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REVIEW ARTICLE

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Effect of cross-linked vs non-cross-linked collagen membranes on bone: A systematic review

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The aim of this study was to conduct a systematic review to compare the clinical outcomes of two different resorbable collagen membranes in terms of regenerated bone volume, postoperative complications and membrane degradation during bone regeneration procedures. Randomized controlled trials (RCT) or controlled trials (CT) that compared both techniques were reviewed on four electronic databases up to December 2015, a manual search was performed on the bibliography of the collected articles and the authors were contacted for additional references if undetected on the electronic and manual search. Membrane exposure was evaluated as a dichotomous outcome and the statistical unit was the membrane. The results were presented as relative risk (RR) with a 95% confidence interval. Eight RCTs and one CT were included in this study. The majority of the studies depicted a bone augmentation area, which ranged from 46.15% to 94.6% for the non-cross-link membranes and from 44% to 92.6% for the cross-link membranes at the 4-6 month re-entry surgery. From a total of 289 patients, a forest plot concerning the membrane exposure was constructed using the obtained RR of the included studies. The overall RR was 1.43 (95% CI: 0.85-2.39) with no statistically significant differences between the two groups, although with a marginal tendency towards higher exposure in the cross-link membrane group. This systematic review suggests the different membranes present themselves as appropriate for bone regeneration procedures, although cross-link membranes present higher rates of postoperative complications. However, more RCT with higher sample sizes are needed to evaluate the different membranes. The suggested lack of clinical differences between the compared membranes suggest that further cost-benefit ratio, tissue integration and postoperative complication oriented studies should be performed so that clinicians can take a patient-centred, evidence-based decision.

KEYWORDS
bone grafting, membranes, regeneration, systematic review/meta-analysis

1 | INTRODUCTION

In 1969, Brånemark et al.[1] described the use of intraosseous dental implants as a safe and reliable alternative to tooth supported or removable prosthesis rehabilitation. This clinical option was shown to reduce the complications and disadvantages of conventional rehabilitations. However, new challenges have been presented particularly in implant survival and success rates reliant on residual bone volume that, due to systemic or local factors, needs to be augmented in specific cases.[2]

The concept of guided bone regeneration (GBR) has been used in experimental maxillofacial reconstruction since the mid-1960s.[3] According to Dahlin et al.,[4] the use of a membrane technique prevents the migration of fibroblasts and soft connective tissue cells into the intended regeneration site. In the intervening period, the evolution of these bone volume growth techniques has improved.[5-7] In 1996 Hermann and Buser,[8] discussed the critical surgical factors in undertaking an adequate and predictable regeneration: use of an appropriate membrane, attaining primary soft tissue healing, creation and maintenance of a membrane-protected space, close adaptation and stabilization of the membrane to the surrounding bone and sufficient length of healing period. Wang and Boyapati in 2006[9] also published the PASS principles: primary wound closure without tension to enable proper healing by means of first intention and reduction of the risk of membrane exposure, angiogenesis to promote blood supply, space maintenance to create a bed for the undifferentiated mesenchymal cells and clot stability to allow for the proper development of these cells.

Based on these principles an ideal membrane used in the GBR technique plays an important role in creating space and to allow sufficient time for the newly formed bone to mature.[10] Although different non-resorbable and resorbable membranes have been developed and their use extensively studied, there is still the need to develop a better membrane for clinical use, which should be biocompatible, cell-occlusive, space creating, allow for tissue integration and be clinically manageable.[5,11] The first grafting materials used for GBR were the non-resorbable membranes made of polytetrafluoroethylene (e-PTFE; Teflon), which had been shown to halt the migration of epithelial cells to the regenerated site where narrow bone was being produced.[12-14] The other non-resorbable membranes in use are titanium reinforced ePTFE, high-density-PTFE or titanium mesh, which are mainly used in oral and maxillofacial surgery.[15] However, these membranes require a second surgical procedure for removal and they have a higher risk of exposure to the oral environment, thus increasing the risk of secondary infection and hindering bone regeneration.[16-20]

