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Review

Histological and Histomorphometric Effectiveness of the Barrier Membranes for Jawbone Regeneration: An Overview of More Than 30 Years' Experience of Research Results of the Italian Implant Retrieval Center (1988–2020)

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Abstract: With the advent of implant dentistry, height and width of the bone site are fundamental to perform implant placements. There are several techniques to restore the amount of bone loss and one of them is guided bone regeneration, which is based on the employment of a membrane in order to bypass non-osteogenic cell invasion in the bone healing area, dispersing every interference with bone regeneration. Two expert reviewers performed a retrospective evaluation of all scientific papers published by the Implant Retrieval Center Laboratory of University "G. D'Annunzio" of Chieti-Pescara in the last three decades, and they implemented it by also similar conducting research on the main scientific databases, i.e., PubMed, Scopus, and EMBASE. The search was conducted up to December 2020, and a total of 843 articles published by the Implant Retrieval Center Laboratory of University "G.D'Annunzio" of Chieti-Pescara were identified and evaluated. After the application of inclusion and exclusion criteria, a total of 27 manuscripts were included for the qualitative synthesis: 8 animal studies, 17 human studies, and 2 in vitro articles. The present overview shows the importance of translational research for barrier membranes for bone regeneration, and additionally, the need for experts in different fields and research centers to produce high quality data in future research.

Keywords: membranes; collagen barriers; scaffold; bone regeneration; research; overview

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1. Introduction

Implant dentistry has transformed rehabilitation treatments, bringing an enhancement to patients' life quality. A suitable height and width of the bone site are parameters required to perform dental implant placements. There are several techniques to restore the amount of bone loss; for example, the split crest method [1], bone-grafting strategies [2], or guided bone regeneration (GBR). GBR is widely used in oral surgery and implantology. It is based

on employing a membrane to bypass non-osteogenic cell invasion in the bone healing area, dispersing every bone regeneration interference. Thus, only osteoprogenitor cells can reach the bone defect site [3–5]. According to Bornstein et al., "additional bone augmentation was indicated in more than 50% of cases" of implant placement, and GBR was the most common technique performed [6].

Indeed, a fundamental aspect of GBR is the membrane used. Membranes' properties are closely connected with their materials and structure. Therefore, ideal features should be biocompatibility, integration capability with native tissues, stopping other cell invasions, keeping space for blood clot organization, easy clinical management, adequate stiffness, and plasticity to withstand the compression of the overlying soft tissue [7–12]. Membranes can be divided into two generations: non-resorbable membranes, mainly polytetrafluoroethylene (PTFE) in its expanded form (e-PTFE); and resorbable membranes, including collagen forms [13–16]. On the one hand, non-resorbable membranes offer the clinician a shaping site chance and a good barrier effect thanks to a metal core; on the other, they have to be suddenly removed if they are exposed before the healing process ends due to bone infection risk, and they also need a second surgery to be excised. Instead, there are resorbable barriers derive from animals. They should reabsorb in a couple of months due to hydrolysis or enzymatic degeneration, so they have a restricted power in stopping epithelial cell invasion and do not provide a space-making effect because they do not have a metal core. However, there is a low infection risk related to unwanted exposure, and they do not need surgery to be removed.

Nevertheless, collagen membranes overcome their lower space-making effect due to the current technique by the addition of a bone graft into the defect to create a scaffold easily colonizable by desired bone cells. Collagen-based membranes can be obtained from human skin, bovine Achilles tendon, porcine skin, and porcine inner organs [17]. This kind of barrier has different degradation times depending on the animal source, and it means that they could be reabsorbed before the optimal tissue maturation period. Several bioengineering methods are recommended to avoid this adverse event; for example, cross-linking with chemical agents such as glutaraldehyde, genipin, 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), or ultraviolet radiation. Despite the collagen stability improvement after chemical treatment, residues of these agents are responsible for inflammation in the site of placement [18].

Another fundamental characteristic of membranes is the porosity of the structure. It is suggested that the pore size directly influences bone regeneration capability. With that, a better occlusivity towards soft tissue cells can be ensured [19].

Membrane properties are so crucial that the third generation with biologically active components is under development, such as a delivery medium for growth factors and antibiotic molecules [20]. The present study aimed to investigate the membrane's outcomes for bone regeneration procedures in quantitative and qualitative effectiveness during translational evaluations performed Italian Implant Retrieval Center over 30 years.

