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REVIEW ARTICLE

Efficacy of biomaterials for lateral bone augmentation performed with guided bone regeneration. A network meta-analysis

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1 | INTRODUCTION

The application of a membrane to exclude non-osteogenic tissues from interfering with bone regeneration is the key principle behind guided bone regeneration (GBR).[1-3] The process of bone regeneration under a barrier membrane follows a series of well-orchestrated, correlated steps that recapitulate the normal osteogenesis process. All these steps are characterized by the succession of different concentrations of specific growth factors and osteogenic molecules and have been previously described in detail from a histological, transcriptomic, and proteomic point of view.[4-7]

Since the introduction of GBR in the late 1980s,[1] different non-resorbable and resorbable barriers have been successfully employed to promote bone regeneration of atrophic ridges and of bone defects around teeth and implants, for socket preservation and sinus augmentation.[3] As highlighted by the XIII consensus of the European Federation of Periodontology, there is currently no ideal membrane in the market that fulfills all desired characteristics in terms of degradability, porosity, mechanical properties, integration, and biological activity, hence the choice between the available barriers should be made by the clinician on a case by case situation.[8]

Bone substitutes have been successfully used in combination with membranes with the aim of increasing barrier support by reducing the risk of collapse, acting as a scaffold for bone ingrowth (osteoconductive properties), and protecting the augmented volume from undesired resorption[9-12] (for review Ref. [13]). While autologous bone is still seen as the "gold standard", being the only material that can combine osteogenic, osteoinductive, and osteoconductive properties, it has obvious limitations related to availability, need for a second site of surgery, and increased patient's morbidity.[8] Therefore, a variety of allografts, xenografts, and alloplastic materials have been proposed over the years. There is currently no clear evidence on which combination of membrane (resorbable vs. non-resorbable) and bone substitute is more effective for different bone regenerative purposes in the oral cavity.

Bioactive agents or factors are so-called because they are natural mediators of tissue repair capable of eliciting a response from a living tissue, organism or cell, such as osteoblast differentiation, angiogenesis, matrix mitosis, or the formation of hydroxyapatite.[14] Several pre-clinical and clinical studies have documented the potential of different bioactive factors in enhancing bone regeneration in the cranial and maxillofacial area, although controversies on their efficacy and effectiveness have also been raised.[15] There is currently no clear evidence on which bioactive factors (alone or in combination with other biomaterials) are more effective in GBR procedures.

With the aim to provide evidence-based indications to clinicians facing the dilemma of which biomaterials to choose when applying GBR to treat peri-implant bone defects, comparative effectiveness research using network metanalysis offers the possibility of

providing evidence for all possible comparisons amongst a set of interventions that facilitates constructing a hierarchy between competing treatments.

To the best of our knowledge, such an approach has never been applied to compare the biomaterials used for GBR in the oral cavity. Hence, this systematic review and network meta-analysis aims to fill this knowledge gap and to assess the effect of different biomaterials (membranes, bone substitutes, and bioactive factors) for GBR performed simultaneous to implant placement to treat dehiscence, fenestration, or for contouring.

2 | MATERIALS AND METHODS

The study protocol of this systematic review was registered in PROSPERO (registration number: CRD42022303388) and was conducted in line with the Cochrane Handbook.[16]

2.1 | Aims and objectives

The aim of this review was to evaluate the efficacy of different biomaterials (membranes, bone substitutes, and bioactive factors) on the stability of GBR when performed simultaneously with implant placement.

2.2 | Focused questions

For this systematic review, we considered two focused questions:

1. Focused question (FQ) 1: *In patients receiving GBR simultaneous to implant placement, what is the impact of biomaterials (membranes, grafts, bioactive factors) on the stability of peri-implant bone levels as assessed through 2D or 3D radiographs in RCTs/CCTs with ≥ 12 months of follow-up?*
2. Focused question (FQ) 2: *In patients receiving GBR simultaneous to implant placement, what is the impact of biomaterials (membranes, grafts, bioactive factors) on bone defect dimension (width and/or height) changes as evaluated at re-assessment procedures performed at ≥4 months post GBR in RCTs/CCTs?*

2.3 | Criteria for considering studies for this review based on the PICOS

2.3.1 | Types of participants (P)

For both focused questions

Adult (>18 years old) patients (both men and women) that received implant placement and simultaneous GBR to treat a fenestration or dehiscence, or for contour augmentation. No post extraction immediate implants were considered, but only implants placed in a ridge healed for ≥4 weeks post extraction (i.e., early or late implant placement (Morton, Gallucci et al. 2018)).

2.3.2 | Types of interventions and comparisons (I)

For both focused questions

GBR performed with a membrane or combination of a membrane and bone grafts/bioactive factors. Membranes may include resorbable barriers (e.g., polymer-based or collagen-based), as well as non-resorbable barriers (e.g., polytetrafluoroethylene, PTFE).

2.3.3 | Comparison (C)

For both focused questions

Same protocol of GBR, but with another type of membrane or with another combination of membrane and bone grafts/bioactive factors; or same biomaterials for GBR but according to a different surgical technique.

2.3.4 | Outcomes (O)

Primary outcomes

For FQ 1 we considered changes in radiographic (2D or 3D) peri-implant bone levels at ≥12 months post loading follow-up; for FQ 2 we considered changes in bone defect dimension (width and/or height) evaluated at re-assessment procedures.

Secondary outcomes

Changes in defect depth and intrabony component as measured at re-assessment procedures; changes in the regenerated buccal bone measured at re-assessment procedures; changes in the volume of peri-implant hard and soft tissues (via CBCT and/or intraoral scans) at ≥12 months post loading follow-up; changes in probing pocket depth (PPD) and recession (REC) at ≥12 months post loading follow-up; changes in bleeding on probing or gingival inflammation at ≥12 months post loading follow-up; patient-reported outcome measures (PROMs) (including adverse events, patient's satisfaction); implant success (based on well-defined criteria, such as Albrektsson et al. 1986, Buser et al. 1990, Ong et al. 2008) and survival at ≥12 months post loading follow-up; incidence of biological complications, including peri-mucositis, peri-implantitis and implant mobility; aesthetic scores (e.g., pink aesthetic score – PES, white aesthetic score – WES, papilla fill index – PFI) at ≥12 months post loading follow-up; need for re-grafting.

2.3.5 | Types of studies (S)

For FQ 1: RCTs and CCTs with a minimum follow-up of 12 months post implant loading; for FQ 2: RCTs and CCTs in which re-assessment

procedures (second stage surgery and/or 3D radiographic image) were performed to assess changes in defect dimension at ≥4 months after GBR.

2.4 | Search methods for study identification

A sensitive search strategy was developed aiming to identify all RCTs and CCTs meeting the inclusion/exclusion criteria. The research strategy included terms related to the Population and the Intervention/Comparison investigated in this review, which were combined with the boolean operator "AND" (Appendix S1).

Four main databases were searched, MEDLINE via OVID, EMBASE, Web of Science, and The Cochrane Database (including the Central Register of Controlled Trials (CENTER)), updated to December 2021 and then a new search was performed on 19th September 2022 to identify any new publication. The limitation to human studies was performed following the double negation strategy suggested by the Cochrane Handbook, i.e., combining the results with NOT (exp animals/not humans.sh.). The Cochrane Highly Sensitive Search Strategy for identifying randomized trials was also applied. Any ambiguous or incomplete data were researched further by contacting the researchers responsible for the work.

Bibliographies of review articles on this topic and of all studied included for data extraction were screened and the database Web of Science was used to identify all the papers that cited the included papers. Conference abstracts were excluded.

In the attempt to include both published and unpublished data a specific theses database, www.theses.com/ was searched and a hand search was performed for the last 2 years for the journals that published more about this topic and with a high impact factor (*Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Dental Research*, *Journal of Periodontal Research*, Clinical Oral Investigations and Clinical Oral Implants Research).

Gray literature was searched in opensigle.inist.fr. Clinicatrials.gov was searched to identify potential ongoing or already completed RCTs/CCTs meeting the inclusion and exclusion criteria. In case a relevant unpublished trial was identified, an attempt to contact the authors and to retrieve the data was made.

Only studies published in English, Italian, Greek, Turkish, German, French, Indian, and Spanish were considered.

2.5 | Study selection

A two-stage screening (title and abstracts first, then full-text) was carried out independently and in duplicate by two reviewers (EC and SC). At second stage, a data screening and abstraction form was devised to verify the study eligibility, carry out methodological quality assessment, and extrapolate data on study characteristics and outcomes for the included studies.

Any disagreement was resolved by discussion and if necessary, a third reviewer (ND) was consulted.

The level of agreement at each of the two-stage screening was assessed by calculating Cohen's Kappa statistics.

Multiple reports of the same study were collated, so that each study, rather than each report, was the unit of interest in the review, as indicated in the Cochrane Handbook.[16]

2.6 | Assessment of risk of bias in included studies

Quality assessment was conducted independently by one experienced reviewer (SC), as part of the data extraction process, and 30% of the studies were also assessed by a second reviewer (EC) for quality purposes. The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was employed for CCTs, while the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (updated August 2019) was employed for RCTs.

2.7 | Data extraction and management

Data extraction was performed independently by two reviewers (EC and NG), with all primary outcomes checked in duplicate, as well as 50% of secondary outcomes. Firstly, data on the general characteristics of the study (title, authors, source and year of publication, source of funding, etc.) were extracted. Secondly, verification of the study eligibility was carried out, based on the inclusion/exclusion criteria. Thereafter the rest of the data were extracted, including details about population, interventions, and primary and secondary outcomes.

Whenever numerical data were not presented, WebPlotDigitizer was employed to extrapolate the raw data, as suggested by the Cochrane Handbook (Li et al., 2022). The reviewers independently extracted the data with the manual tool and the average values were used. In case of missing or incomplete data and the absence of further clarification by study authors, the report was excluded from the analysis.

2.8 | Data synthesis and statistical analysis

A Bayesian network meta-analysis was performed using a random-effects model, in order to synthesize data from studies assessing radiographic changes after treatment (FQ1), defect resolution in terms of vertical dehiscence (% of resolution), and defect width (reduction from baseline) (FQ2) and considering different combinations of membranes, grafts, and bioactive factors. Networks geometry was assessed and represented using the *igraph* package in R.[17] A Bayesian method based on Makarov chain Monte Carlo simulation[18] was implemented using R software v4.1.3 (R Core Team, Vienna, Austria) and the package gemtc.[19] Uninformative priors were used. Each model was calculated by generating at least 50 000 adapt and 400 000 sample iterations, with thinning = 15. Heterogeneity was assessed using I^2 statistics.[20] Relative treatment effects, forest plots,

and ranking probabilities were obtained, as well as an estimation of the surface under the cumulative ranking (SUCRA) value.[21] Here, a higher probability value indicates a more effective treatment. We also constructed an overall network diagram, where the nodes in the network represented the available treatments. The thickness of the connecting lines is proportional to the number of studies that provided direct comparison between the two nodes. The Brooks–Gelman–Rubin diagnostic plots were visually assessed to evaluate the convergence of each model.[22] A node-splitting approach was used to assess the consistency of direct and indirect comparisons, but due to the paucity of connections, it was impossible to complete the analysis.[23]

By using the median of defect width and height (where available) as threshold, we distinguished between large and small defects. This parameter was used as a regressor in a network meta-regression based on Bayesian models (with normal likelihood and identity link) that were produced using at least 5000 adapt and 100 000 sample iterations, with thinning = 10.[24,25]

Publication biases were assessed by funnel plot and Egger's test.[26]

3 | RESULTS

3.1 | General characteristics of included studies

Results are herein presented following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-analysis for Network Meta-analysis (PRISMA-NMA) checklist.[27]

A total of 5297 unique records were identified and screened for title and abstract, which led to 64 articles eligible for full-text screening (Figure 1). Thirty-four articles eventually met the inclusion/exclusion criteria (reasons for exclusion are reported in the Appendix S2). Two additional articles were identified after updating the search in September 2022, leading to a final number of 36 articles included for qualitative analysis. A high level of agreement was found between the reviewers during both stages of the screening process ($K > 0.9$). Articles describing different follow-ups or outcomes from the same clinical trial were grouped together, thus resulting in a total of 23 original trials which included 20 RCTs (15 single-center RCTs[29-51] and 5 multi-centric RCTs[52-61]) and 3 CCTs.[62-64] Five RCTs had a split-mouth design.[29-35]

The main characteristics of the included studies are summarized in Table 1. The majority of the studies were conducted in a university/hospital setting, although two took place in private practice[49,50,64] and three in a mixed setting (private practice and university).[57-60] While four studies did not report on source of funding, the majority (12 studies) indicated that Industry (implant and/or biomaterial companies) funded entirely or partially the studies and/or provided them for free the biomaterials (Table 1).

While all studies reported that overall patients were considered in good systemic health, different inclusion/exclusion criteria were applied, with some studies simply reporting a generic statement of good systemic health, others providing a list of specific diseases in the exclusion criteria, and others also including patients with well-controlled diseases (Table 1).