In the early 1990s the use of resorbable membranes[21-23] were described and developed to avoid some of the soft tissue complications of non-resorbable membranes.[24,25] Recently, a multitude of options have been introduced to the market and resorbable membranes can now be manufactured from different materials (natural or synthetic).[6] Although the durability of the barrier effect may be diminished over the healing period[26,27] they have several advantages such as a single-step surgical procedure, which decreases patient morbidity and the risk to the newly regenerated tissues,[28] good tissue integration with lower risk of membrane exposure,[29,30] radiolucency that allows imaging and their resorption eliminates the potential effects of stress shielding the regenerated bone.[20] Natural membranes can be made of collagen but have the major handicap of rapid in vivo degradation failing to provide the structural integrity necessary for bone regeneration.[31] Therefore, given the need to improve the process of degradation of resorbable collagen membranes, physical, chemical and enzymatic processes were developed to improve durability by cross-linking the existing collagen fibres and thus creating resorbable cross-linked collagen membranes.[32,33]

Owing to the reported drawbacks with membrane use, practitioners are often discouraged about performing full GBR procedures in preference to partial GBR procedures without membranes.[34,35] Therefore, it is critical to provide the readers clear guidance when it comes to membrane choice.

The purpose of this article is to systematically review the available literature to ascertain the clinical outcomes of two different resorbable collagen membranes in terms of regenerated bone volume, postoperative complications and membrane degradation during bone regeneration procedures.

2 | MATERIAL AND METHODS

This systematic review was conducted following PRISMA guidelines[36,37] and was registered on the Prospero database with the trial no. CRD42015029503. The focused question for this systematic review was based on the PICO format[38] (population, intervention, comparison, outcome):

Population: Healthy adult human patients in need of bone regeneration procedures to place dental implants for fixed oral rehabilitation.

Intervention: Bone regeneration with the use of resorbable non-cross-link collagen membrane.

Comparison: Bone regeneration with the use of cross-link collagen membrane.

Outcomes: Regenerated bone volume, degradation of membrane and the post-surgery complications such as exposure of the barrier membrane, pain, infection or oedema.

2.1 | Criteria in the selection of studies

Eligibility criteria included articles published between 2000 and 2015. These could be meta-analyses, systematic reviews, randomized clinical trials, controlled clinical trials, pragmatic clinical trials, clinical trials and clinical studies.

2.2 | Data source and electronic search strategies

An electronic search was carried out on 29 December 2015 using the following databases: PubMed/Medline, EMBASE, the Cochrane Oral Health Group Trials Register and Lilacs. The search strategy was adapted to each database following the guidelines used for Medline search.

The first search on Medline was conducted through MeSH using the terms: 'collagen membrane', 'resorbable membrane', 'crosslink membrane', 'cross-link membrane', 'cross-linked membrane', 'non-crosslink membrane', 'non-cross-link membrane', 'non-cross-linked membrane', not finding any results by the proposed terms, making this search method unfeasible.

Additional electronic searches were done in PubMed with the following terms:

dental implant AND cross-linked OR noncross-linking OR collagen membrane OR resorbable membrane OR cross-link membrane OR crosslinked membrane OR cross-linked membrane OR non crosslink membrane OR non-cross-link membrane OR non-crosslinked membrane OR noncross-linking membrane

guided bone regeneration AND cross-linked OR noncross-linking OR collagen membrane OR resorbable membrane OR crosslink membrane OR crosslinked membrane OR cross-linked membrane OR non crosslink membrane OR non-cross-link membrane OR non-crosslinked membrane OR noncross-linking membrane

Individual terms were also used to ensure that all the intended articles about the subject were included.

2.3 | Additional strategies and other resources

To obtain additional results a manual search was conducted at the European University of Madrid and at the Public Libraries of Complutense University. The following journals were hand-searched for potentially relevant studies: *Clinical Implant Dentistry and Related Research*, *International Journal of Oral & Maxillofacial Implants*, *Journal of Oral Implantology*, *Clinical Oral Implants Research*, *Journal of Clinical Periodontology* and *Journal of Periodontology*.

In addition, all the references of the included articles were assessed to determine if any other manuscript regarding the subject was present. If so, the title and abstract were analysed to ascertain if they met the inclusion criteria. The corresponding authors of the included studies were contacted via email and, when contact was possible, the authors were questioned concerning the existence of additional works of the same genre.