2. Materials and Methods

A retrospective evaluation of all scientific papers published by the Implant Retrieval Center Laboratory of University "G. D'Annunzio" of Chieti-Pescara in the last three decades was performed; it was implemented by also conducting this research on different electronic databases, such as PubMed, Scopus, and EMBASE. The articles screened were limited to papers dealing with membrane applications for bone regeneration. The scientific publications were submitted for qualitative analysis.

2.1. Inclusion Criteria

Articles published up to December 2020 were included without language and initial date restrictions. The articles screened were limited only to papers dealing with membrane application for bone regeneration. The scientific publications were submitted for qualitative analysis. According to the search criteria, human studies, in vitro studies, and animal

model studies were applied to the search paradigm. Articles that did not conform to the inclusion criteria and literature reviews were also excluded from the evaluation.

2.2. Selection of the Studies

Data and study selection was performed independently by two expert reviewers (M.T. and A.P.). They used a uniquely designed data-collection form created in the Excel software package (Microsoft Office, Redmond, WA, USA) for the systematic recording of data. In the case of abstracts not being available, the paper's full text was obtained and checked. Literature reviews, case reports, and book chapters were excluded from the qualitative analysis. For excluded articles, a description was included about the reasons for exclusion.

2.3. Data Extraction

Data from included articles were extracted and evaluated. The papers were categorized into in vitro assays, animal studies, and human research. The animal and human studies were assessed according to the first author, type of membrane and complex, control sites, research times, and study outcomes.

3. Results

3.1. Papers Selection

The electronic search procedure is presented in Figure 1. The search was conducted before 20 December 2020, and a total of 843 articles published by the Implant Retrieval Center Laboratory of University "G.D'Annunzio" of Chieti-Pescara were identified and evaluated. A total of 43 literature reviews were excluded from the present investigation, and the full text was analyzed to evaluate the qualitative synthesis eligibility. A total of 770 papers were excluded for the following reasons: topic research (n = 763), book chapters (n = 3), and case reports (n = 6). A total of 27 manuscripts were included for the qualitative synthesis: 8 animal studies [13,14,21–26], 17 human studies [13,13,15,16,27–39], and 2 in vitro articles. The in vitro studies evaluated the osteogenic gene expression BMP2, RUNX2 and ALP and the mechanical characteristics of the experimental membranes (Table 1). The histological new bone formation (NBF) represented the most diffused evaluation of the included in vivo studies on animals and humans (Tables 2 and 3).

3.2. In Vitro Studies

A total of two studies were performed within in vitro cell cultures [40,41]. Radunovic et al. studied the collagen membranes used to deliver graphene oxide to evaluate multipotent cell populations' differentiation and proliferation [41]. De Marco et al. evaluated graphene oxide/collagen membranes' complex effects on fibroblast cell activity [40].

3.3. Animal Studies

A total of six studies were performed on rabbit models: two articles on calvaria defects [22,42], three papers on tibiae defects [23,24,26], and one paper on the knee [43]. Moreover, one article studied dogs' post-extraction defect model [14] and one paper studied calvaria defects on rats [21]. Different typologies of membranes were evaluated: electrically charged Gore-Tex augmentation membranes (GTAM), collagen membranes, polylactic acid derivates, composite polymer-hydroxyapatite membranes, expanded PTFE membranes, Gore-Tex membranes.

3.4. Human Studies

A total of five studies were performed associated with implant defects, six articles in the post-extraction alveolar socket, one study on periodontal defects, and five studies on jawbone defects. The follow-up range was from three months to seven years. For all of the studies conducted, histological and histomorphometric assessments on retrieved biopsies were included.