Periodontal status of the participants was poorly reported, but most of the studies indicated that patients either received periodontal treatment or that no active periodontal disease was present at recruitment. Likewise, supportive periodontal care protocol and frequency were scarcely documented. A variety of implant systems and implant surfaces were considered and implant distribution also differed, going from studies that focused only on the aesthetic anterior area, to studies that included premolar/molar areas and to studies that considered both anterior and posterior areas (Table 1). Antibiotic and post-operative regimes also varied (Appendix S3), but the majority of the studies indicated that antibiotic treatment started on the day of the surgery and continued for a period between 4 to 10 days and that painkillers were prescribed according to patients' needs. In two studies corticosteroids were also prescribed.[50,52]

3.2 | Primary outcomes

3.2.1 | Focused question 1 (FQ 1)

Nine studies (13 articles)[32,34-37,40,45,46,49,56,57,59,61] answered FQ1. All studies employed 2D x-rays to assess changes in peri-implant bone levels, apart from four studies that also employed CBCT scans.[34,36,46,61]

Overall, different combinations of membranes (resorbable vs. non-resorbable) and grafts (xenograft alone or combined with autograft or with bone morphogenic protein 2 (BMP-2), alloplastic graft alone or combined with autograft) resulted in similar interproximal radiographic peri-implant bone remodeling at 1 and 3 years (Table 2). Only one study employed CBCT to assess peri-implant bone levels at 12-month follow-up and it indicated that freeze-dried bone allograft (FDBA) or a combination of deproteinized bovine bone mineral (DBBM) and autologous bone associated with a double layer collagen membrane led to similar facial bone wall thickness and facial vertical wall peak. However, regardless of the biomaterial applied, a significant decrease in the mean thickness of the buccal regenerated bone was observed at 12 months.[61]

Three studies had a 5-year follow-up. One indicated that when performing GBR with a non-cross-linked collagen (NCL) membrane and DBBM, adding BMP-2 did not lead to improved interproximal peri-implant radiographic outcomes.[32] The same group also showed stable 3D radiographic bone levels after 5 years of GBR performed with DBBM and either polyethylene glycol (PEG) or NCL membrane.[46] Likewise, Naenni et al.[36] showed similar 2D radiographic interproximal bone levels when a titanium-reinforced e-PTFE membrane or an NCL membrane was applied together with DBBM for the regeneration of peri-implant dehiscences. However, when looking at 3D bone level data (CBCT measurements), they suggested a significantly higher loss of horizontal bone thickness at 5 years of

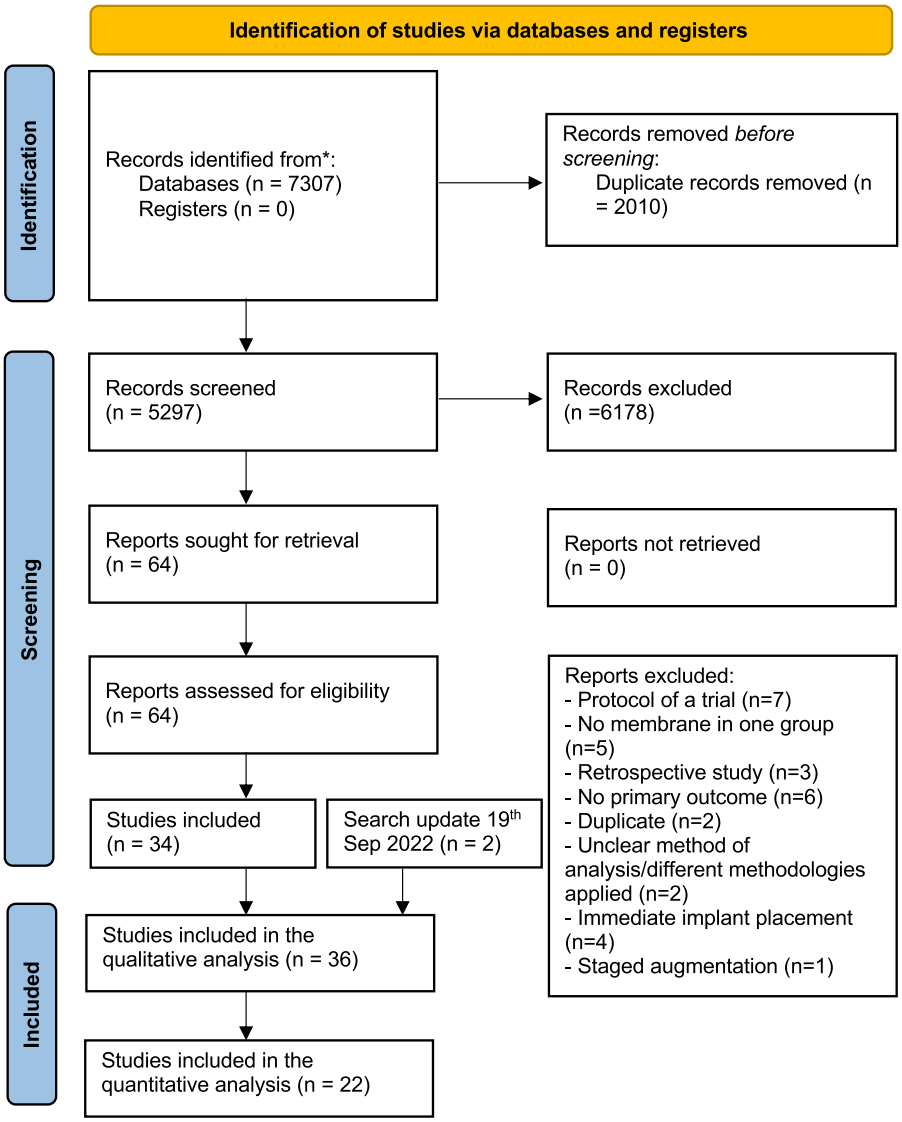

FIGURE 1 Flow chart of the study selection process (adapted from[28]).

follow-up in case a non-resorbable collagen membrane was applied. Remarkably, these significant differences in hard tissue changes did not impact on the overall buccal contour when comparing the two groups. As a matter of fact, regardless of the observed hard tissue resorption, the overlying soft tissue (measured with an intraoral scan) seemed to have compensated for the loss of horizontal bone thickness with an increase in soft tissue thickness.

The longest follow-up was reported by Jung et al.[34] in a study investigating the addition of BMP-2 to DBBM and an NCL membrane. They showed stable and comparable 2D peri-implant radiographic bone levels, with a mean interproximal bone loss at 17 years of 1.16 mm and 0.70 mm in case BMP-2 was applied or not, respectively. The authors also performed a CBCT scan at 17 years, which showed a mean buccal bone thickness ranging from 1.36 to 3.09 mm when BMP-2 was applied and from 1.18 to 3.39 mm when BMP-2 was not applied.

Two networks were drawn for the 12-month data. The first network included three studies[35,37,45] and the treatment ranking based on SUCRA indicated PEG membrane combined with DBBM granules as the treatment with the highest probability to perform better as compared to NCL membrane combined with DBBM, expanded polytetrafluoroethylene membrane (e-PTFE) membrane combined with DBBM and NCL membrane combined with an alloplastic graft in terms of 12-month peri-implant bone level stability (Table 3). However, the forest plot comparing the best-performing treatment with the other treatments did not indicate statistical significance (Figure 2A). The heterogeneity (I^2) was 16%.

The second network included two studies[56,57] and the treatment ranking based on SUCRA suggested that the combination of a non-crosslinked collagen membrane with an allograft had the highest probability to perform better as compared to the same type of membrane associated with autologous bone and DBBM graft in terms of 12-month peri-implant bone level stability (Table 3). Also, in this case, the forest plot did not indicate a statistically significant difference between the treatments. The heterogeneity (I^2) was 25% (Figure 2B).

TABLE 1 Main characteristics of the included studies.

Study	Study design/follow-up	Country; Setting	Funding	Patients enrolled/ dropouts
Annen, Ramel et al. 2011[33]	Split-mouth RCT/6 months	Switzerland; Hospital/ University	Grant from Geistlich Biomaterials + Institut Straumann provided study material	9/0
Naenni et al. 2017, Basler et al. 2018, Naenni et al. 2021[36-38]	RCT/6 months, 3 years, 5 years	Switzerland; University	Research grant from the Swiss Dental Association; Geistlich Biomaterials and Dentsply provided biomaterials and implants	27/4 at 3 years, 7 at 5 years
Lee, Lee et al. 2015, Lee, Park et al. 2019[39,40]	RCT/4 months, 3 years	Korea; Hospital/University	Medical Device Comparative Clinical Trial and Performance Evaluation Program funded by the Small and Medium Business Administration and National Research Foundation of Korea	30/1 at 4 weeks, 1 at 8 weeks, 9 at 3 years
Becker et al. 2009, Schwarz et al. 2012, 2014, 2017[52-55]	Multi-center RCT for 4-month data (single center for long-term data)/4 months, 4 years, 6 years, 8 years	Germany; University	Grant from Geistlich Biomaterials. Camlog provided the implants	54/5 at 4 months, 30 at 4 years, 35 at 6 and 8 years
Benic et al. 2019[41]	RCT/6 months	Switzerland; University	Osteology Foundation and the Clinic of Reconstructive Dentistry, Center of Dental Medicine, University of Zurich. Implants provided by Dentsply Implants	29/5
Carpio et al. 2000[42]	RCT/6 months	USA; University	USPHS grant and support from Osteohealth Inc. Implant innovations donated implants, surgical instruments, and prosthetic components and Osteohealth provided bone grafting supplies	48/0
Deesricharoenkiat et al. 2021[43]	RCT/6 months	Thailand; University	Straumann Group (Thailand) Co., Ltd.	20/0
Jung, Glauser et al. 2003, Jung et al. 2009, 2022[31,32,34]	Split-mouth RCT/6 months, 3 years, 5 years	Switzerland; University	Clinic for Fixed and Removable Prosthodontics and Dental Material Science, University of Zurich	11/1 at 6 months, 0 at 3 years, 1 at 5 years

Age; male/female	Smoking status (S/NS)	Systemic conditions	Periodontal status	SPT	Implant system/distribution
50.2 ± 14.6; 6/3	No heavy smokers (>20 cigarettes a day)	Excluded: insulin-dependent diabetes, history of malignancies, radiotherapy or chemotherapy in the past 5 years, use of medication that impact on bone turnover and mucosa healing, allergy to penicillin, and diseases affecting bone connective tissue metabolism	NI	NI	NI
51.85 ± 29.7; 13/14	6S (≤10 cig/day)/21	Good health	PPD <4 mm; 3 had a history of periodontitis	NI	OsseoSpeed, Astra Tech, Dentsply/21 U (4 central incisors, 8 lateral incisors, 9 premolars); 6 L (6 premolars)
53.3 (Interv 1: 52.1; Interv 2: 54.6); 16/14 (Interv 1: 9/5; Interv 2: 5/9)	Heavy smokers (>20 cigarettes/day) excluded	Healthy (including well-controlled medical illnesses). Excluded: history or radiation therapy to the neck and head, hormones or bisphosphonate therapy intake, severe or uncontrolled systemic disease	Unclear but advanced or untreated periodontitis was an exclusion criterion	NI	Implantium and NR line, Dentium (21), TS III Osstem (2), bone level SLA Straumann (3), Luna Shinhung (1)/10 incisors, 7 bicuspids, 11 molars
Interv 1: 44.9 ± 13.4 Interv 2: 42.4 ± 15.9; 15/34 (Interv 1: 6/17; Interv 2: 9/17)	OS	Excluded: history of malignancy, radiotherapy or chemotherapy in the past 5 years, intake of medications that may have an impact on bone turnover and mucosal healing, steroid in the past 6 months, bisphosphonates or fluorides at bone therapeutic levels, and vitamin D and metabolites at therapeutic levels, diseases that affect bone or connective tissue metabolism	Unclear but in the 4–6 years follow-up an exclusion criterion was untreated periodontitis	Proper recall/periodontal maintenance by the referring dentist (for the 8-y follow-up pts)	Camlog/NI
Interv 1: 62 (43.5–78.6) Interv 2: 58.1 (28.7–78.8); 5/7 (both interventions)	No heavy smokers (>20 cigarettes a day)	No medical history in which any elective oral surgical intervention would be contraindicated	Unclear but no active periodontal disease	NI	OsseoSpeed EV, Denstply Implants/Interv 1: 7 U, 5 L (4 incisors, 5 premolars, 3 molars); Interv 2: 6 U, 6 L (3 canines, 9 premolars)
NI	NI	Systemically healthy. Excluded: diabetes, hyperparathyroidism, osteoporosis, severe liver or kidney condition, active sinusitis, cancer, addiction to drugs or alcohol, use of immunosuppressants or corticosteroids	Unclear but all presurgical therapies were performed including periodontal treatment	NI	Implant innovation/NI
50.5 ± 15.3 (Interv 1: 50.8 ± 11.25; Interv 2: 50.2 ± 19.17); 10/10 (Interv 1: 6/4; Interv 2: 4/6)	OS	Good systemic health. Excluded: neck radiation therapy and/or chemotherapy	PPD <4 mm	Unclear, but poor compliance with OH was an exclusion criterion	Straumann/upper jaw (Interv 1: 7 central and 3 lateral incisors; Interv 2: 8 central and 2 lateral incisors)
Median 53 (27–75); 7/4	NI	Good general health	NI	NI	Mk III and Mk IV Branemark, Nobel Biocare/Implants located in the same jaw. Interv 1: 8 premolars, 2 molars, 1 canine; Interv 2: 7 molars, 3 premolars, 1 canine

(Continues)

TABLE 1 (Continued)