2.4 | Data collection and quality assessment

To assess the risk of bias and the quality of the included articles a questionnaire from the Critical Appraisal Skills Program (CASP) of the Public Health Resource Unit (2006)[39] was used.

Two operators who did not have access to their counterpart evaluations performed independent assessments. An inter-rater reliability test was performed with a kappa of 0.88, which was above the 0.8 to be considered as good agreement.[40] On completion the evaluations that differed between them were discussed until a consensus was reached.

Studies with more than half of the questions in the CASP questionnaire rated as negative were considered to have a high risk of bias. Therefore, only the trials whose CASP evaluations were ≥50% were selected for the final analysis in this review.

The studies used for this review were those that, after being detected in the electronic databases or by means of manual search or being supplied by the authors of previous studies, could surpass the three phases of evaluation.

2.5 | Data analysis

All data collection was done using an Excel document designed to express all the data regarding the variables included in this study as a table in the results. A meta-analysis on post-surgery complications was performed for membrane exposure, which was evaluated as a dichotomous outcome, and the statistical unit was the membrane. The I^2 statistic was used to measure the proportion of statistical heterogeneity of the proposed outcome, and Cochran's test was used to determine the possible significance. As statistical heterogeneity was present, a random-effects model was utilized with the DerSimonian-Laird[41] approach.[42,43] The results were shown as a relative risk with a 95% confidence interval. These data were analysed using OpenMeta[Analyst].statistical software version 10.10[44] for Mac.

3 | RESULTS

3.1 | Literature research and included studies

The selection process on the studies included is shown in Figure 1. The search resulted in 520 articles after removing the duplicates in the various databases. Of these, after the analysis of their abstracts, nine were identified for possible inclusion in this review. In addition, one more article was found to be eligible in the manual search. Although only two of the authors, who were contacted, responded; no additional data were added to this review. The remaining articles were subjected to the CASP quality assessment[39] (Table 1) of which one article[45] was excluded for presenting a CASP evaluation with a high risk of bias. Thus, a total of nine articles remained.

3.2 | Population and intervention

All included studies were clinical trials comparing two distinctly processed resorbable membranes used for bone regeneration, of which eight were randomized studies and one was a controlled clinical trial.[29] A total of 363 patients were studied and the mean follow-up ranged from 4 months to 6 years. An Excel table was built to collect the following information: study characteristics (design, blinding, CASP evaluation score, number of patients in each group, time of follow-up); type of materials used (implant brand, bone substitute, membranes, if applicable); bone augmentation (indicated as defect fill in millimetres or percentage defect fill or percentage defect area reduction); membrane present at time of re-entry; post-surgery complications (membrane exposure, other types of complications); and peri-implant status. Detailed data of the included studies are shown in Table 1.

3.3 | Description of the studies

3.3.1 | Surgical variables

All the authors specified the brand of the dental implants used when bone regeneration was required except for Tal et al.[46] From which, Camlog® (Basel, Switzerland) was the most frequently used