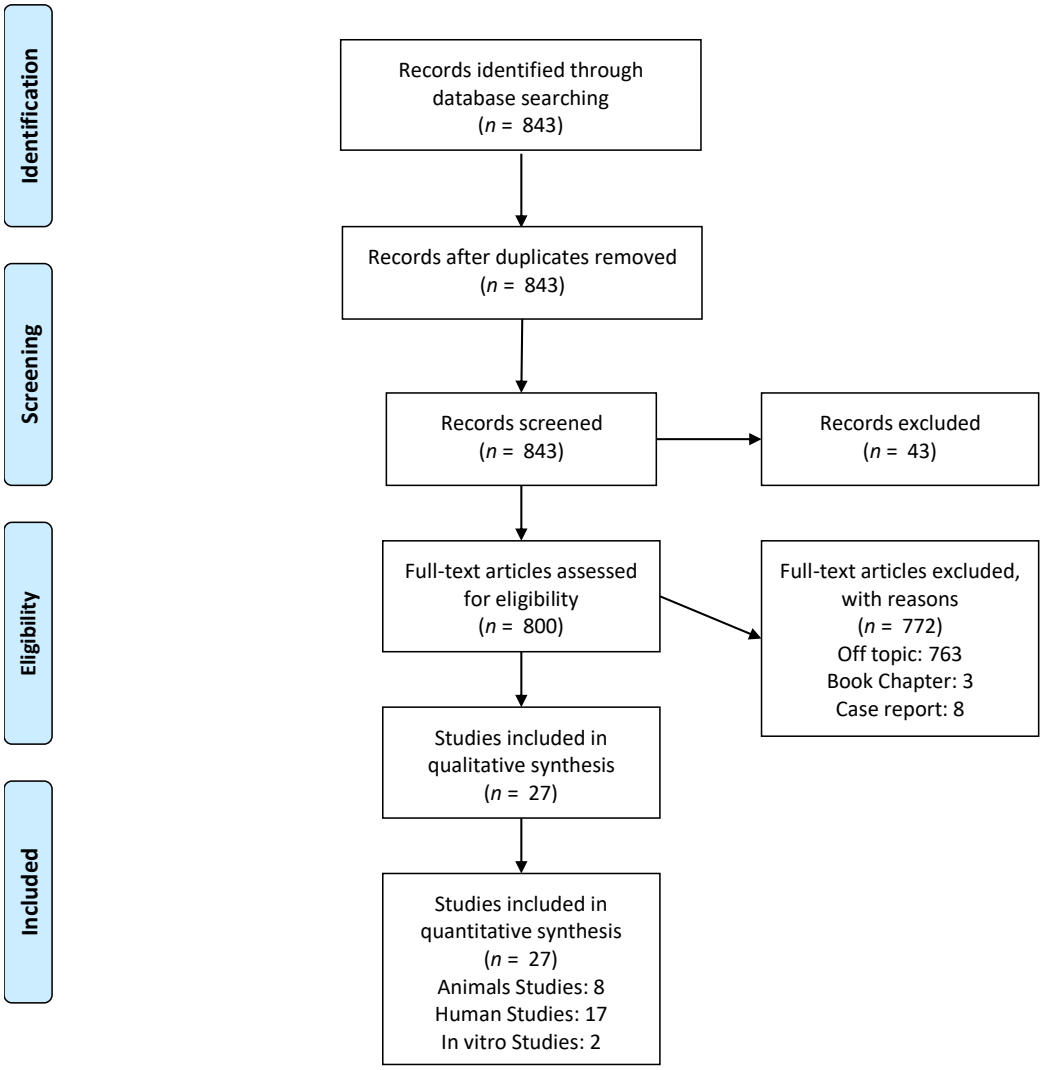

Figure 1. Flow diagram (PRISMA format) of the screening and selection process.

Table 1. Summary of the in vitro studies included for the qualitative analysis

Authors	Results	Experiment	Ex-Model	N	Defect	Test	Ctr	Time	Membrane Deformation	Genes
De Marco, et al. ***Biomed. Mat.*** **2017** [40]	Graphene oxide increased the roughness and the total surface exposed to the cells	Fibroblast Activity	In Vitro	—	—	Collagen Membrane + Graphene Fibroblast Activity (2 ug vs 10 ug)	Collagen Membrane	1, 3, 7, Days	Control: 1.9 ± 0.6 nm Test: 1.4 ± 0.9 nm	—
Radunovic, et al. ***J. Biomed. Mater. Res. A.*** **2017** [41]	Graphene oxide collagen membranes induce the differentiation of dpscs into osteogenic cells	Dental Pulp Stem Cells activity	In Vitro	—	—	Graphene + Collagen Membrane + Dental Pulp Stem Cells	Membrane + Stem Cells Without Graphene Oxide	Day 3, 7, 14, 28		2–10 µg/mL GO Increased expression of BMP2, RUNX2 and SP7

Table 2. Summary of the animal studies included.