Study	Study design/follow-up	Country; Setting	Funding	Patients enrolled/ dropouts
Jung, Halg et al. 2009, Ramel et al. 2012, Jung et al. 2015[44-46]	RCT/6 months, 3 years, 5 years	Switzerland; University	Clinic for Fixed and Removable Prosthodontics and Dental Material Science, University of Zurich, and a research grant from the Institut Straumann AG.	37/1 at 3 years
Jung et al. 2020[59]	Multi-center RCT/6 months, 18 months	Switzerland, Germany, Hungary, Spain, Sweden, Belgium; University and private practice	Institut Straumann AG.	117/3
Benic et al. 2022[47]	RCT/6 months	Korea; University	Research grant by Dentium, Seoul, South Korea, by the Department of Periodontology, Yonsei University College of Dentistry, Seoul, and by the Clinic of Reconstructive Dentistry, Center of Dental Medicine, University of Zurich, Switzerland.	40/5
Lee, Kim et al. 2015[48]	RCT/6 months	Korea, Hospital	NI	34/7
Mattout et al. 1995[62]	CCT/6–15 months	France; unclear	Groupe d'Etudes en Parodontologie et Implantologie	19/0
Mau et al. 2019, Tsai et al. 2022[56,61]	2-center RCT/1 year	USA, Taiwan; University/ Hospital	Grant from the International Team for Implantology (ITI)	48/0
Merli et al. 2015, 2018[49,50]	RCT/6 months, 3 years	Italy; private practice	Tommen Medical AG provided the implants free of charge, as well as Jason membrane and Ceros TCP	50/18 at 3 years
Park et al. 2008[51]	RCT/6 months	USA; University	University of Michigan Periodontal Graduate Student Research Fund + a gift grant from Zimmer Dental Inc.	23/1

Age; male/female	Smoking status (S/NS)	Systemic conditions	Periodontal status	SPT	Implant system/distribution
Interv1: 48 (32–72) Interv 2: 54 (23–80); NI	NI	Good general health	Periodontally healthy (PPD 1–3 mm)	Unclear but strict maintenance program	Straumann standard plus implants with 1.8 mm of polished neck/posterior mandible or maxilla
48.7 ± 14.3 (Intervention 1: 49.6 ± 13.6; Intervention 2: 47.8 ± 13.9); 37/80 (Interv 1 14/46; Interv 2: 23/34)	Patients smoking >10 cigarettes a day excluded	Excluded: systemic diseases, use of steroids, pregnancy, physical handicaps, intravenous bisphosphonates, alcoholism or chronic drug abuse, history of local irradiation therapy, mucosal disease or oral lesion	Unclear but untreated periodontitis was an exclusion criterion	NI	Straumann BL/posterior mandible/maxilla
Interv 1: 57.2 ± 16.6 Interv 2: 60.9 ± 14.7; 19/16	No heavy smoking (>20 cigarettes per day)	No medical history in which any elective oral surgical intervention would be contraindicated	Unclear but no active periodontal disease	NI	Two-piece dental implant (NR line, Dentium)/10 incisors, 3 canines, 11 premolars, 11 molars
61 ± 7.25; NI	OS	No systemic contraindications	NI	NI	Standard internal type implant, Camlog/NI
47 (22–65); 6/24 (at site level)	NI	NI	NI	NI	Brânemark dental implants/NI
Interv 1: 32.75 ± 16.30; 11/13 Interv 2: 40.88 ± 12.75; 7/17	Patients smoking >1 pack of cigarettes per day or chewing betel nut excluded	Excluded: diabetes, AIDS, hepatitis B or C, local inflammation in the oral mucosa (e.g. lichen planus), high risk of endocardial infection; blood disease or current use of anticoagulants; bone metabolic disease; (for example, Paget's disease); use of bone metabolism medicines; (for example, Bisphosphonates); current treatment by chemotherapy or radiation to the head and neck; use of steroid therapy	PPD <5 mm, no BOP, and a PI of <15%	NI	Straumann BL/maxillary incisors or premolars
Interv 1: 56 ± 13.0 Interv 2: 53.4 ± 12.4; 33/17	No heavy smoking (>20 a day); 7S (4 Interv 1 and 3 Interv 2)	Excluded: patients irradiated in the head and neck area, undergoing chemotherapy or immunosuppressive therapy over the previous 5 years; intravenous BP, uncontrolled diabetes, substance abusers	NI	NI	Element RC Inicell Implants/maxilla
28–71; 10/13	Excluded if smoking >10 a day; 1S	Systemically healthy; excluded any medical contraindications for implant surgery	Unclear but all subjects completed periodontal therapy when needed and OHI + a thorough periodontal prophylaxis were given 3 weeks before the stage I surgery.	OHI was repeated at each follow-up appointment, and prophylaxis was again performed at 3 months post-implantation	Tapered Screw-Vents, Zimmer Dental Inc./10U, 16L

(Continues)

TABLE 1 (Continued)

Study	Study design/follow-up	Country; Setting	Funding	Patients enrolled/ dropouts
Schneider et al. 2014[60]	Multi-center RCT/6 months	Switzerland; Hospital/ University and private practice	Inion Oy, Tampere, Finland.	40/0
Simion et al. 1997[30]	RCT with a split-mouth component (if a patient had >1 site requiring implants the split-mouth technique was adopted)/24-28w	Italy; Hospital/University	NI	9/0
Temmerman et al. 2020[29]	Split-mouth RCT/4 months	Belgium; University	Grant from the International Team for Implantology (ITI)	14/0
Wessing et al. 2017, Urban et al. 2019[57,58]	Multi-center RCT/6 months, 1 year	Austria, Germany, Hungary, Italy, Spain; University and private practice	Nobel Biocare Services AG	64/17 at 6 months, 22 at 1 year
Van Assche et al. 2013[35]	Split-mouth RCT/6.5 months, 1 year	Belgium; University	Partially sponsored by Institut Straumann AG, Basel, Switzerland, and the Department of Periodontology, Catholic University Leuven, Belgium	14/0
Wen et al. 2018[64]	CCT/6 months	Taiwan; private practice	NI	19/0
Veis et al. 2004[63]	CCT/6 months	Greece; University	NI	37/5

Note: Details about the biomaterials employed in the different interventions are reported in Tables 2 and 4. Data are reported as mean ± SD whenever available, otherwise, ranges are reported.

Abbreviations: L, lower jaw; NS, non-smokers; OHI, oral hygiene instructions; PMPR, professional mechanical plaque removal; S, smokers; U, upper jaw.

Age; male/female	Smoking status (S/NS)	Systemic conditions	Periodontal status	SPT	Implant system/distribution
Interv 1: 44.6 ± 18.4 Interv 2: 47.2 ± 17.8; NI	No heavy smoking (>20 a day)	Excluded: history of malignancies, radiotherapy or chemotherapy within the past 5 years, taking medications or having treatments affecting bone turnover and mucosal healing, diseases which affect bone or connective tissue metabolism, substance abuse, insulin-dependent diabetes	Unclear but all patients were enrolled in hygienic phase before tx	Evaluation of OH and OHI provided at follow-up visits 7–10 days, 1 month (±1 week), 3 months (±2 weeks), and 6 months (±2 weeks) post operation	Mk III Branemark, Nobel Biocare/26 U, 14 L. Interv 2: 54% in the anterior maxillary or mandibular segments, 46% in the posterior; in Interv 1 this relation was 59%–41%.
50.4 (30 to 64)/NI	NI	Good health	NI	NI	Nobel Biocare/16 U, 2 L
54.6 (21–77); 8/6	0S	Excluded: systemic diseases or medications that could interfere with the healing, previous radiation therapy of the jaws	NI	NI	Straumann BL/20 U, 8 L
Interv 1: 38.6 ± 15.3 Interv 2: 48.9 ± 17.0; 29/20 (Interv 1: 13/11; Interv 2: 16/9)	Excluded if smoking >10 a day; 38NS (21 Interv 1 and 17 Interv 2), 4 smoking 0–4 a day (2 Interv 1 and 2 Interv 2), 7 smoking 6–10 a day (1 Interv 1 and 6 Interv 2)	Excluded: health conditions that do not permit surgery, previous tumors, chronic bone disease or irradiation in the planned implant area, undergoing treatment with an interfering medication, such as steroid therapy or bisphosphonates, history of past or ongoing alcohol or substance abuse, uncontrolled diabetes. 1 patient with treated diabetes (Interv 2)	Unclear but no acute or untreated periodontitis	NI	Nobel Re-place CC/35 U (17 Interv 1 and 18 Interv 2), 14 L (7 Interv 1 and 7 Interv 2)
55 (39–73); 2/12	No heavy smoking (>20 a day); 2S but	Excluded: alcohol or drug abuse, psychiatric problems, uncontrolled diabetes, or uncontrolled systemic disease.	Unclear but edentulous maxilla, while mandible received periodontal treatment	NI	Straumann Standard and Standard Plus/maxilla
43.3 ± 14.9/11/8	Excluded if smoking >10 a day	Systemically healthy. Medical contraindications such as history of intravenous BP were exclusion criteria	Unclear but all patients received initial periodontal treatment (oral hygiene instructions and PMPR) 3 week before implant placement	NI	Zimmer Tapered Screw Vent/17 U, 2 L, 14 incisors, 3 canines, 2 premolars
NI	Excluded heavy smoking	Excluded: systemic chronic diseases	NI	NI	

TABLE 2 Details of primary outcomes retrieved from studies fulfilling FQ1.

12 months follow-up						
	Intervention 1					
Study	N defects/N of patients with outcomes	Biomaterials	Bone level at surgery (mm) (mean ± SD)	Bone level at loading (mm) (mean ± SD)	Bone level at follow-up (mm)	Bone level change (mm) (mean ± SD)
Naenni et al. 2021, Basler et al. 2018[36,37]	11/11	Non-cross-linked collagen membrane +DBBM		0.23 ± 0.49	0.23 ± 0.19	
Mau et al. 2019, Tsai et al. 2022[56,61]	24/24	Non-cross-linked collagen membrane + allograft	0 (bone level implant)			Loading to 12 months: −0.32 ± 0.56
Urban et al. 2019[57]	19/19 at loading, 18/18 at 12 months	Non-cross-linked collagen membrane +autologous bone+ DBBM		−1.37 ± 0.77	−1.34 ± 0.8	Loading to 12 months: 0.01 ± 0.66
Van Assche et al. 2013[35]	14/14	Non-cross-linked collagen membrane + DBBM	−1.49 ± 0.95 (subcrestal implants)	−0.19 ± 1.05	0.75 ± 0.78	
Ramel et al. 2012[45]	19/19	PEG membrane and DBBM	1.80 ± 0.02		2.24 ± 0.57	Surgery to 1 year: 0.43 ± 0.56
18 months follow-up						
Jung et al. 2020[59]	57/57	PEG membrane + alloplastic biphasic calcium phosphate	0.25 ± 0.16	0.54 ± 0.43	0.67 ± 0.46	Surgery to loading: 0.32 ± 0.45; surgery to 18 months: 0.45 ± 0.43
3 years follow-up						
Basler et al. 2018[37]	11/11	Non-cross-linked type I and III collagen membrane+ DBBM		0.23 ± 0.49	0.19 ± 0.21	
Merli et al. 2018[49]	32/25 at surgery, unclear/18 at 3 years	Non-cross-linked collagen membrane+ DBBM+ autologous bone	0.07 ± 0.13		1.69 ± 1.66	Surgery to 3 years: 1.61 ± 1.68
Lee, Park et al. 2019[40]	13/13	Non-cross-linked collagen membrane± DBBM				Loading to 3 years: 0.19 ± 0.38 (mesial), 0.00 ± 0.14 (distal)
Jung, Windisch et al. 2009[32]	11/11	Non-cross-linked collagen membrane + DBBM moistened in rhBMP-2 solution		1.33 ± 0.39 (mesial), 1.28 ± 0.24 (distal)	1.37 ± 0.33 (mesial), 1.36 ± 0.32 (distal)	Loading to 3 years: −0.04 ± 0.21 (mesial), −0.08 ± 0.27 (distal)
Ramel et al. 2012[45]	19/19 at surgery, 18/18 at 3 years	PEG membrane and DBBM	1.80 ± 0.02		2.41 ± 0.89	Surgery to 3 years: 0.61 ± 0.89
5 years follow-up						
Jung, Windisch et al. 2009[32]	11/11 at loading, 10/10 at 5 years	Non-cross-linked collagen membrane + DBBM moistened in rhBMP-2 solution		1.33 ± 0.39 (mesial), 1.28 ± 0.24 (distal)	1.36 ± 0.43 (mesial), 1.39 ± 0.43 (distal)	Loading to 5 years: −0.07 ± 0.31 (mesial), −0.11 ± 0.31 (distal)
Naenni et al. 2021[36]	11/11 at loading, 9/9 at 5 years	Non-cross-linked collagen membrane +DBBM		0.23 ± 0.49	0.31 ± 0.45	
17 years follow-up						
Jung et al. 2022[34]	11/11 at loading, 8/8 at 17 years	Non-cross-linked collagen membrane + DBBM moistened in rhBMP-2 solution		1.33 ± 0.39 (mesial), 1.28 ± 0.24 (distal)	2.51 ± 1.64 (mesial), 2.36 ± 1.70 (distal)	Loading to 17 years: −1.17 ± 1.61 (mesial), −1.14 ± 1.69 (distal)

Note: Data are grouped based on the follow-up time. All studies assessed radiographic peri-implant bone levels via 2D x-rays, apart from 4 studies[34,36,46,61] that also employed CBCT scans (data not presented in the table). Abbreviations: DBBM, deproteinized bovine bone mineral; PEG, polyethylene glycol; e-PTFE, expanded polytetrafluoroethylene; TCP, tricalcium phosphate.

Abbreviations: DBBM, deproteinized bovine bone mineral; PEG, polyethylene glycol; e-PTFE, expanded polytetrafluoroethylene; TCP, tricalcium phosphate.