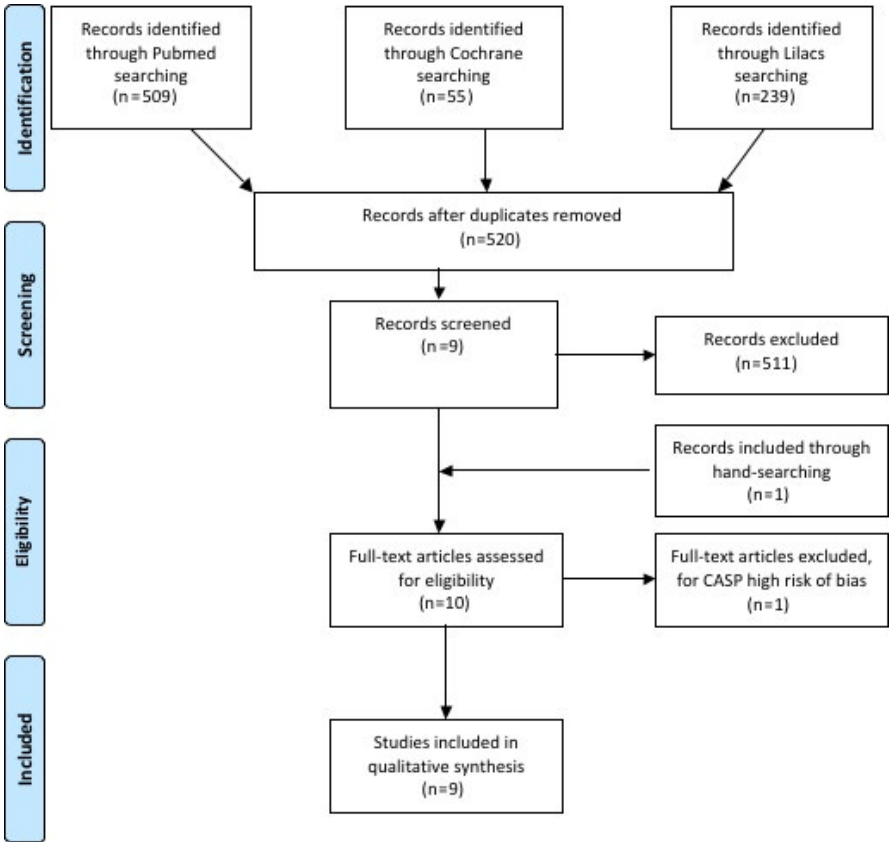

FIGURE 1 PRISMA flowchart diagram of the search strategy. Articles are sorted by identification, screening and eligibility

with a percentage of 40.27%,[47-50] followed by Straumann® (Basel, Switzerland) with 15.14%.[51-53] Moses et al.[29] and Lee et al.[53] are the only researchers to have used different types of implants in the same study (Calcitek-Spline [Carlsbad, CA, USA], 3i Implant Innovations [Palm Beach Gardens, FL, USA], Steri-Oss® [Yorba Linda, CA, USA] and Straumann®, Dentium® (Gwanggyo-ro, Korea), Osstem® (Seoul, Korea), Luna Implant System® (Seoul, Korea) respectively).

Within the basic requirements for GBR, graft material is critical for proper volume. Therefore, all the authors indicated the type of graft material used. The majority of the included studies in this systematic review used Bio-Oss® (Geistlich Biomaterials, Wolhusen, Switzerland), which is a particulated bovine-derived xenograft and can be applied alone or mixed with particulated autogenous bone, equating to 90% of the patients. The other types of grafts used were the tri-calcium phosphate Cerasorb®[29] or allogenic bone particles ICB®.[50]

All the clinical trials included in this systematic review compared the non-cross-link and cross-link membranes, except for one that contained three study groups, non-cross-link, cross-link and non-resorbable membranes made of e-PTFE.[29] The Bio-Gide® membrane (Geistlich Biomaterials) is a porcine-derived type I and type III collagen membrane used as reference for all the studies included, the collagen non-cross-link membrane comprising 48.64% of the total patients. From the cross-linked membranes, the Ossix® membrane (ColBar Life Sciences, Lod, Israel) was the most frequently used at 53.18% of patients, while the others were a prototype from Geistlich Biomaterials virtually identical to Bio-Gide® except for its chemically cross-linking named 10806 or VN, at 38.15% of patients and a dehydrothermally porcine pericardium-derived type I cross-linked collagen membrane at 8.67%.

3.3.2 | Outcomes: volumetric bone measurements

The amount of bone volume regeneration was measured by the use of a millimetre periodontal probe with previously established methods, namely, the measurement of height as the distance from the most apical aspect of the buccal crestal bone to the implant platform margin and the width as the widest mesio-distal dimension of the buccal defect. Depending on the manuscripts the results were presented as a mean percentage, median gain in millimetres of bone augmentation or frequency distribution of residual defect height at 4 months.

The majority of the studies detected from poor to acceptable bone augmentation area, which ranged from 46.15% to 94.6% for the non-cross-link membranes and from 44% to 92.6% for the cross-link membranes at 4-6 months re-entry surgery.