Authors	Results	Ex-Model	N	Defect	Test	Ctr	Time	New Bone Formation (NBF)
Diomede, et al. ***Int. J. Mol. Sci.*** **2018** [21]	The combination improved the osteogenic differentiation in vitro	Rats	16	Calvarial Defect (Scraped)	Human Periodontal Ligament Stem Cells + Conditioned Medium + Pericardium Collagene Membrane	—	6 Weeks	No NBF EVO group, partial NBF EVO + hPDLSCs and EVO + CM groups. Complete NBF EVO + CM + hPDLSCs
Al-Hezaimi, et al. ***J. Oral Implantol.*** **2015** [14]	No significant difference was found in quantity of nonresorbed bone particles.	Dog	8	Post Extractive	Group 1, Control; Group 2, Allograft + With Dptfe Membrane; Group 3, The Buccal Plate Overbuilt With Allo-graft+Dptfe Membrane; Group 4, Allograft + Dual Layer Membranes	—	16 Weeks	Group 1 (34 ± 19.35%) Group 2 (43 ± 29.41%) Group 3 (56.5 ± 25.01%) Group 4 (92.5 ± 10.4%)
Chierico ***Clin. Oral Implants Res.*** **1999** [22]	Negatively charged membranes supported new-bone formation	Rabbits	36	Calvarial Defect	Electrically Charged Gore-Tex augmenta-tion membranes GTAM	Unfilled	5 Days, 10 Days, 3 Weeks, 5 Weeks, 10 Weeks and 20 Weeks	Negative charged: 27.95%
Piattelli, et al. ***Biomateri-als*** **1998** [24]	On the outer portion of the membrane, many multinucleated giant cells (mgc) were present, and membrane fragments were present inside the cytoplasm of these cells	Rabbits	—	Tibiae	Polylactic Acid Resorbable Membranes	Unfilled	1–4 Weeks	Some NBF trabeculae near the implant surface 300–400 µm
Piattelli, ***Biomateri-als*** **1997** [23]	No significant adverse soft and hard tissue reaction	Rabbits	—	Tibiae	Composite Polymer-Hydroxyapatite Membranes	—	4–6 Months	NBF in direct contact with the implant Surface with cells +ALP
Piattelli ***J. Periodontol.*** **1996** [42]	All membranes were filled by cells and osteoid tissue: a small percentage of the bone inside the membrane was mineralized	Rabbits	—	Calvarial Defect	E-PTFE Membranes	Unfilled	3, 6, 9, and 12 Weeks	Mature cortical NBF outer membrane surface
Piattelli ***Biomateri-als*** **1996** [43]	Amount of bone was roughly equivalent in all experimental sites	Rabbits	—	Knee defects	Guidor, Gore-Tex	—	6, 9, and 12 Weeks	Portions of NBF appeared in close contact with the implant surface.
Colangelo ***Implant Dent.*** **1993** [26]	The membrane covered cavities were completely filled with regenerated bone.	Rabbits	12 Sites	Tibiae	Resorbable Collagen Membranes	Unfilled	30 Days	Collagen membrane group showed a complete recorticalization and NBF compared to the control.

Table 3. Summary of the human studies included.