Intervention 2					
N defects/N of patients with outcomes	**Biomaterials**	**Bone level at surgery (mm) (mean ± SD)**	**Bone level at loading (mm) (mean ± SD)**	**Bone level at follow-up (mm)**	**Bone level change (mm) (mean ± SD)**
12/12	Titanium reinforced e-PTFE membrane+ DBBM		0.12 ± 0.09	0.1 ± 0.7	
24/24	Non-cross-linked collagen membrane + DBBM+ autologous graft	0 (bone level implant)			Loading to 12 months: −0.21 ± 0.41
21/21 at loading, 20/20 at 12 months	Non-cross-linked collagen membrane+ autologous bone+ DBBM		−1.84 ± 0.78	−1.39 ± 1.02	Loading to 12 months: 0.42 ± 1.04
14/14	Non-cross-linked collagen membrane + alloplastic graft (60% hydroxyapatite and 40% β-TCP)	−1.41 ± 0.88	0.14 ± 0.93	0.95 ± 1.16	
18/18	Non-cross-linked collagen membrane + DBBM	1.84 ± 0.10		2.04 ± 0.35	Surgery to 1 year: 0.21 ± 0.36
57/57	Non-cross-linked collagen membrane + alloplastic biphasic calcium phosphate	0.26 ± 0.29	0.50 ± 0.65	0.75 ± 1	Surgery to loading: 0.29 ± 0.66; surgery to 18 months: 0.41 ± 0.81
12/12	Titanium reinforced e-PTFE membrane +DBBM		0.12 ± 0.09	0.16 ± 0.1	
29/25 at surgery, unclear/14 at 3 years	Non-cross linked collagen membrane+ β-TCP+ autologous bone	0.12 ± 0.27		1.21 ± 0.98	Surgery to 3 years: 1.02 ± 0.94
6/6	Cross-linked, collagen membrane+ DBBM				Loading to 3 years: 0.00 ± 0.13 (mesial), 0.27 ± 0.48 (distal)
11/11	Non-cross-linked collagen membrane+ DBBM moistened in 0.01% trifluoroacetic acid		1.20 ± 0.40 (mesial), 1.32 ± 0.47 (distal)	1.23 ± 0.38 (mesial), 1.21 ± 0.39 (distal)	Loading to 3 years: −0.02 ± 0.33 (mesial), 0.10 ± 0.42 (distal)
18/18	Non-cross-linked collagen membrane + DBBM	1.84 ± 0.10		2.17 ± 0.63	0.33 ± 0.64
11/11 at loading, 10/10 at 5 years	Non-cross-linked collagen membrane+ DBBM moistened in 0.01% trifluoroacetic acid		1.20 ± 0.40 (mesial), 1.32 ± 0.47 (distal)	1.25 ± 0.57 (mesial), 1.21 ± 0.46 (distal)	Loading to 5 years: −0.03 ± 0.44 (mesial), 0.13 ± 0.56 (distal)
12/12 at loading, 11/11 at 5 years	Titanium reinforced e-PTFE membrane+ DBBM		0.12 ± 0.09	0.21 ± 0.12	
11/11 at loading, 8/8 at 17 years	Non-cross-linked collagen membrane+ DBBM moistened in 0.01% trifluoroacetic acid		1.20 ± 0.40 (mesial), 1.32 ± 0.47 (distal)	1.83 ± 0.93 (mesial), 2.13 ± 0.84 (distal)	Loading to 17 years: −0.57 ± 1.03 (mesial), −0.82 ± 1.07 (distal)

The network drawn for the 3-year follow-up included four studies[32,37,40,45] and the treatment ranking based on SUCRA suggested PEG membrane combined with DBBM granules as the treatment with the highest probability to perform better, whereas a cross-linked collagen (CL) membrane combined with DBBM was the worst performing treatment (Table 3). However, the forest plot did not show significant differences between the best-performing treatment and the other treatments (Figure 2C). The heterogeneity (I^2) was 12%.

Only limited studies and with different follow-ups assessed the stability of the regenerated bone through CBCT scans, therefore no network meta-analysis could be performed.

TABLE 3 Details of SUCRA calculated for the networks drawn for FQ1.

Treatment	SUCRA
Network 1–12 months [3 studies]	
PEG membrane+DBBM	0.8015122
NCL collagen membrane+DBBM	0.4188511
Titanium-reinforced e-PTFE membrane+DBBM	0.4080622
NCL collagen membrane+alloplastic graft	0.3715744
Network 2–12 months [2 studies]	
NCL collagen membrane+allograft	0.7820517
NCL collagen membrane+DBBM+autologous graft	0.5970967
Resorbable NCL collagen membrane+autologous bone+DBBM	0.1208517
3 years [4 studies]	
PEG membrane+DBBM	0.8017363
Titanium-reinforced e-PTFE membrane + DBBM	0.5884888
NCL collagen membrane+DBBM in rhBMP-2 solution	0.4951538
NCL collagen membrane+DBBM	0.4584988
CL porcine collagen membrane+DBBM	0.1561225

Abbreviations: CL, cross-linked; DBBM, deproteinized bovine bone mineral; e-PTFE, expanded polytetrafluoroethylene; NCL, non-cross-linked; PEG, polyethylene glycol.

3.2.2 | Focused question 2 (FQ 2)

Twenty-two studies evaluated vertical dehiscence resolution and changes in defect width at re-entry (Table 4) and they all assessed these parameters clinically after raising a flap, with the help of a periodontal probe, apart from one study that also employed a CBCT scan.[43] Re-entry was performed between 4 and 6.5 months after implant surgery.

Overall, most of the studies reported similar outcomes regardless of the membrane and grafts applied. However, two studies indicated better outcomes when an NCL rather than a CL membrane was used in combination with DBBM,[33,39] whereas this was not confirmed by another study.[52] Two RCTs showed comparable dehiscence and defect width reduction when an e-PTFE or a NCL membrane was applied in association with DBBM alone or combined with autologous graft,[38,42] and one of these studies also highlighted that the outcome mainly depended on the initial fixation of the barrier.[42]

In terms of graft morphology, one study indicated superior dehiscence resolution when a block DBBM rather than particulate

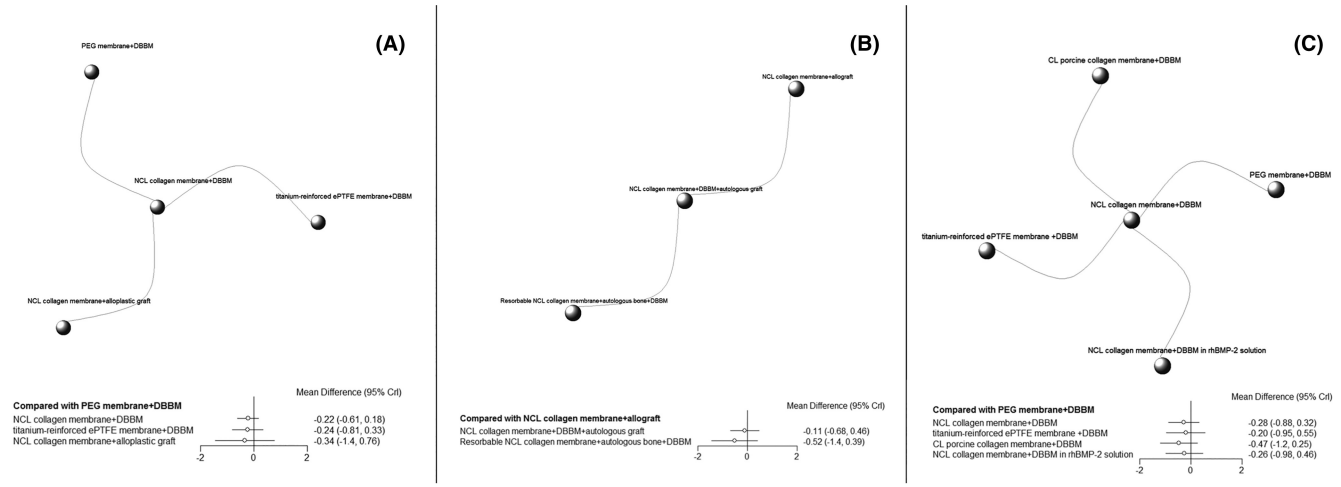

FIGURE 2 (A) Network geometrical plot involving three studies for FQ1 at 12 months of follow-up and the forest plot estimating the mean difference and 95% credible interval in peri-implant bone levels between the treatment with the highest probability of being the best and the remaining ones; (B) network geometrical plot involving two studies for FQ1 at 12 months of follow-up and the forest plot estimating the mean difference and 95% credible interval in peri-implant bone levels between the treatment with the highest probability of being the best and the remaining ones; (C) network geometrical plot involving four studies for FQ1 and at 3 years of follow-up and the forest plot estimating the mean difference and 95% credible interval in peri-implant bone levels between the treatment with the highest probability of being the best and the remaining ones. CL, cross-linked; NCL, non-cross-linked.

DBBM was applied in combination with a NCL membrane, with 11 out of 12 (91.7%) block sites and 3 out of 12 (25%) particulate sites clinically showing a complete vertical defect fill at re-entry.[41] On the contrary, the use of a particulate versus soft-type block of biphasic calcium phosphate associated with a CL membrane did not differ in terms of vertical dehiscence resolution at re-entry.[47] However, the authors highlighted that the morphology of the defect played a significant role, with non-containing defects showing incomplete vertical defect fill in 61.9% of the cases, regardless of the graft used. Remarkably, when using an allograft associated with e-PTFE membrane to treat peri-implant bone dehiscence defects, Veis et al.[63] reported that defect resolution improved more in case the graft had been collected from the symphysis or ramus rather than from the tuberosity.

Two studies investigated the use of bioactive factors, and they showed that adding BMP-2 to DBBM or acemannan to DBBM and autologous bone[31,43] did not increase dehiscence resolution.

For the *vertical dehiscence resolution* two networks were drawn, one with 14 studies[29,31,33,35,36,39,41,42,44,48,50,52,59,60] (Figure 3A) and one with two studies[51,64] (Appendix S4). The treatment ranking based on SUCRA suggested that out of the 14 studies included in the largest network, the use of a NCL membrane combined with a DBBM bone block or a CL membrane combined with autologous bone and DBBM had the highest probability of being the most effective treatment in terms of percentage of vertical dehiscence resolution at re-entry, while the worst treatment was the combination of a CL membrane with DBBM particles (Table 5). However, the forest plot did not suggest a significant difference between the treatments (Figure 3A). The heterogeneity (I^2) was 6%.

A regression analysis was performed based on the initial defect dimension to test whether defect size played a role in dehiscence resolution. The coefficient associated with the variable "large defect" was −14.3, thus suggesting a possible lower efficacy of the GBR treatments in the presence of initially large defects, However, owing to the large 95% credible interval (−60.8; 29.3), this trend did not reach statistical significance.

Details on the second network are reported in Supplementary Material (Appendices S4 and S5). Briefly, the treatment ranking based on SUCRA suggested that the treatment with the highest probability to perform better in terms of dehiscence reduction was the combination of acellular dermal matrix and allograft particles, as compared to a collagen membrane combined with allograft alone or associated with DBBM. Nevertheless, the forest plot did not indicate a statistically significant difference between the treatments. The heterogeneity (I^2) was 20%.

For the changes in *defect width* from baseline to re-entry, two networks were drawn, one including 11 studies[29,33,35,38,39,42,44,48,50,52,60] (Figure 3B) and one including 2 studies[51,64] (Appendices S6 and S7). The treatment ranking based on SUCRA suggested that out of the 11 studies included in the largest network, the use of a CL membrane associated with autologous bone and DBBM and the use of a titanium-reinforced e-PTFE membrane combined with DBBM particles had the highest probability of being the best treatment to reduce defect width at re-entry, while the worst treatment was represented by the combination of a CL membrane with DBBM particles (Table 5). However, the forest plot did not indicate a significant difference between treatments (Figure 3B). The heterogeneity (I^2) was 5%. A regression analysis was performed to test whether the initial defect size played a role in defect width changes. The coefficient associated with the variable "large defect" was −0.87, thus suggesting a possible lower efficacy of the GBR treatments in the presence of initially large defects, However, owing to the large 95% credible interval (−3.1; 1.3) and the fact that it includes 1 (i.e., no effect), this trend did not reach statistical significance.

Details on the second network are reported in Supplementary Material (Appendices S6 and S7). Briefly, the treatment ranking based on SUCRA suggested that the treatment with the highest probability to perform better in terms of reduction of defect width was the use of a collagen membrane with a combination/mixture of allograft and DBBM particles, while the combination of allograft particles alone with acellular dermal matrix or a collagen membrane had a similar probability of being the second and third best treatment respectively. However, the forest plot did not indicate a statistically significant difference between the treatments. The heterogeneity (I^2) was 20%.

Additional network meta-analyses were performed to investigate the role of different membranes in promoting dehiscence resolution and defect width changes by considering only those studies that used the same graft but a different barrier (Appendices S8 and S9). The treatment ranking (based on SUCRA) indicated that the use of a titanium-reinforced e-PTFE membrane had the highest probability of being the best treatment for dehiscence resolution, followed by a NCL membrane (based on 11 studies). On the contrary, a CL membrane had the highest probability of being the best treatment for defect width reduction, followed by a titanium-reinforced ePTFE membrane (based on 9 studies). Nevertheless, the forest plots did not show a statistically significant difference between the different barriers.

Funnel plot did not show evidence of small-study effects, which was also confirmed by Egger's test (Appendix S10).

