thereby resulting in an enhanced antibacterial property. In this study, released MNA due to CE from an MNA-grafted PDA-coated membrane exhibited antibacterial activity [24].

The other studies reported Dox-coated membranes with enhanced antibacterial activities [26,43]. Zhao et al. reported porous chitosan/gelatin/Dox-coated Ti-niobium membrane [43]. Lian et al. reported a Dox-modified PLGA membrane [26].

3.2.3. Chlorhexidine and Antimicrobial Peptides

In 2020, Boda et al. reported an AMPs- or CHX-loaded oxidized pectin-coated chitosan membrane [44]. The D-enantiomer of GL13K (D-GL13K) derived from the human salivary parotid secretory protein and the L-enantiomer of innate defense regulator—1018 (IDR-1018)—were used as AMPs. CHX, D-GL13K, and IDR-1018 were coated on the membrane via the co-electrospinning method or the surface absorption method. In this study, the AMPs-loaded pectin-coated chitosan membrane showed an antimicrobial property that was comparable to CHX against *Streptococci* [44].

3.3. Improved Physical/Mechanical Properties

In addition to EGCG, chitosan, PDA, and AMTN, various materials have been employed to improve the physical and mechanical properties of the membrane [12,14,37,39,43,49].

3.3.1. Recombinant Spider Silk Proteins and Pectin Derivatives for Improved Cell Adhesion

Natural silk has been applied for dental fields due to the structure and features that make it biocompatible [105]. Synthetic polymer membranes are inert and biocompatible; however, they are hydrophobic and less prone to cellular adhesive physical properties [6]. Recombinant spider silk protein not only demonstrates great mechanical characteristics

such as strength and elasticity but also great biological characteristics such as biocompatibility, biodegradability, and improved wetting capacity [106,107]. In 2020, Tasiopoulos et al. reported recombinant spider silk protein with a cell-binding motif from a fibronectin (FN-silk)-coated PTFE membrane [45]. In this study, the FN-silk-coated membrane showed higher cell adherence and proliferation properties in both human keratinocytes from soft tissue and human osteosarcoma cells from bone [45].

Pectin is structurally and functionally the most complex polysaccharide present in plant cell walls [108]. Pectin plays important roles in not only mediating plant growth, morphology, and development, but also in gelling and stabilizing the polymers in various foods and medicines [108,109]. Boda et al. reported an oxidized pectin-coated chitosan membrane [44]. The pectin-coated side of the membrane showed a two-fold increase in the mucoadhesive property to the mucosal mimic porcine esophagus than the non-coated side. On the contrary, the non-coated side of the chitosan membrane showed a 3–4 fold stronger adhesion to hard tissue mimicking hydroxyapatite discs than the pectin-coated side [44].

3.3.2. Metal Reinforcement—Titanium and Magnesium

Choy et al. reported a vapor-phase Ti-infiltrated collagen membrane via titanium oxide atomic layer deposition [46]. The Ti-coated collagen membrane led to enhancement in both the tensile strength and Young's modulus compared to the non-coated collagen membrane. Furthermore, the Ti-coated membrane was retained for a longer time than a non-coated collagen membrane that was rapidly degraded by up to 90% within 1 week [46].

Zhang et al. reported a Mg core-reinforced PLA membrane to improve the mechanical–physical properties [47]. The membrane was fabricated by combining two PLA membranes with a fluoride-coated AZ91 (9 wt% Al, 1 wt% Zn) (FAZ91) Mg alloy core by hot pressing. Compared to only the PLA membrane control group, the FAZ91—Mg-reinforced PLA membrane group showed a significantly higher maximum load, stiffness, and faster degradation because FAZ81-Mg promoted the absorption and the degradation of the PLA wrap but was not too delayed [47].

3.3.3. Graphene Oxide

Graphene is a flat monolayer of carbon atoms that are tightly packed into a 2-dimensional honeycomb lattice [110]. Due to its solubility in water and biocompatibility, graphene oxide (GO) has been used as biomaterials [48,111]. De Marco et al. reported a GO-coated collagen membrane [48]. The GO-coated membrane showed a lower deformability with a higher stiffness, an increased roughness, and an increase in the total surface that was exposed to the cells [48].

3.4. No Significant Difference

There exist studies about coated membranes that showed no significant advanced effect compared to the control group.

In 2017, Byun et al. reported a HA-coated Mg membrane to improve biocompatibility [22]. In the result, there were no significant differences or new bone volume, bone volume fraction, or bone surface density between the HA-coated Mg group and the control group [22].

In 2020, Steigmann et al. reported an ion implantation (II) and physical vapor deposition (PVD)-treated Mg membrane to improve biocompatibility [50]. In this study, the PVD-coated membrane demonstrated the absence of a positive influence on the gas cavity formation and advanced immune response compared to the noncoated Mg membrane. The authors concluded that a pure Mg membrane represents a promising alternative to the non-resorbable membrane [50].

In 2020, Toyama et al. reported an atmospheric pressure plasma (APP)-treated Ti membrane and analyzed its effect on the differentiation of BMSCs [51]. In this study, the APP-coated Ti membrane was identified to increase cell migration and gene-level expression of osteogenic markers; however, the suppression of mineralization was observed in an

in vitro experiment. Furthermore, in the in vivo experiment, the new bone formation was not significantly different between APP-coated and noncoated Ti membranes [51].

4. Conclusions

The paradigm of the barrier membrane is changing from only inert (or biocompatible) physical barriers to bioactive osteo-immunomodulatory for effective guided bone and tissue regeneration. For this purpose, numerous studies on coating various bioactive materials on the membrane to improve osteogenesis, antimicrobial properties, and physical/mechanical properties by various techniques have been performed. However, there is a limitation that there exists only a few clinical studies on humans to date. Efforts are needed to implement the use of coated membranes from the laboratory bench to the dental chair unit. Further clinical studies are needed in the patients' group for long-term follow-up to confirm the effect of various coating materials.

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