Authors	Results	Ex-Model	N	Defect	Test	Ctr	Time	New Bone Formation (NBF)
Cerrai, et al. ***J. Mater. Sci. Mater. Med.*** **1999** [27]	The copolymer presented good biological tolerance, is resorbable under physiological conditions and can promote cell growth.	Human	—	Periodontal Defects	Composites Of Hydroxyapatite And Bioresorbable Block Copolymers.	—	6 Months	NBF present in innermost parts of the membranes, with NBF trabeculae closely to the graft.
Degidi, et al. ***J. Oral Implantol.*** **2003** [28]	No dehiscences were observed. In all cases, the space under the titanium mesh was completely filled by bone.	Human	18 Patients	Alveolar Defect	Micromesh With Autologous Bone And A Resorbable Membrane	—	7 Years	NBF under the resorbable membrane.
Assenza, et al. ***J. Oral Implantol.*** **2001** [29]	No residual bone defects were observed, and an increase in the alveolar width or height was observed. No untoward effects on bone regeneration were observed in the cases with membrane exposure.	Human	22 Patients	Alveolar Defect	Micromesh With Autologous Bone And A Resorbable Membrane	—	6 Months	mature NBF with marrow spaces in contact with the membrane
Majzoub, et al. ***Clin. Oral Implants Res.*** **1999** [30]	In the laminar bone-treated sites, the membrane maintained its integrity in almost all cases.	Human	26 Sites	Implant-Associated Defects	Electrically Charged GTAM Membranes	Demineralized Laminar Bone Sheets	8 Months	
Malchiodi, et al. ***Int. J. Oral Maxillofac. Implants*** **1998** [31]	At second-stage surgery in all patients, it was possible to see tissue, under the mesh, that had the macroscopic characteristics of	Human	25 Patients Sites	Alveolar Defect	Titanium Mesh In Edentulous Ridge Expansion	—	8 Months	Mature NBF superficially covered by a thin soft tissue layer
Simion, et al. ***Int. J. Periodontics Restorative Dent.*** **1998** [32]	Direct correlation between the density of the pre-existing bone and the density of the regenerated bone. The mean percentage of new bone-titanium contact was from 39.1% to 63.2%.	Human	58 Implant	Jaws	Vertical Ridge Augmentation Around Dental Implants Using A Membrane Technique And Autogenous Bone Or Allografts	—	6 Months	NBF: 75.17 ± 26.72

Table 3. *Cont.*

Authors	Results	Ex-Model	N	Defect	Test	Ctr	Time	New Bone Formation (NBF)
Simion, et al. ***Clin. Oral Implants Res.*** **1997** [44]	The Pla/Pga membranes started to resorb in the early stages: this process concluded itself between the 3rd and 4th weeks of exposure.	Human	8 Device	Lower Jaw	Pla/Pga Membrane Separated The Composite Chambers	—	4 Weeks	—
Simion et al. ***Int. J. Oral Maxillofac. Implants.*** **1996** [15]	Very little or no bone formation was detected in control specimens.	Human	21 Implant Defects	Lower Jaw	Seven Defects Were Treated With Pla/Pga Membranes, and Five Were Treated With E-PTFE Membranes, And Four Were Left	Untreated (Control Sites).	6 months	Higher NBF in membranes is for fresh extraction sockets implants
Piattelli et al. ***Biomaterials*** **1996** [25]	Defects filled by a newly formed tissue with the macroscopic features of mature bone.	Human	—	Alveolar Defect	Granulate Of Biphasic Calcium Phosphate Ceramic (Bcp), E-Ptfe Membranes	—	6 Months	In some regions, the granules appearedto be cemented by the NFB
Piattelli, et al. ***Biomaterials*** **1996** [13]	E-PTFE membranes showed material interstices of the membranes, in many cases the presence of connective tissue cells and collagen fibres, and in two cases the presence of bone.	Human	10 Patients	Alveolar Defect	E-PTFE Membranes	—	6 Months	The NBF was locatedin a central portion of E-PTFE Membranes
Simion, et al. ***Int. J. Periodontics Restorative Dent.*** **1996** [39]	The implant showed an angular bony defect at the smooth collar, but the bone-implant, direct contact rate seemed, to be elevated in the remaining implant surface.	Human	Case Report	Alveolar Defect, Implant Retrieed	E-PTFE Membranes With DFDBA + Implant	—	4 Years	Higher NBF compared to membranes alone after 6 months
Donath et al. ***Eur. J. Oral Sci.*** **1996** [36]	DFDB with expanded polyte-trafluorethylene (e-PTFE) membranes. Was slowly resorbed	Human	Case Report	Bone Defects	Demineralized Freeze-Dried Bone In Conjunction With E-PTFE Barrier	—	6 Months	DFDB particles partial NBF DFDB no NBF.