3.3 | Secondary outcomes

3.3.1 | Changes in defect depth, intrabony component, and augmented buccal bone at re-entry procedures

Different combinations of barriers and bone grafts led to comparable changes in *defect depth* and *intrabony defect component* at re-entry (Appendix S11). Only one study indicated improved changes in defect depth when using a NCL membrane rather than a CL one in association with DBBM particles.[33] Remarkably, Tsai et al.[61] highlighted the importance of defect concavity (i.e. depth) in predicting the buccal regenerated bone, as the deeper the concavity (>2 mm), the more stable the bone graft would be, with less chances of displacement.

TABLE 4 Details of primary outcomes for FQ2.

Study	Intervention 1					
	N defects/N of patients	Biomaterials	Initial defect (mm) (mean ± SD)	Re-entry (mm) (mean ± SD)	Change (mm) (mean ± SD)	% defect resolution (mean ± SD)
Annen et al. 2011[33]	9/9	DBBM particles+ cross-linked collagen membrane	V: 4.6 ± 1.9 W: 3.4 ± 1.1	V: 2.8 ± 2.8 W: 2.4 ± 1.7	V: 1.8 ± 1.6 W: 1 ± 1	V: 44 ± 40
Naenni et al. 2017[38]	13/13	DBBM particles+ non-cross-linked type I and III collagen membrane	V: 4 ± 2.07 W: 3.08 ± 0.18	V: 0.77 ± 0.85 W: 0.73 ± 0.33	V: 3.41 ± 2.33	V: 85
Lee, Lee et al. 2015[39]	14/14	DBBM particles+ non-cross-linked collagen membrane	V: 5.1 ± 2.4 W: 3.8 ± 1.3	V: 0.2 ± 0.6 W: 0.4 ± 0.9	V: 5 ± 2.5 W: 3.5 ± 1.2	
Becker et al. 2009[52]	23/23	DBBM particles+ cross-linked collagen membrane	V: 4.26 ± 2.18 W: 4.39 ± 1.33	V: 1.26 ± 1.42 W: 1.73 ± 1.94	V: 3 ± 2.5 W: 2.65 ± 2.27	V: 60.18 ± 53.58
Benic et al. 2019[41]	12/12	DBBM bone block + non-cross-linked collagen membrane	V: 4.54 ± 2.5	V:0.04 ± 0.14		V:98.6
Carpio et al. 2000[42]	23/23	50% DBBM particles & 50% autologous bone particles + non-cross-linked collagen membrane	V: 4.39 ± 0.49 W: 3.63 ± 0.28	V: 2.65 ± 0.61 W: 1.95 ± 0.6		V: 39.6 W: 46.2
Deesricharoenkiat et al. 2021[43]	10/10	Autogenous bone chips and 50:50 DBBM particles + particulate acemannan + non-crossed linked collagen membrane	V: 7.6 ± 3.23			
Jung et al. 2003[65]	10/10	DBBM particles moistened in rhBMP-2 solution + non-cross-linked collagen membrane	V: 7 ± 2.67	V: 0.2 ± 0.35		V: 96
Jung, Halg et al. 2009[44]	19/19	DBBM particles + PEG hydrogel membrane	V: 5.95 ± 1.9		V: 5.63 ± 1.84[a] W: 3.9 ± 4.05[a]	V: 94.9
Jung et al. 2020[59]	57/57	Alloplastic biphasic calcium phosphate + PEG hydrogel membrane	V: 4 ± 0.9	V: 1.7 ± 1.4	V: 2.5 ± 1.5	V: 59.7 ± 32.5
Benic et al. 2022[47]	17/17	Soft-type block made of particulate synthetic BCP embedded into a native porcine-derived collagen matrix + cross-linked, collagen matrix	V: 4.94 ± 1.88	V: 1 ± 1.7	V: 3.94 ± 2.55	V: 77 ± 35.3
Lee, Kim et al. 2015[48]	Unclear/14	Autologous/allogenic bone and DBBM particles + cross-linked collagen membrane	V: 3 ± 1.9 W: 3.9 ± 1.3	V: 0.2 ± 0.5 W: 0.3 ± 0.7		V: 89.69 ± 24.36
Mattout et al. 1995[62]	11/unclear	Allograft particles mixed with tetracycline + e-PTFE membrane	V: 6.8 ± 2.82 W: 2.8 ± 0.5	V: 0 W: 0		
Merli et al. 2015[50]	32/25	DBBM particles+ autologous bone + non-cross-linked collagen membrane	V: 4.9 ± 1.8 W: 3.4 ± 1	V: 0.4 ± 0.8 W: 0.3 ± 0.6	V: 4.5 ± 2 W: 3.1 ± 1.2	V
Park et al. 2008[51]	9/unclear	Allograft particles + acellular dermal matrix	V: 6.58 ± 2.79 W: 3.48 ± 1	V: 1.47 ± 1.19 W: 1.61 ± 1.6	V	V: 73.89 ± 17.58
Schneider et al. 2014[60]	20/20	DBBM particles+ PLGA membrane	V: 6.3 ± 2.1 W: 2.3 ± 2.1	V: 1.2 ± 2.4 W: 0.2 ± 0.7	V: 5.1 (95%CI 3.3, 6.8) W: 2.1 (95%CI 1.1, 3.2)	
Simion et al. 1997[30]	9/6	autogenous bone particles + PLA/PGA membrane	V: 6.67 ± 2.4	V: 0.67 ± 1.03	V: 6 ± 2.68	V: 88.56 ± 21.7

Intervention 2					
N defects/N of patients	**Biomaterials**	**Initial dehiscence (mm) (mean ± SD)**	**Re-entry (mm) (mean ± SD)**	**Change (mm) (mean ± SD)**	**% defect resolution (mean ± SD)**
V: 9/9	DBBM+ non-cross-linked collagen membrane	V: 5.7 ± 2.7 W: 3.4 ± 1	V: 1 ± 1.2 W: 1.7 ± 1.9	V: 4.7 ± 3.3 W: 1.8 ± 1.6	V: 78 ± 31
14/14	DBBM particles+ titanium reinforced e-PTFE membrane	V: 2.36 ± 2.09 W: 3.19 ± 0.33	V: 0.21 ± 0.8 W: 0.23 ± 0.23	V: 2.14 ± 2.06	V: 90.7
14/14	DBBM particles + cross-linked collagen membrane	V: 4.5 ± 2.2 W: 3.5 ± 1.1	V: 1.1 ± 1.2 W: 1.7 ± 1.6	V: 2.9 ± 2.3 W: 1.7 ± 2.2	
26/26	DBBM particles+ non-cross-linked collagen membrane	V: 3.44 ± 1.49 W: 4.28 ± 2.13	V: 1.5 ± 1.88 W: 1.65 ± 1.65	V: 1.94 ± 2.13 W: 2.63 ± 2.36	V: 46.15 ± 73.34
12/12	DBBM particles+ non-cross-linked collagen membrane	V: 4.58 ± 2.12	V: 0.75 ± 0.62		V: 80.5 ± 18.5
25/25	50%DBBM particles & 50% autologous bone particles + e-PTFE membrane	V: 4.18 ± 0.39 W: 4.36 ± 0.4	V: 2.26 ± 0.66 W: 2.65 ± 0.56		V: 45.9 W: 39.2
10/10	Autogenous bone chips and DBBM particles + non-crossed linked collagen membrane	V: 7.1 ± 3.21			
10/10	DBBM particles moistened in 0.01% trifluoroacetic acid + non-cross-linked collagen membrane	V: 5.8 ± 1.81	V: 0.4 ± 0.66		V: 91
18/18	DBBM particles+ non-cross-linked collagen membrane	V: 4.5 ± 1.54		V:4.25 ± 1.16[a] W: 3.9 ± 4.18[a]	V: 96.4
57/57	Alloplastic biphasic calcium phosphate + non-cross-linked collagen membrane	V: 4.6 ± 1.8	V: 1.5 ± 1.1	V: 3.2 ± 2.1	V:64.4 ± 27.2
18/18	Particulate synthetic BCP (60% hydroxyapatite and 40% β-TCP) + cross-linked, collagen matrix	V: 5.17 ± 2.43	V: 1.36 ± 1.91	V: 3.81 ± 3.22	V: 65.9 ± 46.1
Unclear/13	Autologous/allogenic bone and DBBM particles + non-cross-linked collagen membrane	V: 2.8 ± 1.7 W: 3.8 ± 1.2	V: 0.4 ± 0.3 W: 1.1 ± 0.9		V: 81.99 ± 16.07
19/unclear	e-PTFE membrane	V: 4.84 ± 1.82 W: 2.75 ± 0.78	V: 0.8 ± 1.55 W: 0.64 ± 1.12		
29/25	Beta TCP+ autologous bone non-cross linked collagen membrane	V: 5.3 ± 1.9 W: 4 ± 1.4	V: 0.5 ± 0.9 W: 0.5 ± 0.9	V: 4.7 ± 2.4 W: 3.5 ± 1.7	
9/unclear	Allograft particles+ cross-linked collagen membrane	V: 6.23 ± 3.51 W: 3.49 ± 0.73	V: 1.42 ± 1.35 W: 1.5 ± 1.8		V:68.14 ± 30.1
20/20	DBBM particles + titanium-reinforced ePTFE membrane	V: 7.2 ± 2.7 W: 2.5 ± 1.9	V: 0.3 ± 1.1 W: 0	V: 6.9 (95%CI 5.5, 8.2) W: 2.5 (95%CI 1.6, 3.4)	
9/7	Autogenous bone particles + e-PTFE membrane	V: 6.28 ± 3.16	V: 0.11 ± 0.22	V: 6.17 ± 3.17	V: 98.2 ± 3.61

TABLE 4 (Continued)

Study	Intervention 1					
	N defects/N of patients	Biomaterials	Initial defect (mm) (mean ± SD)	Re-entry (mm) (mean ± SD)	Change (mm) (mean ± SD)	% defect resolution (mean ± SD)
Temmerman et al. 2020[29]	14/14 (but 12/12 with re-entry data for V and 11/11 for W)	DBBM particles + non-cross-linked collagen membrane	V: 3.89 ± 1.88 W: 3.11 ± 0.66	V: 2.07 ± 1.75 W: 1.85 ± 1.31	V	V: 46.7 W: 40.5
Wessing et al. 2017[58]	24/24 (but 23/23 with re-entry data)	Autologous bone+ DBBM particles + resorbable non-cross-linked collagen membrane	V: 5.1 ± 2.1 W: 3.3 ± 0.9	V: 1 ± 1.3 W: 1.7 ± 2.1	V: 4.1 ± 2.2 W: 1.5 ± 2.3	V: 81 ± 24 W: 44 ± 70
Van Assche et al. 2013[35]	14/14 (but 12/12 with re-entry data for V and 2 for W)	DBBM particles + non-cross-linked collagen membrane	V: 6.4 ± 1.6 W: 3 ± 0.6	V: 1.5 ± 1.2 W: 0.4 ± 1.1		V: 75
Wen et al. 2018[64]	9/9	Allograft+ DBBM particles + non-cross-linked collagen membrane	V: 3.8 ± 3.58 W: 3.64 ± 1	V: 0.06 ± 0.17 W: 0.21 ± 0.63		V: 98.32
Veis et al. 2004[63]	16/unclear	Autologous bone from ramus+ e-PTFE	V: 4.47 ± 1.22	V: 1.13 ± 0.99	V: 3.34 ± 0.9	V: 70.6

Study	Intervention 3		
	N defects/N of patients	Biomaterials	Initial dehiscence (mean ± SD)
Annen et al. 2011[33]			
Naenni et al. 2017[38]			
Lee, Lee et al. 2015[39]			
Becker et al. 2009[52]			
Benic et al. 2019[41]			
Carpio et al. 2000[42]			
Deesricharoenkiat et al. 2021[43]			
Jung et al. 2003[65]			
Jung, Halg et al. 2009[44]			
Jung et al. 2020[59]			
Benic et al. 2022[47]			
Lee, Kim et al. 2015[48]			
Mattout et al. 1995[62]			
Merli et al. 2015[50]			
Park et al. 2008[51]	8/unclear	Allograft	V: 5.81 ± 1.86 W: 3.32 ± 0.8
Schneider et al. 2014[60]			
Simion et al. 1997[30]			
Temmerman et al. 2020[29]			
Wessing et al. 2017[58]			
Van Assche et al. 2013[35]			
Wen et al. 2018[64]			
Veis et al. 2004[63]	14/unclear	Autologous bone from chin + e-PTFE	V: 4.79 ± 1.12

Note: All studies clinically assessed the changes in vertical dehiscence. Only[43] also assessed the changes with the help of a CBCT (data not reported).

Abbreviations: BCP, biphasic calcium phosphate; DBBM, deproteinized bovine bone mineral; TCP, tricalcium phosphate; V, vertical dehiscence; W, defect width.

[a] Data graphically presented in the paper and extracted with WebPlotDigitizer.