The two publications from Schwarz et al.[48,49] aimed to assess the peri-implant health 4 years after bone augmentation. The residual defect on a follow-up of 4 months from the GBR surgery was also recorded and categorized in to three groups. This was done according to the defect size found at re-entry from bone augmentation as: 0 mm for absence of residual defect or control group; ≤1 mm for minimal residual defect or test group 1; and ≥1 mm for the advanced residual defect or test group 2, and the results are expressed in Table 1.

The Friedmann et al.[52] article in addition to determining bone volume augmentation in vivo by previously described methods, included

ex vivo measurements. This was undertaken before and after the reflection of a muco-periosteal flap at the bone regeneration surgery to document hard and soft tissue dimensions and at the re-entry 6 months later to make comparisons. The morphometric outcomes given by the authors compare the median width and height results taken from the casts between both surgeries by taking two reference points and were expressed in millimetres. The results are reported in Table 1.

3.3.3 | Membrane durability

The barrier durability and integrity on regenerated bone dehiscence's was carried out by Tal et al.[46] and Lee et al.[53] from histologic sections via biopsies to assess the membrane degradation with 6 and 4 month follow-ups respectively. The findings from the biopsy samples ranged from 77.8% to 100% on membrane remnants from the histologic observations on the cross-link group while no remnant was observed in the non-cross-link membrane group, although no statistical analysis was performed for this outcome.

3.3.4 | Post-surgery complications

Post-surgical complications may appear during a GBR, premature membrane exposure being the most frequent, described in seven of the nine studies included in this systematic review.

Spontaneous non-cross-linked membrane exposures ranged from 11% to 32.1% (individual results depicted in Table 1). From the cross-linked membrane groups, Ossix® cross-linked membranes recorded rates from 12.5% to 50% and for VN® cross-linked membranes, rates ranged from 52.17% to 56%. All authors from the included studies reported statistically significant differences between the two types of membranes for this outcome.

A forest plot concerning the membrane exposure was constructed using the obtained relative risk of the included studies. The obtained heterogeneity was Q=9.34 (df=6) and the I^2=35.78%, corresponding to a moderate heterogeneity value. The overall relative risk was 1.43, with 95% confidence intervals, as expressed in Figure 2. According to the analysed data, no statistically significant differences were obtained between the two groups although with a marginal tendency to higher exposure in the cross-link membrane group.

With regard to other post-surgery complications, inflammation and swelling have been assessed by Becker et al.[47] corresponding to 30.4% and 13% respectively, as well as Annen et al.[51] reporting infection/membrane removal in 33.3% for the cross-link membranes group, while no other complication was described for the non-cross-linked membrane groups in both studies.

4 | DISCUSSION

The objective of this study was to investigate through the current literature the different biological behaviours between two types of resorbable membranes on bone augmentation procedures for implant placement. The use of membranes allows for the hindrance of the migration of connective tissue maintaining a space where the bone is in formation.[9] All membranes employed have advantages and disadvantages that should be analysed to optimize our clinical procedures.[7] All the clinical studies that were included in this review directly compared two types of resorbable membranes for GBR carried out in humans and always under conditions as close as possible to those observed in daily clinical practice. Of the 10 studies included for this systematic review, nine were randomized controlled trials (RCTs) and one was controlled clinical trial, achieving a high evidence-based level with a low risk of bias as determined by the CASP quality assessment[39] performed.

From the outcomes considered in this systematic review and assessed by the different authors, the regenerated bone volume was the main variable in determining when to perform a GBR technique. Except for Tal et al.[46] who aimed to analyse the degradation rate of the resorbable collagen membranes the remaining articles included in this review determined the osseous volumetric changes. The difficulty for the comparative assessment is the heterogeneity of the methodologies in reporting data due to different benchmarks and methods of calculation. The studies included in this systematic review obtained an increase on bone volume through a bone regeneration procedure, and despite some authors, suggesting results subtly superior on cross-link membranes[29,47,52] by means of volumetric analysis, no study found a statistically significant difference between both membranes. In fact, Brunel et al. and Mattson et al.[32,54] noted that the slower resorption degree of the collagen membranes depends on the intensity of cross-linking between the collagen fibres of the resorbable membranes and therefore suggest an increase in regenerated bone volume in membranes with longer resorptions. Even though a large sample size makes a study more difficult in human and economic terms, the sample size of the included clinical trials in this review are too small and resulted in an inability to detect statistical differences between groups, leading to the necessity to perform additional RCTs with adequate sample sizes.

