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REVIEW ARTICLE

Clinical efficacy of guided bone regeneration in peri-implantitis defects. A network meta-analysis

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1 | INTRODUCTION

Peri-implantitis is defined as a bacterial biofilm-mediated inflammatory disease affecting soft and hard tissues surrounding dental implants in function.[1,2] The untreated disease features an accelerating progression pattern, which ultimately leads to implant loss.[3,4] The major scopes of peri-implantitis treatment encompass resolution of inflammation and suppression of further marginal bone loss.[5] As nonsurgical approaches have demonstrated only limited efficacy in reliably obtaining those treatment end points, surgical interventions are frequently required.[6,7] Surgical therapeutic strategies for peri-implantitis management comprise nonreconstructive therapy alone or with adjunctive resective measures, reconstructive measures, or a combination thereof (referred to as combined therapy).[8] In fact, in addition to resolution of inflammation, reconstructive therapy seeks to regenerate the bone defect, achieve re-osseointegration, and limit postoperative soft tissue recession.[9]

The 15th European Workshop on Periodontology expounded on the indication criteria for reconstructive peri-implantitis therapy and defined them as implant sites featuring intrabony three or four wall-contained defects with ≥3 mm depth in the presence of keratinized mucosa.[9] Clinically, estimations of one recent meta-analysis pointed to more favorable radiographic bone-level changes following the use of reconstructive measures in conjunction with surgical peri-implantitis therapy, whereas no differences were obtained between reconstructive and nonreconstructive approaches with respect to the changes in probing depth (PD) values.[10] The results of another systematic review and meta-analysis in addition to the improved radiographic defect fill/resolution revealed greater PD reduction and less postoperative soft tissue recession following implementation of adjunctive reconstructive compared to the open flap debridement surgery.

A large variety of reconstructive protocols have been employed to treat peri-implantitis-related bone defects, including either the application of bone-filler particles (e.g., autogenous bone, allogenic bone, xenogenic bone, and alloplastic bone-substitute materials) with or without adjunctive use of biologically active materials (i.e., enamel matrix derivatives and platelet concentrates) or the performance of guided bone regeneration (GBR), which additionally involves the use of a barrier membrane.[8,11] In fact, one recent analysis intended to assess the efficacy of various reconstructive peri-implantitis therapies, but due to the strict inclusion criteria (i.e., nondiabetic patients or patients with controlled diabetes and at least 10 patients per treatment arm for controlled studies or at least 30 patients for prospective case series) and the subsequently limited number of included studies, the most effective reconstructive approach could not be determined.[10] Consequently, at present, the clinical data remain inconclusive as to which reconstructive protocol may be considered a standard of care at peri-implantitis sites or whether the adjunctive application of a barrier membrane provides any clinical benefits for the treatment outcomes. Therefore, the aim of this analysis was designed to assess the clinical efficacy of GBR-supported reconstructive surgical measures employed in conjunction with surgical peri-implantitis therapy.

2 | MATERIALS AND METHODS

The review protocol was developed and structured according to the PRISMA (Preferred Reporting Items for Systematic Review

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and Meta-Analyses) Statement.[12] The review was registered in PROSPERO, an international prospective register of systematic reviews (registration number: CRD42022331737).

2.1 | PICOS question

The protocol aimed to address the following two PICOS question:

In patients with peri-implantitis, what is the long-term (≥12 months) clinical efficacy of different GBR-supported reconstructive surgical measures compared to non-GBR-supported reconstructive surgical treatment in terms of changes in bleeding/suppuration on probing and probing pocket depth?

2.1.1 | Population

Patients with peri-implantitis.

2.1.2 | Intervention

GBR-supported reconstructive measures (i.e., including the use of a barrier membrane with or without the application of a bone graft/substitute, or with or without the application of biologics).

2.1.3 | Comparisons

Another GBR (i.e., a different barrier membrane with or without the application of a bone graft/substitute, or with or without the combination of biologics)/or non-GBR-supported surgical measure (i.e., a bone graft/substitute with or without the application of biologics).

2.1.4 | Outcomes

Primary: Changes in PD and/or of bleeding scores (BOP or bleeding index [BI]), and/or suppuration on probing (SUP); *secondary*: Changes in peri-implant soft tissue level (Rec) and radiographic marginal bone levels (RBL), radiographic defect fill (RDF), disease resolution, or treatment success, as defined by composite outcome, and implant survival.

2.1.5 | Study design

Randomized clinical trials (RCTs), controlled clinical trials (CCTs), and prospective comparative case series studies with a follow-up of ≥12 months and >5 patients per treatment arm.

2.2 | Inclusion and exclusion criteria

2.2.1 | Inclusion criteria

1. RCTs, CCTs, and prospective comparative case series investigating clinical efficacy of GBR-supported reconstructive measures in conjunction to surgical peri-implantitis treatment.
2. Studies with at least two treatment arms investigating different GBR approaches or comparing GBR-supported reconstructive approach to non-GBR-supported treatment modality.
3. Studies with a sample size of >5 patients per treatment group.
4. Follow-up period ≥12 months.
5. Studies providing case definitions of peri-implantitis based on clinical and radiographic parameters.
6. Studies reporting on clinical changes in bleeding scores (i.e., BI/BOP), SUP, and/or PDs.
7. Studies enrolling systemically healthy or systemically compromised patients (i.e., uncontrolled diabetes) were included.

The literature search was restricted to English language.

2.2.2 | Exclusion criteria

1. Inclusion of less than six patients per treatment arm.
2. Implementation of open flap debridement and resective treatment approaches (i.e., surgical interventions including soft tissue resection, bone resection/recontouring).
3. Observational studies, case reports, and review articles.
4. Lack of peri-implantitis case definition.
5. Lack of clinical data on the changes in BOP/BI, SUP, or PD.