Intervention 2					
N defects/N of patients	**Biomaterials**	**Initial dehiscence (mm) (mean ± SD)**	**Re-entry (mm) (mean ± SD)**	**Change (mm) (mean ± SD)**	**% defect resolution (mean ± SD)**
14/14 (but 11/11 with re-entry data for V and 9/9 for W)	Autologous + DBBM particles + non-cross-linked collagen membrane	V: 4.64 ± 2.16 W: 2.96 ± 0.72	V: 2.28 ± 1.97 W: 1.75 ± 1.55		V: 50.9 W: 40.9
25/25 (but 24/24 with re-entry data)	Autologous + DBBM particles + non-cross-linked collagen membrane	V: 4.9 ± 1.9 W: 3.2 ± 1	V: 1.7 ± 2.1 W: 2.5 ± 1.9	V: 3.3 ± 2.8 W: 0.6 ± 2.2	V: 62 ± 61 W: 11 ± 78
14/14 (but 13/13 with re-entry data for V and 2 for W)	Alloplastic graft (60% hydroxyapatite and 40% β-TCP) + non-cross-linked collagen membrane	V: 6.4 ± 2.2 W: 2.8 ± 0.5	W: 0.5 ± 1.3		V: 68
10/10	Allograft + non-cross-linked collagen membrane	V: 3.85 ± 1.7 W: 3.02 ± 0.78	V: 0.09 ± 0.28 W: 0.31 ± 0.42		V: 97.91 ± 7
16/unclear	Autologous bone from tuberosity+ e-PTFE	V: 4.31 ± 1.24	V: 2.4 ± 0.82	V: 1.91 ± 0.7	V: 47.5

Re-entry (mean ± SD)	**Change (mean ± SD)**	**% defect resolution (mean ± SD)**
V: 2.21 ± 1.96 W: 1.94 ± 1.18		V: 63.56 ± 23.88
V: 1.11 ± 0.86	V: 3.68 ± 1	V: 76.7

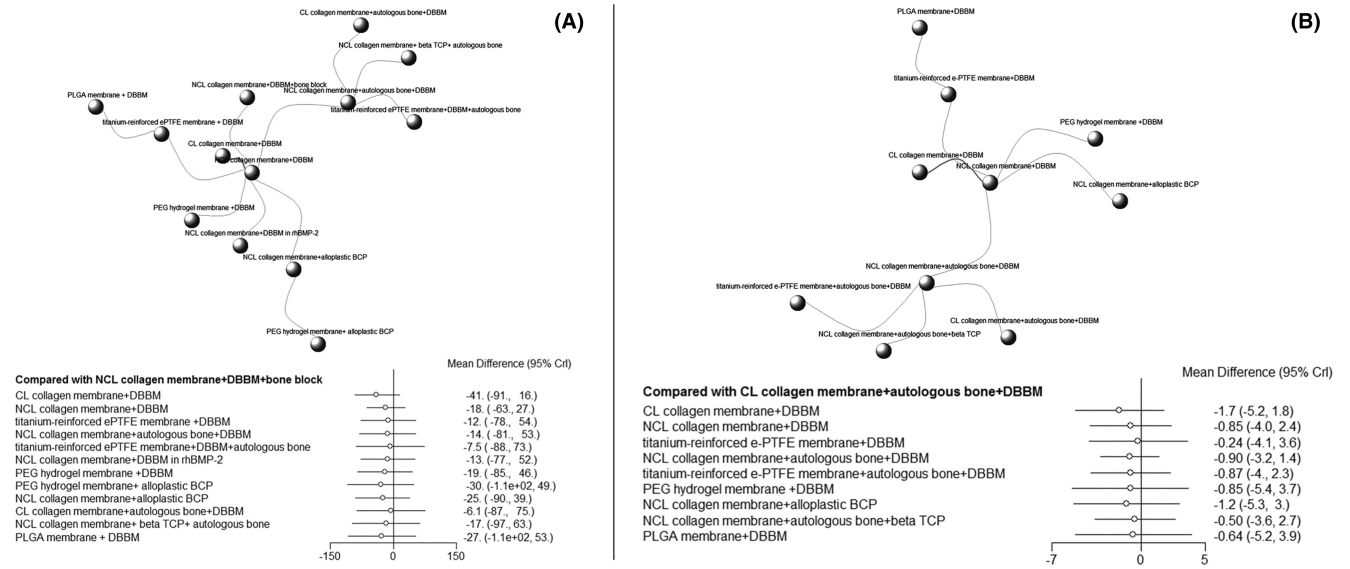

FIGURE 3 (A) Network geometrical plot involving 14 studies for vertical dehisce resolution at re-entry (FQ2) and the forest plot estimating the mean difference and 95% credible interval in dehiscence resolution between the treatment with the highest probability of being the best and the remaining ones; (B) network geometrical plot involving 11 studies for defect width resolution at re-entry and the forest plot estimating the mean difference and 95% credible interval in defect width changes between the treatment with the highest probability of being the best and the remaining ones. CL, cross-linked; NCL, non-cross-linked.

In terms of stability of the *augmented bone*, overall studies reported a reduction of the regenerated buccal bone at re-entry, which was documented either clinically or radiographically (CBCT scans) (Appendix S12). Three studies based on clinical measurements showed that the use of a titanium-reinforced e-PTFE membrane was associated with significantly less horizontal bone thickness reduction at re-entry as compared to a collagen membrane[38] or poly-lactic co-glycolic acid (PLGA) membrane[60] (all associated with DBBM particles), while Park et al.[51] indicated that whenever a membrane was employed in the sandwich bone augmentation technique, the regenerated bone at re-entry was more stable as compared to the use of the graft only.

Seven studies employed CBCTs and three of them reported comparable reduction of the regenerated bone regardless of the biomaterials employed.[29,39,43] On the contrary, adding an outer layer of DBBM to a cancellous bone allograft (inner layer) and cortical bone allograft (middle layer) combined with a collagen membrane in the sandwich bone augmentation technique improved the stability of the regenerated bone in one study.[64] Moreover, a titanium-reinforced e-PTFE membrane instead of a collagen one (both combined with DBBM) led to significantly less horizontal bone thickness resorption at re-entry.[38] Remarkably, Benic et al.[41] showed that a block compared to a particulate DBBM (both combined with a collagen membrane) was superior regarding the dimension of the augmented hard tissue after 6 months of healing, while comparable augmented bone was observed when a synthetic biphasic calcium phosphate (BCP) block or a particulate BCP were employed in association with a collagen membrane.[47]

3.3.2 | Peri-implant clinical parameters

Comparable peri-implant clinical data in terms of probing pocket depth (PPD), plaque, and bleeding scores were reported in the included studies, which remained stable at up to 17 years of follow-up (Appendix S13). One study indicated that from 4 to 8 years of follow-up, the median clinical attachment level at the vestibular aspect improved regardless of the type of biomaterials received during GBR. However, these changes were significantly higher when a NCL rather than a CL collagen membrane had been employed (0.7 mm vs. 0.5 mm).[53] Moreover, in the same study, a correlation was observed between high residual defect height at re-entry and the incidence of mucosal recession at 4 years, which was also confirmed at 8 years and was independent from the type of membrane (CL or NCL) applied in combination with DBBM.[53,55]

3.3.3 | Adverse events, PROMs, and biological complications

Details on the adverse events described by the included studies can be found in Supplementary Material (Appendix S14). Most of the studies reported on the incidence of soft tissue dehiscence and membrane/graft exposure. When comparing NCL to CL membranes, few studies reported a tendency for higher complications (exposure and risk of infection) with the latter membranes.[33,48,52] One study was also interrupted earlier than anticipated because of unacceptable safety issues and severe infections related to the use of a CL membrane, which was exposed in 56% of the cases and in

TABLE 5 Details of SUCRA calculated for the networks drawn for FQ2.

Treatment	SUCRA
Vertical dehiscence [14 studies]	
NCL collagen membrane+DBBM+bone block	0.7468616
CL collagen membrane+autologous bone+DBBM	0.6473623
Titanium-reinforced e-PTFE membrane+DBBM+autologous bone	0.6306673
Titanium-reinforced e-PTFE membrane + DDBM	0.5864779
NCL collagen membrane+DBBM in rhBMP-2	0.5724104
NCL collagen membrane+autologous bone+DBBM	0.5444511
NCL collagen membrane+DBBM	0.4969491
NCL collagen membrane+ beta TCP+ autologous bone	0.4963374
PEG hydrogel membrane +DBBM	0.4738579
NCL collagen membrane+alloplastic BCP	0.3971193
PLGA membrane + DBBM	0.3745805
PEG hydrogel membrane+ alloplastic BCP	0.3442406
CL collagen membrane+DBBM	0.1886844
Defect width [11 studies]	
CL collagen membrane+autologous bone+DBBM	0.7202526
Titanium-reinforced e-PTFE membrane+DBBM	0.6782441
NCL collagen membrane+autologous bone+beta TCP	0.5868396
PLGA membrane+DBBM	0.5323000
PEG hydrogel membrane +DBBM	0.4842667
NCL collagen membrane+DBBM	0.4805763
Titanium-reinforced e-PTFE membrane+autologous bone+DBBM	0.4649956
NCL collagen membrane+autologous bone+DBBM	0.4428181
NCL collagen membrane+alloplastic BCP	0.4039407
CL collagen membrane+DBBM	0.2057663

Abbreviations: BCP, biphasic calcium phosphate; CL, cross-linked; DBBM, deproteinized bovine bone mineral; e-PTFE, expanded polytetrafluoroethylene; NCL, non-cross-linked; PEG, polyethylene glycol; PLGA, poly-lactic co-glycolic acid.

33% of the cases was associated with infection so that it had to be removed.[33]

When comparing non-resorbable to resorbable membranes, one study indicated higher soft tissue dehiscence and membrane exposure for e-PTFE compared to NCL membrane.[42] On the contrary, Naenni et al.[38] reported an increased dehiscence rate for NCL membranes compared to e-PTFE membranes (30% vs. 14% – 4 vs. 2). All dehiscences in the NCL group occurred within the first week after surgery and they all healed without the need for further surgical intervention. This outcome contradicts to some extent the results from other studies that reported a higher dehiscence rate for non-resorbable membranes as compared to NCL membranes.[66,67] The authors hypothesized that this might be due to the fact that the surgeon was aware of having to prematurely remove non-resorbable membranes in case of bacterial colonization, therefore they may have tried not to over-contour when using e-PTFE barriers, while this was probably not the case when they applied NCL barriers.[38] One study suggested a higher rate of soft tissue dehiscence or fenestration for PLGA membranes as compared to e-PTFE membranes (five patients vs. two patients), although most of the cases of PLGA exposures resolved spontaneously (three out of five), while both e-PTFE exposures required surgical removal of the barrier.[60]

Remarkably, when comparing a PEG hydrogel membrane to a NCL membrane, overall a similar incidence of soft tissue dehiscence was reported, although a tendency for a higher prevalence of adverse events was associated with the PEG membrane (30% vs. 10.5%).[59] One study indicated the possibility of developing delayed dehiscence (after 5–7 weeks) when a PEG membrane was employed, but it is unclear if this was attributed to the lack of keratinized mucosa and the perforating implant shoulder or to the PEG membrane itself.[44]

While the use of a block (of DBBM or biphasic calcium phosphate) compared to a particulate graft (of DBBM or biphasic calcium phosphate) did not have an impact on the development of soft tissue dehiscence,[41,47] adding an allograft under an e-PTFE membrane led to premature exposure in eight sites versus only one site where the graft was not employed.[62]

In terms of PROMs, a validated questionnaire, the Oral Health Impact Profile-14 (OHIP-14), was employed in three studies, which indicated no differences in terms of quality of life when performing GBR with DBBM and either a PLGA membrane or an e-PTFE membrane,[60] or when employing two different types of NCL membranes in association with autologous bone and DBBM[57], or when a NCL membrane was combined with DBBM associated or not with BMP-2.[34]

VAS was employed in three studies to assess post-surgical pain, as well as functional and aesthetic satisfaction with implant rehabilitations, but comparable results were obtained irrespective of the materials used.[32,34,49,50]

Only limited studies reported on the incidence of developing peri-mucositis and peri-implantitis (biological complications). In patients undergoing GBR for the treatment of dehiscence-type defects with DBBM combined either with a CL or a NCL membrane, Schwarz et al.[53] indicated that the incidence of peri-implantitis over a follow-up period of 8 years was mainly noted at implant sites exhibiting implants residual defect height>1 mm at re-entry. In particular, in the group receiving a CL membrane the incidence of mucositis was 80% at 4 years, 60% at 6 years, and 44.4% at 8 years, while the incidence of peri-implantitis was 20% both at 4 and 6 years, and 0% at 8 years. In the group treated with an NCL membrane, the incidence of mucositis was 55.5% at 4 years, 33.3% at 6 years, and 30% at 8 years, while the incidence of peri-implantitis was 33.33% both at 4 and 6 years and 30% at 8 years.

In patients undergoing GBR with a NCL membrane combined with autologous bone and either DBBM or beta-tricalcium

phosphate (ß-TCP), three cases of peri-implantitis developed in two patients at the 3-year follow-up only in the group receiving DBBM.[49] In a 17-year follow-up study, Jung et al.[34] indicated 1 case of peri-implantitis out of the 8 patients completing the split-mouth study and it belonged to the group of implants that received GBR treatment with DBBM, BMP-2, and a NCL membrane.

3.3.4 | Implant success/survival

Of the 23 included original studies, none provided sufficient information for speculation about implant success. Data about implant loss and implant survival can be found in Supplementary Material (Appendix S15). Briefly, the majority of the studies reported no failures and a 100% implant survival rate at ≥12 months of follow-up.[32,34,35,37,41,45,46,49,53-57,61] A few studies reported differences in implant survival rate between treatment groups (Appendix S15), but the clinical significance of such difference is disputable.[29,36,62] Remarkably, studies reporting data on longer follow-up periods had a high rate of withdrawals and dropouts, which makes their survival data not reliable.[34,40,49,53-55]

3.3.5 | Aesthetic scores

Only 3 studies assessed aesthetic scores. A similar 1-year pink aesthetic score (PES) was reported for two different NCL membranes combined with DBBM and autologous bone[57] and for a NCL membrane combined with DBBM and autologous graft or with an allograft.[56] Likewise, Merli et al.[49] showed comparable 3-year PES when GBR was performed with a NCL membrane combined with DBBM and autologous bone or with β-TCP and autologous bone.