Concerning post-surgical complications, the membrane exposure was the most frequent complication for the included studies in this systematic review, except for Schwarz et al.[48,49] who did not evaluate this complication. To enable a better comparison between studies this outcome was evaluated as a dichotomous analysis (present or absent). At this point the differences between membranes show a tendency to a higher exposure rate in the cross-linked membranes although due to small sample sizes no statistical significance was obtained. These results should be discussed in the context where GBR takes 4-6 months to complete, and as demonstrated by von Arx et al.[55] and Tal et al.,[46] the cross-link membranes have longer degradation times compared with the non-cross-link membranes so they have greater probability to become exposed to the oral environment over similar follow-up periods. This biological behaviour could also be the reason why cross-link membranes present higher prevalence of other post-surgery complications such as inflammation, swelling or infection.

In fact, there is no clear evidence in the literature regarding the process by which there is a higher prevalence of exposure in the cross-link membranes vs non-cross-link membranes and if there is any correlation with the resorption degree of the membranes.[46] Some possible mechanisms for explaining the higher rate of exposure with

TABLE 1 Study characteristics of RCTs selected for this review

Authors	Journal	Year	Study design	Blinded?	CASP	Patients (n)	Follow-up	Implant brand	Bone graft
Moses et al.	COIR	2005	CT	No	6/10	86 (GC: 17; GT1: 28; GT2: 41)	6-8 mo	Sulzer Dental (Calcitek-Spline), Steri-Oss, and 3i Implant Innovations	Autogenous + bovine bone mineral (Bio-oss) OR tri-calcium phosphate (Cerasorb)
Tal et al.	COIR	2008	RCT	No	6/10	52 (GC: 26; GT: 26)	6 mo	/	Bovine bone mineral (Bio-oss)
Becker et al.	COIR	2009	RCT	Double	10/10	49 (GC: 23; GT: 26)	4 mo	Camlog	Bovine bone mineral (Bioss, Geistlich)
Annen et al.	Eur J Oral Impl.	2011	RCT	Double	7/10	9 (GC: 9; GT: 9)	6 mo	Straumann	Bovine bone mineral (Bio-oss, Geistlich)
Friedmann et al.	JCP	2011	RCT	Single	9/10	37 (GC: 17; GT: 20)	6 mo	Tissue-level Standard plus (Straumann)	Xenograft (BoneCeramic, Straumann)
Schwarz et al.	COIR	2012	RCT	Double	9/10	24 (G0: 8; G1: 8; G2: 8)	4 y	Camlog	Bovine bone mineral (Bio-oss, Geistlich)
Schwarz et al.	COIR	2014	RCT	Double	9/10	42 (GC: 22; GT: 20)	6 y	Camlog	Bovine bone mineral (Bio-oss, Geistlich)
D-W Lee et al.	JOI	2015	RCT	N/A	7/10	34 (GC: 16; GT: 18)	10-12 mo	Camlog	Autogenous or allogenic bone particles (ICB) and bovine bone mineral (Bio-oss)
J-H Lee et al.	JPIS	2015	RCT	Single	8/10	30 (GC: 15; GT: 15)	4 mo	Implantium and NR line (Dentium); TS III (Osstem); Bone level (Straumann); Shinhung (Luna implant system)	Bovine bone mineral (Bio-oss, Geistlich)

CLM, cross-linked membranes; G0, G1, G2: Groups were divided according to defect characteristics during re-entry; GC, group control; GT, group test; NCLM, non-cross-linked membrane; RCT, randomized controlled trial; VG, vertical gain; WG, width gain.

*No statistical differences.