Table 3. *Cont.*

Authors	Results	Ex-Model	N	Defect	Test	Ctr	Time	New Bone Formation (NBF)
Piattelli, et al. *J. Periodontol.*1996 [35]	The membrane was filled by a tissue with the macroscopic features of bone, and the newly-formed tissue almost covered the two implants. Histologic examination showed that all retrieved miniscrews were in direct contact with bone. Histomorphometric analysis of bone contact gave a mean value of 42.5 +/− 3.6% for five of the six examined miniscrews.	Human	Case Report	Vertical Augmentation	Resorbable Freeze-Dried Dura Mater Membrane	—	6 Months	NBF macroscopically in the space under the membrane
Simion, et al. *Int. J. Periodontics Restorative Dent.*1994 [37]		Human	5 Patients, 15 Sites	Vertical Augmentation Implant	Membrane Technique Associated With Osseointegrated Implants	—	6 Months	NBF of 42.5 ± 3.6%
Simion, et al. *J. Periodontol.* 1994 [16]	The study showed the possibility that oral bacteria may contaminate eptfe membranes exposed to the oral cavity.	Human	5 Sites	Vertical Augmentation Implant	Polytetrafluoroethylene Membrane	—	4 Weeks	The retrieved samples demonstrated the presence of mature NBF under Polytetrafluoroethylene Membrane
Fontana, et al. *J. Periodontol.* 1994 [38]	There was a partial dehiscence of the membrane in only 4% of the cases.	Human	69 Patients	Post-Extraction Dental Implants	Freeze-Dried Dura Mater	—	3 To 6 Months	NBF closely adapted to the implants
Simion, et al. *Int. J. Periodontics Restorative Dent.* 1994 [39]	Guided tissue regeneration techniques are capable of producing new bone osseointegrated with titanium dental implants.	Human	—	Post-Extraction Sockets	(1) E-PTFE Membranes + Autografts, (2) E-PTFE Membranes + DFDB, (3) E-PTFE Membranes + A Demineralized Allograft (4) E-PTFE Membranes Alone	—	6 Months	Autogenous graft provided the densest and the greatest amount of NBF.

4. Discussion

The use of membranes in bone regeneration procedures has been validated in the regenerative medicine literature [45–47]. Adopting a barrier to preserve and separate the regenerative compartment from the epithelium compartment is necessary to avoid soft tissue infiltration. This aspect is fundamental to guarantee the blood clot organization, the bone graft's protection, and new bone formation during the healing period [2,40,48]. Moreover, the membrane should be histologically characterized with a high level of tol-

erance by the host tissues, the absence of macrophage infiltrations, and no significant adverse reactions of soft and hard tissues [49–51]. The complete substitution of the membranes' components is one of the significant aspects of entire processes; although using a non-resorbable membrane clinically requires a second stage surgery for its removal, it can create a favorable environment for graft stabilization, vascularization, and osteointegration [52,53]. Both in animal and human studies, a higher level of new bone formation was detected in association with different typologies of bone graft [24,30,42,43,54]. No evidence of the differences between bone particle resorption patterns was seen with histological analysis [14]. Therefore, in the case of longer follow-ups, earlier mature bone effectiveness was detected in animal studies in association with useful space-maintaining capabilities [23]. Freeze-dried dura mater membrane has been successfully proposed, associated with immediate post-extraction implant positioning [38]. Fontana et al. reported that after six months, in a total of 69 patients treated with an immediate post-extraction implant, there was partial dehiscence of the membrane in a small number of clinical cases (<4%) [38]. Chierico et al. reported that negatively charged membranes, on rabbits, could increase the new bone formation in the absence of bone graft materials. The Pla/Pga membrane, after a healing period of four weeks, was histologically still recognizable, and the substitution process continued over six months from the first stage of surgery [24,33,44]. The membrane exposure represents critical aspects due to bacteria contamination and oral biofilms adhesion. Simion et al. reported that through scanning electron microscopic and histologic examinations after four weeks of exposure, the bacteria contamination could occur on PTFE membranes [54–56]. Thus, there is a possibility of bone graft disappearance caused by local infection. In the present study, it was possible to observe that translational research is essential to evaluate bone regeneration membrane barriers. After thirty years of studies in the Implant Retrieval Center Laboratory of University "G. D'Annunzio" of Chieti-Pescara, different products have been tested and developed by our research group, all of which produced data from in vitro assays to implants in the surgical bed. All of this is to ensure the biomaterials' quality for the patients.

5. Conclusions

Within this overview's limitations, it was possible to demonstrate the importance of translational research for barrier membranes for bone regeneration, which may be used in the surgical bed. With this, the importance of experts in different fields and a research center that produces high quality data for the future implantology and perio-implantology research is fundamental.

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