3.4 | Risk of bias

Amongst the 20 original RCTs included, the RoB 2 tool indicated that in 13 studies there were some concerns about the risk of bias, mainly because there was no appropriate analysis of the assignment to groups (intention-to-treat analysis), whereas seven studies were judged at low risk of bias [Figure 4 and Appendix S16].

The analysis of the risk of bias focused on primary outcomes at different time-points revealed that the judgment was highly influenced by the number of subjects available at the longer follow-ups. Considering the high drop-out rates, the results should be considered as highly biased for follow-ups longer than 1 year.

The 3 CCTs were assessed through the ROBINS-I tool, according to which one study was at serious risk of bias and two at moderate risk, mainly because of inadequate control of confounding factors [Figure 5 and Appendix S17].

4 | DISCUSSION

4.1 | Key findings

This systematic review and network meta-analysis gathered the best available evidence (represented by RCTs and CCTs) to evaluate the efficacy of different biomaterials (membranes, bone substitutes, and bioactive factors) for GBR performed simultaneous to implant placement. Overall, data on peri-implant bone levels (FQ1), dehiscence closure, and changes in defect width at re-entry (FQ2) did not indicate a clear superiority of a specific biomaterial (or combination of biomaterials) over another. In other words, it is suggested that whenever a secluded space is created by placing a barrier membrane and enough space is provided to ensure the proliferation of bone-forming cells while excluding unwanted epithelial and connective tissue cells, bone regeneration occurs in a predictable way, regardless of the biomaterials employed. Nevertheless, a detailed analysis of the secondary outcomes, including the stability of the buccal regenerated bone and the risk of complications, as well as considerations on defect size and dimension provided additional relevant information that should be considered when deciding on which biomaterials to use for GBR simultaneous to implant placement.

Hence, we have herein provided a detailed discussion on key clinically relevant aspects that emerged from the review and that could guide clinicians when performing GBR simultaneous to implant placement.

4.2 | The influence of biomaterials on peri-implant bone levels

A key determinant for the long-term success of an implant restoration is the available bone at a three-dimensional level. Adequate bone seems to be essential not only to enable a prosthetically driven placement of the implant but also to maintain soft-tissue margin and interdental papillae overtime. Despite the very limited available literature, it has been recommended that a minimum thickness of buccal bone wall of 2 mm is necessary after implant placement in a healed site to ensure adequate soft-tissue support and to avoid the complete resorption of the buccal bone wall following restoration.[68-72] Therefore, whenever a fenestration or dehiscence occurs during implant placement or we lack the minimum of 2 mm buccal bone, it is advisable to perform simultaneous bone regeneration, with the aim to generate enough volume of hard tissue to support the mucosa and optimize the appearance of the peri-implant soft tissue.[68-72]

According to the present review, when focusing on the stability of interproximal peri-implant bone levels assessed through 2D x-rays (FQ1), different combinations of membranes and grafts resulted in similar outcomes at 12 months of follow-up. The two networks performed suggested that PEG combined with DBBM granules and an NCL membrane combined with an allograft had the highest

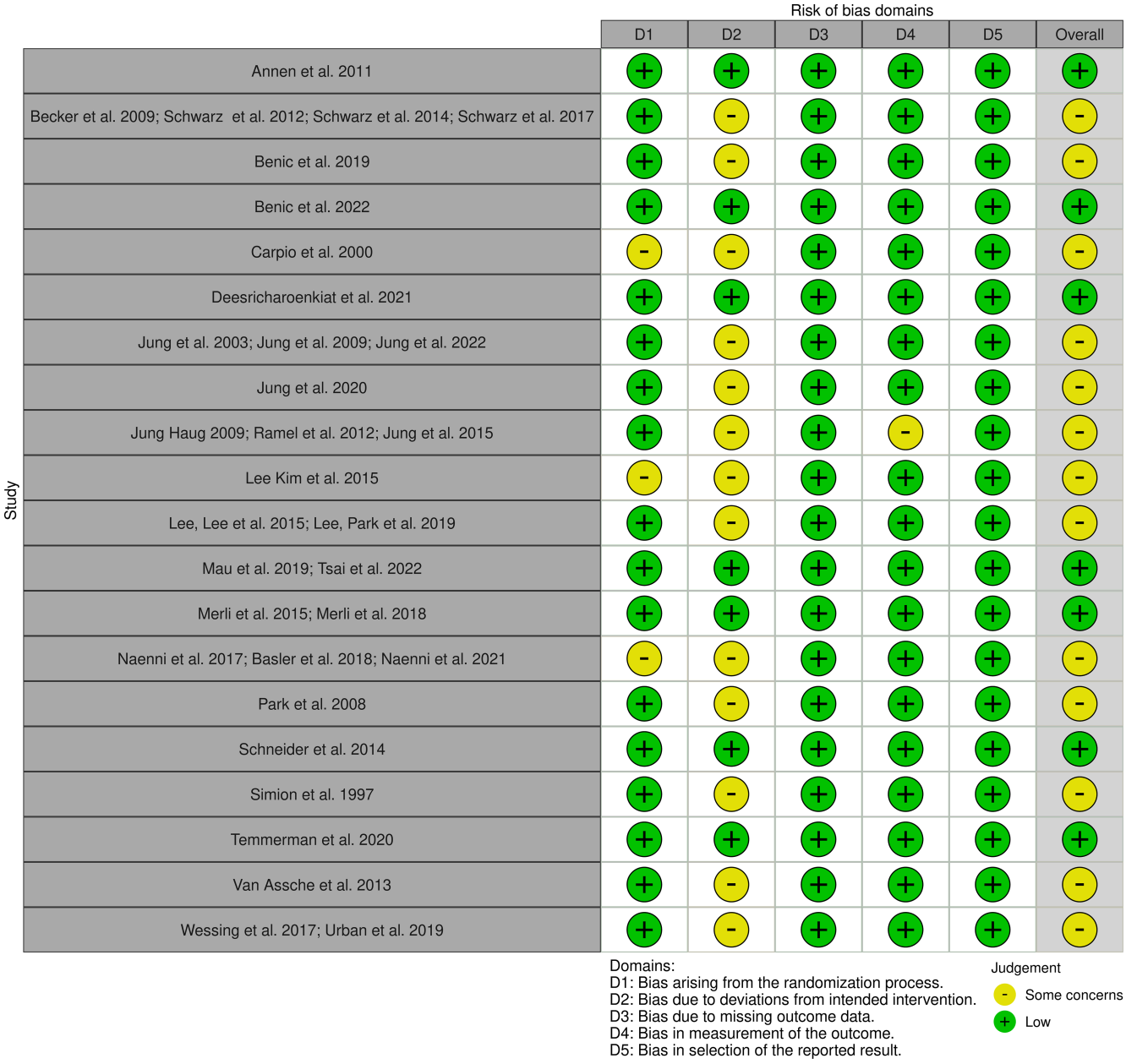

FIGURE 4 Risk of bias assessment based on RoB 2 for the RCTs included in the review.

probability to perform better (Figure 2), but no statistical significance was reached compared to other biomaterials and the limited number of studies included suggests caution in interpreting such trend. Similar interproximal bone levels were also reported in the few studies with 5-year follow-up[32,36] and in a study with 22-year follow-up.[34] However, the long-term data provided by the included studies should be considered at high risk of bias due to the high number of dropouts.

While 2D x-rays are useful tools to assess interproximal bone levels, their value to evaluate the efficacy and long-term stability of GBR procedures aimed at treating buccal dehiscence/fenestration is obviously limited.[73] As such, analyses based on 3D assessments, like CBCT scans, can provide more useful information on the success of the regenerated buccal bone and on its stability throughout time. Interestingly, when looking at the stability of the buccal regenerated bone overtime, all studies suggested that regardless of the biomaterial employed a certain resorption of the augmented bone should be anticipated and that this can already be detectable at re-entry, thus confirming a previous review.[74] Interestingly, a recent study indicated that the "individual phenotypical dimension" (which represents the natural alveolar crest contour before tooth loss) may be a predictor of how much buccally one can regenerate bone when applying the GBR concept.[75] Hence, over-augmentation beyond the boundary line of the bony envelope may not be a successful strategy.

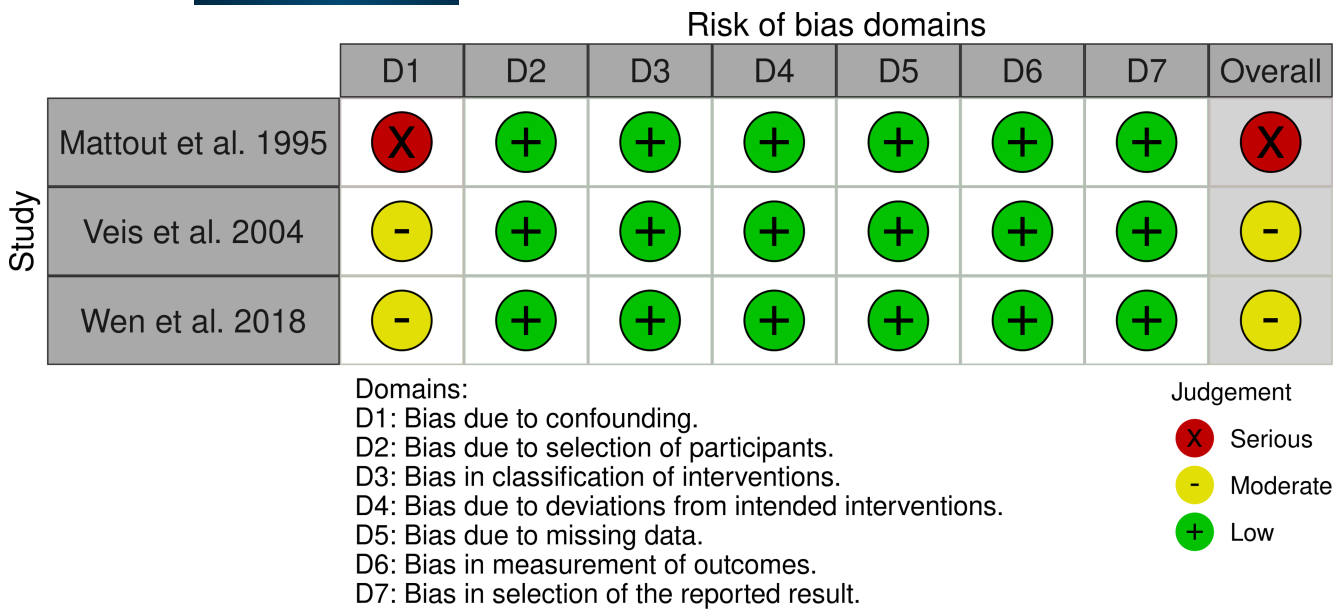

FIGURE 5 Risk of bias assessment based on ROBINS I for the CCTs included in the review.

Only four of the included studies employed CBCTs to document the stability of the regenerated bone at ≥12 months, hence no robust conclusions can be drawn. Nevertheless, one of these studies indicated a significantly higher loss of horizontal bone thickness at 5 years of follow-up in case an NCL collagen membrane was applied as compared to a titanium-reinforced e-PTFE membrane (from 1.39 ± 0.90 mm to 0.48 ± 0.77 mm and from 1.60 ± 0.98 mm to 1.00 ± 0.95 mm, respectively).[36] Remarkably, these significant differences in hard tissue changes did not impact on the overall buccal contour. Regardless of the observed hard tissue resorption, the overlying soft tissue (measured with an intraoral scan) seemed to have compensated for the loss of horizontal bone thickness with an increase in soft tissue thickness. It should be noticed that the significant difference in the stability of the regenerated buccal bone assessed through CBCT did not match with the outcomes resulting from 2D x-rays, where comparable interproximal bone remodeling was documented in the two groups, thus highlighting the importance of employing 3D radiographic examinations to evaluate the outcomes of GBR, at least for research purposes.

4.3 | The influence of biomaterials on dehiscence resolution and defect width reduction

Since the main goal of GBR procedures is to successfully cover exposed implant threads by newly formed bone, dehiscence resolution is an important outcome to consider when assessing the efficacy of different biomaterials. This is also in consideration of the fact that a correlation between high residual defect height at re-entry and the incidence of mucosal recession has been suggested.[53,55]

Based on the two networks drawn in this review, it is not possible to clearly recommend a specific GBR treatment modality, since the heterogeneity between the studies was large, with a plethora of different barrier membranes and grafting materials employed. In the largest network (based on 14 studies), the treatment ranking based on SUCRA suggested that the use of a NCL membrane combined with a DBBM bone block had the highest probability of being the best treatment in terms of vertical dehiscence resolution at re-entry, while the worst treatment was the combination of a CL membrane with DBBM particles (Figure 3A). However, no statistical significance was reached.

Previous reviews showed that interventions combining bone replacement grafts with a barrier membrane were associated with superior dehiscence resolution as compared to the use of the graft alone.[76,77] In the present review, we only focused on GBR-related procedures, meaning that the placement of a membrane (with or without a bone graft/bioactive factor) was a prerequisite to include a study, as such data on the efficacy of using a bone graft alone could not be drawn.

Besides dehiscence resolution, the effect of GBR should be also assessed in terms of defect width resolution, but also in this case the network meta-analyses did not suggest a clear superiority of a biomaterial over another (Figure 3B).