**Statistical differences.

Control membrane	Test membrane	Bone augmentation	Membrane exposure	Membrane degradation	Peri-implant status	Post-surgery complications
e-PTFE non-resorbable (Gore-Tex)	NCLM (Bio-Gide, Geistlich); CLM (Ossix)	% Defect area reduction:* GC: e-PTFE: 97.3±4.91% GT1: Bio-Gide: 94.6±6.69%; GT2 Ossix: 92.2±13.78%	GC: e-PTFE: 42.1%; GT1: Bio-Gide: 32.1%; GT2: Ossix: 39% **	/	/	/
NCLM (Bio-Gide, Geistlich)	CLM (Ossix)	/	GC (NCLM): 6 cases (23.1%)** GT (CLM): 13 cases (50%)	Membrane remnants at re-entry: GC (NCLM): 0/18 specimens GT(CLM): 14/18 specimens	/	/
NCLM (Bio-Gide, Geistlich)	CLM (VN, Geistlich)	% Defect fill:* GC: NCLM: 46.15±73.34% GT: CLM: 60.18±53.58%	GC: NCLM: 4** GT: CLM: 12	/	/	Inflamed: GC (NCLM):0; GT (CLM): 7 swollen: GC (NCLM): 3; GT (CLM): 10
NCLM (Bio-Gide, Geistlich)	CLM (VN, Geistlich)	Defect fill (mm & %):** GC (NCLM): VG: 4.7 mm, WG: 1.8 mm ->78% GT (CLM): VG: 1.8 mm; WG: 1.0 mm->44%	GC (NCLM): 1 case (11%)** GT (CLM): 5 cases (56%)	/	/	Infection/ membrane removal: GC (NCLM): 0; GT (CLM): 3
NCLM (Bio-Gide, Geistlich)	CLM (Ossix)	Defect fill (mm):* GC (NCLM): VG1: 0.2 mm, VG2: 2.7 mm, WG1: 0.7 mm, WG2: 2.1 mm; GT (CLM): VG1: 1.1 mm, VG2: 2.5 mm, WG1: 1.8 mm, WG2: 3.0 mm	GC (NCLM): 5 cases** GT (CLM): 4 cases	/	/	/
NCLM (Bio-Gide, Geistlich)	CLM (VN, Geistlich)	Re-entry defect size:** G0: 0 mm: 6NCLM; 2CLM G1: ≤1 mm: 2NCLM; 6CLM G2: ≥1 mm: 4NCLM; 4CLM	/	/	Pocket depth: G0: 0 mm: 2.9; G1: 1 mm: 2.8; G2: >1 mm:2.7 Bleeding on probing %: G0: 29.1%; G1: 45.8%; G2: 54.1%	/
NCLM (Bio-Gide, Geistlich)	CLM (VN, Geistlich)	Re-entry Defect size:* G0: 0 mm: 4NCLM; 2CLM G1: ≤1 mm: 2NCLM; 4CLM G2: ≥1 mm: 3NCLM; 4CLM	/	/	Healthy: NCLM: 3; CLM:2 Mucositis: NCLM: 3; CLM: 6 Peri-implantitis: NCLM3; CLM:2	/
NCLM (Bio-Gide, Geistlich)	CLM (Ossix plus)	% Defect area reduction:* GC (NCLM): 94.01±8.35% GT (CLM): 95.52±16.37%	GC: (NCLM): 5 cases** GT(CLM): 2 cases	/	Radiographic marginal bone loss: GC (NCLM): 0.52 mesial, 0.48 distal GT (CLM): 0.53 mesial, 0.52 distal	/
NCLM (Bio-Gide, Geistlich)	Cross-linked porcine pericardium-derived type I collagen membrane (OssGuide, Bioland)	Defect fill (mm):** GC (NCLM): VG: 5.0±2.5, WG: 3.5±1.2 GT (CLM): VG: 2.9±2.3, WG: 1.7±2.2	GC (NCLM): 2 cases (14.3%)** GT (CLM): 3 cases (21.4%)	Membrane remnants at re-entry: GC (NCLM): 0/12 specimens GT(CLM): 10/10 specimens	/	Infection: GC (NCLM): 0; GT (CLM): 1 cover screw exposure: GC (NCLM): 1; GT(CLM):0