4.4 | How to select amongst different biomaterials for GBR

Whereas an evidence-based superiority of one membrane over another and of a bone graft over another could not be demonstrated based on the primary outcomes of this review, different considerations based on the site-specific characteristics of the defects to be treated, risk of complications and adverse events, preferences and skills of the clinicians, availability of the biomaterials, patient preferences and morbidity should be made when selecting amongst the plethora of biomaterials available for GBR.

All types of membranes investigated in the present review were not associated with major adverse events, although few RCTs reported a tendency for higher complications (exposure and risk of infection) with CL as compared to NCL membranes.[33,48,52] One study was even stopped earlier because of safety issues and severe infections related to the use of a CL membrane.[33] As CL membranes do not seem to offer obvious advantages over NCL ones, their increased risk of complication and exposure does not support their use as the first choice, as it has been demonstrated a significantly higher defect reduction (+27%) when membrane exposure does not occur.[78]

On the other end, NCL membranes have a fast resorption time, which may negatively reflect on their occlusive properties[79] and this is why it has been suggested to apply a double layer of membrane to increase their stability and barrier effect.[80] Only one of the studies included in this review applied a double layer of NCL membrane in association with FDBA or with a combination of DBBM and autograft. Despite the 100% implant survival rate, in both cases, CBCT analysis suggested a reduction in the augmented ridge dimension at 12 months, which may question the clinical utility of applying the double layer technique.[56,61] However, since the study lacked a control group where only one layer of collagen membrane was employed, it is also possible to speculate that bone grafting material might play a role and influence the stability of the regenerated bone. As a matter of fact, pre-clinical evidence suggests that a double-layer NCL membrane might reduce the resorption of autologous bone blocks.[81]

Resorbable collagen barriers offer obvious advantages over non-resorbable barriers, including no need for membrane-removal surgery, simplification of the technique and potential cost reduction, decreased patient morbidity, and easier management in case of exposure. Since our review and previous evidence in this field[3,77,82] showed that both types of membranes can successfully promote the regeneration and resolution of dehiscence and fenestration defects, it is suggested that, whenever possible, resorbable membranes should be preferred.[83] However, it is important to recognize that non-resorbable barriers (e.g. e-PTFE) present better mechanical and space-maintenance properties, thus they may offer an advantage in case of non-containing defects (see section 4.5). As a matter of fact, successful regeneration of dehiscence/fenestration defects has been documented with e-PTFE membranes even in the absence of a bone grafting material, which suggests that the primary component of success is provision of space through an undisturbed environment.[62,84]

When comparing non-resorbable to resorbable membranes, one study included in this review indicated higher soft tissue dehiscence and membrane exposure for e-PTFE compared to NCL membrane,[42] while an opposite trend was observed in another study.[38] A previous review did not indicate a significant difference in soft tissue complications (including membrane exposure, soft tissue dehiscence, and acute infection) between resorbable and non-resorbable membranes.[85] Remarkably, when looking at longer follow-ups (mean 56.8 months), another review reported a similar complication rate between ePTFE and NCL membranes (13.9% and 13.6%, respectively), but a higher complication rate for CL membranes (44.4%).[77]

A PEG membrane has been successfully proposed in a few studies for GBR simultaneous to implant placement.[46,60] However, clinicians should be aware that a tendency for higher incidence of adverse events (namely dehiscence) was associated with this type of barrier,[59] as well as the possibility of developing delayed dehiscence (after 5–7 weeks).[44] Our group previously suggested to pay particular attention on the manipulation and surgical use of PEG membranes, which could lead to early rupture of the barrier (in a pre-clinical model), with a negative impact on the healing outcome.[86]

In terms of bone graft, most of the studies included in this review employed DBBM, therefore it was not possible to perform a separate network meta-analysis considering the effect of graft. Nevertheless, a clear superiority of one bone graft over another was not suggested and the few studies using biological factors (BMP- or acemannan)[31,43] did not indicate a benefit in dehiscence/fenestration resolution.

4.5 | The importance of defect morphology

It is intuitive to think that the morphology, size, location (mandible vs. maxilla), and characteristics of peri-implant defects may have a significant impact on their regenerative potential and these aspects should be considered when selecting the biomaterials.

Owing to the heterogeneity in data reporting, it was not possible to perform separate analyses based on the morphology of baseline defects. However, we were able to distinguish between "small" and "large" defects based on vertical height and width and to perform a regression analysis to test whether defect size played a role in dehiscence resolution and changes in defect width (FQ2). For both outcomes it, was suggested a lower efficacy of GBR treatments in the presence of initially large defects, despite the trend did not reach significance.

As previously suggested, the challenge when regenerating peri-implant defects seems to be dependent on the "envelope of bone," or likelihood of the remaining bone to protect the organized blood clot.[87] An older study classified dehiscence and fenestration defects into two classes according to whether peri-implant bone defects reside within the envelope of the adjacent bone (Class I) or outside the envelope (Class II).[87] In a class I defect, in which the volume stability of the region to be augmented is supported by the adjacent bony walls, a bioresorbable membrane in combination with a particulate bone substitute represents most likely the treatment of choice[83] (Figure 6). This is in consideration of the fact that a resorbable membrane offers several advantages over non-resorbable membranes, as previously highlighted.

Conversely, a class II defect is more challenging to treat and the use of a particulate graft combined with a collagen membrane may not be indicated, owing to its scarce morphological stability and the risk of graft displacement under soft tissue pressure.[83,88,89] In such an instance, stabilizing the collagen membrane with fixation pins or using a block graft, or employing a mechanically stably non-resorbable membrane (e-PTFE) might lead to more predictable outcomes.[41,83,88,90]

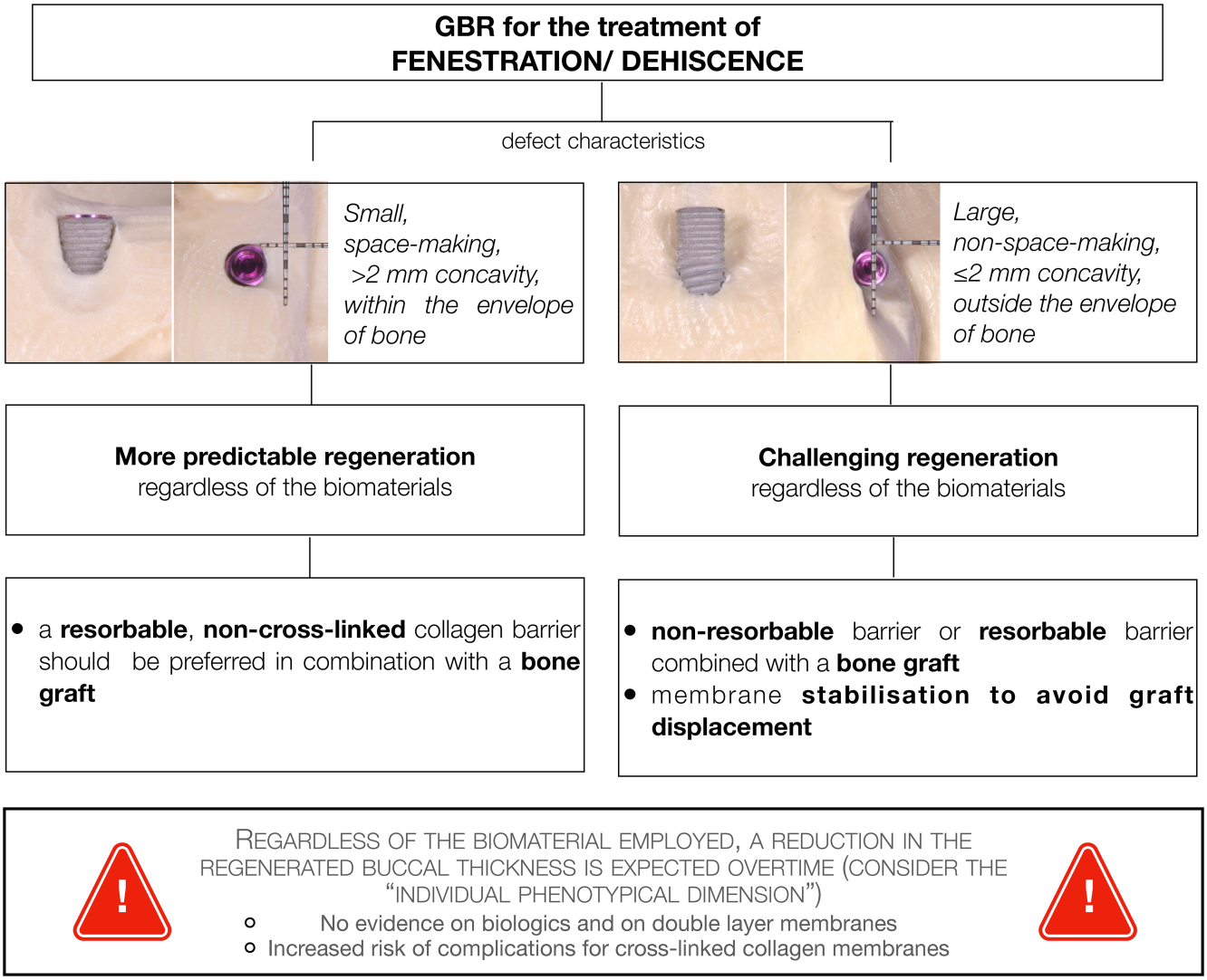

FIGURE 6 Decision tree when performing GBR simultaneous to implant placement.

Another defect parameter that might play a role in the regenerative outcome is the depth or "concavity," defined as the distance between the emergence of adjacent bone to the implant body at the implant-platform level. If the peri-implant bone concavity is more pronounced, a particulate bone graft would be easier to stabilize and less susceptible to displacement, as this parameter defines the bone housing ability of the defect. As a matter of fact, in the study by Tsai et al,[61] the CBCT outcomes of the facial bone wall thickness at three different measurement levels were superior in the group with concavity >2 mm as compared to the group with concavity ≤2 mm, regardless of the grafting material, although the difference did not reach statistical significance.

4.6 | The importance of membrane stabilization

Stabilization of the blood clot is a prerequisite for bone regeneration to take place.[13,91] While space-making defects may not require additional efforts for membrane (and graft) stabilization, using fixation pins or sutures to better anchor the barrier is advisable whenever there is the risk of an unstable wound healing milieu.[88,89] Details on the stabilization of barriers/membranes in the different studies are reported in Supplementary Material (Appendix S18).

In a study included in the present review comparing a resorbable collagen membrane to an e-PTFE membrane associated with DBBM for the regeneration of peri-implant dehiscence defects concomitant to implant placement it was clearly indicated that the membrane stabilization rather than the type of biomaterials used played a major role in the number of post-operative complications.[42] More specifically, in cases where primary barrier fixation was performed with polylactic acid pins, 63.6% of the sites healed uneventfully, as compared to only 28.6% of sites where the membrane was only secured with the implant cover screw and/or by adapting the membrane beneath the flap.

5 | CONCLUDING REMARKS, LIMITATIONS, AND FUTURE PERSPECTIVES

Based on the current evidence there is no clear superiority of one GBR technique over another, hence clinicians should base biomaterial selection on other aspects such as risk of complications, as well as patient-related and defect-related aspects (Figure 6).

The results of the present review should be weighted based on the existing limitations. Firstly, the geometry of the networks was very poor, depending on the plethora of treatments that have been proposed in the literature and the relative paucity of studies. The lack of three-arm studies further limits direct comparisons among treatments. In addition, the heterogeneity of the study protocols was significant and could have affected the reliability of the conclusions, despite the criteria adopted for study inclusion being relatively strict. These elements made it impossible to determine inconsistency of the networks, with mostly indirect comparisons, and therefore this lowers the potential validity of the results.[92]

After carefully reviewing the NMA results, we concluded that the high rate of imprecision for the outcomes considered could have significantly affected the GRADE-NMA judgments due to the sparse direct or indirect evidence. For this reason and due to the lack of evidence, we decided not to perform the GRADE-NMA.[93]

While more robust conclusions could be drawn for the 12-month outcomes, longer-term data should be considered as potentially biased owing to the large number of dropouts and missing data. Future adequately powered studies accounting for the risk of dropouts are needed to assess the long-term performance of different GBR techniques.

It is anticipated that in the future GBR simultaneous to implant placement will be optimized by several strategies targeting both material aspects and host-tissue responses.[8] Fine-tuning barrier and bone graft properties, as well as surgical techniques, becomes of particular relevance when dealing with more challenging scenarios, like class II dehiscence defects. No conclusions could be drawn on the role of bioactive factors in GBR, as a limited number of studies included in this review considered them. However, the rationale behind the possibility of enhancing regenerative outcomes with factors that are natural mediators of tissue repair is intriguing and deserves to be further investigated in RCTs.[15]

In order to optimize biomaterial selection based on the site-specific characteristics of the defects to treat, it is important that future studies will provide detailed information on the morphology (vertical height, width, depth, and intrabony component) of peri-implant defects, thus allowing multi-level analyses on the efficacy of different biomaterials based on defect morphology.

Finally, it is advisable that 3D imaging is employed to assess the stability of the peri-implant regenerated bone. Ideally, the combination of profilometric measures taken with intra-oral scans and CBCT scans would allow to clearly assess the contribution of soft and hard tissues in the overall volume of peri-implant tissues. With the current advancements in 3D technologies, a significant dose reduction can be achieved when performing CBCT scans by adjusting operating parameters, including exposure factors, and reducing the field of view (FOV) to the actual region of interest,[94] thus making this type of analysis less invasive and easier to accept by the patient.

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DATA AVAILABILITY STATEMENT

Data available within the article or its supplementary materials.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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