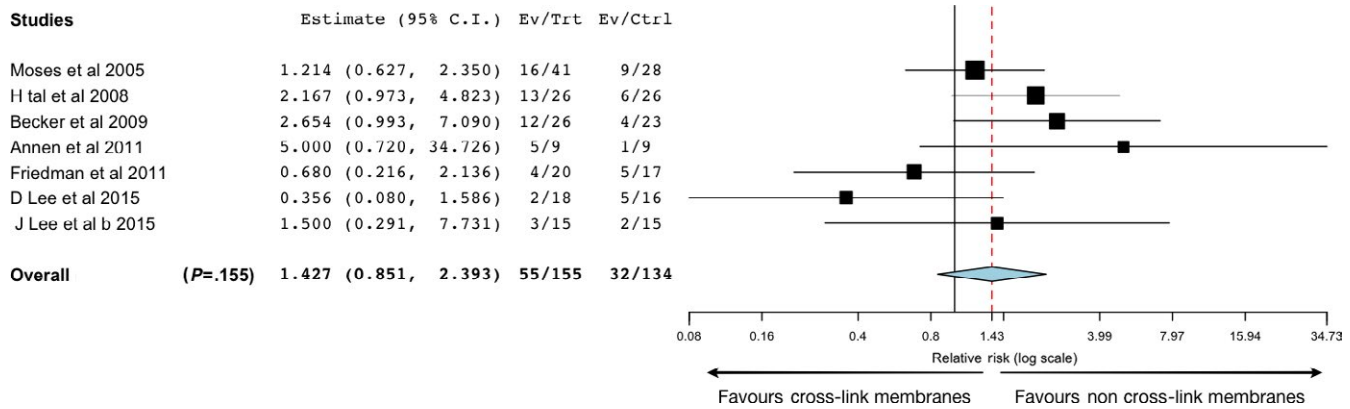

FIGURE 2 Analysis and forest plot for the results of the included studies that determined membrane exposure. Ev/Trt represents the test (cross-linked membranes) group, while Ev/Ctrl represents the control (non-cross-linked membranes) group. Red line represents the average for all results, and the vertical black line represents the no-effect line

cross-link membranes were proposed in the literature, equating from the inflammation induction in several types of cross-linked membranes to lack of cell attachment in the Ossix membrane, interfering in the inflammatory response and soft tissue healing, compromising tissue integration and possibly bone regeneration.[56,57] Thus, the cross-linked membranes could be more prone to exposure to the oral environment. In addition, several studies,[29,47,52] described GBR without impairments and a complete re-epithelization by second intention healing when spontaneous cross-linked membrane exposure occurs.

Biological and surgical variables such as gender, age, type of implant or graft material seem to have no influence on the volumetric changes in terms of GBR. These patterns in bone volume augmentations are in agreement with some studies such as Zitzmann et al.,[18] which make a comparative assessment with non-resorbable membranes and reported a mean defect fill of 92% in non-cross-linked collagen membranes and Jung et al.[30] who reported a 96.4% defect fill over the non-cross-linked membrane groups. Some animal studies, which compared both resorbable membranes, described no statistical differences in defect fill as did Bornstein et al.[58] and Kelley and Kelley.[41]

When assessing postoperative complications, Friedmann et al.[59] did not compare different membranes and only analysed the exposure rate in cross-linked resorbable membranes, which equated to 62%, while Chiapasco and Zaniboni[25] in their systematic review described a mean exposure rate of 5%. The pattern in biodegradation and durability from animal specimens of different types of resorbable membranes and assessed by histological findings from Rothamel et al.[57] and von Arx et al.[55] are in agreement with Tal et al.[46] in their human clinical trial where cross-linked collagen showed more durability during the GBR compared to the non-cross-linked collagen membrane.

5 | CONCLUSIONS

Within the limitations of the present systematic review, it can be concluded that GBR procedures through resorbable collagen membranes achieve volumetric bone gains with no statistical significance between the cross-link and the non-cross-link membranes. However, in terms of biocompatibility, tissue integration and postoperative complications the results suggest that non-cross-link membranes present better results.

Nevertheless, further investigations are needed to clarify better the influence of the location and nature of the soft tissue in the site to be augmented in the biological behaviour within the two types of resorbable membranes.

CONFLICT OF INTEREST

Samuel Berghezan, Duarte N.S. Marques, João M.M. Caramês, Michel Dard, Jaime Jiménez Garcia declares that they have no conflict of interest.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

INFORMED CONSENT

For this type of study, formal consent is not required.

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