2.3 | Information sources and search

Two electronic databases (MEDLINE (via PubMed) and Embase) were searched for relevant articles published until February 2023. The search filter "humans" was applied.

The combination of the following key words:

"treatment" OR "surgical treatment" OR "regenerative treatment" OR "augmentative treatment" OR "reconstructive treatment" OR "therapy" OR "surgical therapy" OR "regenerative therapy" OR "augmentative therapy" OR "reconstructive therapy" OR "antiseptic treatment" "adjunctive treatment" OR "adjunctive therapy" OR "GBR" OR "guided bone regeneration" (MeSH) OR "bone augmentation" (MeSH) OR "graft "OR "allograft "OR "xenograft "OR "bone substitute" OR "bone replacement material" OR "membrane"

AND

"peri-implant disease" OR "periimplant disease" OR "peri-implant infection" OR "periimplant infection" OR "periimplantitis" (MeSH) OR "peri-implantitis."

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TABLE 1 General information.

General information						
Author, year	**Study design**	**Follow-up period (months)**	**Setting**	**Number of patients**	**Number of implants/ functioning time**	**Implant location**
RCTs						
Regidor et al., 2023[19]	RCT	12	Private practice	Test: 19 Control: 20	Test: 19 Control: 20 Test: 11 (4.9) years Control: 11.5 (5.2) years Overall: 11 (4.9) years	Test: Maxilla 12 (57.1%), mandible 9 (42.9%), anterior 1 (4.8%) and posterior 20 (95.2%) Control: Maxilla 10 (45.5%), mandible 12 (54.5%), anterior 2 (9.1%) and posterior 20 (90.9%)
Monje et al., 2022[18]	RCT	12	Private practice	Test: 17 Control: 16	Test: 24 Control: 24 NR	Posterior Maxilla: 54.2% Posterior Mandible: 33.3% Anterior maxilla: 12.5%
Isler et al., 2018, 2022[20,38]	RCT	36	University	Test: 25 Control: 26	Test: 25 Control: 26 Test: 4.82 (1.81) years Control: 5.21 (2.48) years	Test: Maxilla 13 (52%), mandible 12 (48%), anterior 3 (12%) and posterior 22 (88%) Control: Maxilla 7 (26.92%), mandible 19 (73.07%), anterior 3 (11.53%) and posterior 23 (88.46%)
Aghazadeh et al., 2012, 2022[23,39]	RCT	60	Specialist center	Test: 23 Control: 22	Test: 39 Control: 36 NR	Proportion of implants in the maxilla Test: 39.1, Control: 31.8
Prospective comparative case series						
Roos-Jansaker et al., 2007, 2011, 2014[22,40,41]	Prospective case series	60	Specialty clinic and University	Test: 17 Control: 19	Test: 29 Control: 36 Test: 9.4 (3.4) years Control: 8.3 (2.8) years	NR
Schwarz et al., 2006, 2008, 2009[21,42,43]	Prospective case series	48	University	Test: 9 Control: 10	Test: 9 Control: 11 Test: 3.6 (1.9) years Control: 4.0 (0.9) years	NR

Abbreviation: NR, not reported.

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Patient-related information					Implant/prosthesis related information	
Patient age (mean[SD/range])	Gender (female/male)	Systemic conditions	Smoking status	Periodontal status	Implant type/design	Type of prosthetic restoration/ fixation type
Test: 60 (9/38–78) Control: 62.2 (10.2/31–74)	Test: 10/11 (47.6%/52.4%) Control: 14/8 (63.6%/36.4%)	NR	Smoking <10 cig./day Total: 4 (9.3%) Test: 3 (14.3%) Control: 1 (4.5%)	No active periodontal disease	Brand - Straumann: Test: 13 (61.9%), Control: 18 (81.8%); Astratech: Test: 1 (4.8%), Control: 0; Unclear: Test: 7 (33.3%), Control: 4 (18.2%) Surface – Modified: Test: 14 (66.7%), Control: 18 (81.8%); Unclear: Test: 7 (33.3%), Control: 4 (18.2%)	Screw-retained: Test: 13 (61.9%) Control: 12 (54.5%) Cemented: Test: 8 (38.1%) Control: 10 (45.5%)
64.0±9.3	20/13 (60.6%/39.4%)	NR	Smokers were excluded	No active periodontal disease	Anodized: 25 (52.1%) Acid etched: 14 (29.2%) Titanium plasma sprayed: 4 (8.3%) Unknown: 4 (8.3%) Machined: 1 (2.1%)	NR
Test: 57.88 (9.24) Control: 56.15 (9.23)	Test: 9/16 Control: 15/11	NR	Smoking <10 cigarettes a day: Test: 6 (24%) Control: 9 (34.62%)	History of periodontitis: Test: 11 (44%) Control: 13 (50%)	NR	Test: Fixed partial denture 20 (80%) and single crown 5 (20%) Control: Fixed partial denture 19 (73.07%) and single crowns 7 (26.92%)
Test: 67 (7.5) Control: 70.1 (6.2)	Test: 13/10 Control: 14/8	Cardiovascular-related disease: Test: 26% Control: 59.1%, Rheumatoid arthritis: Test: 1 Control: 1	Smoking habit (not further specified) Test: 69.6% Control: 40.9% Pack/year: Test: 18.8 (11), Control: 23.2 (13.4)	History of periodontitis Test: 95.2% Control: 66.7%	Machined Test: 39% Control: 49% Medium rough Test: 61% Control: 51%	NR
Test: 64.9 (7.5) Control: 65.7 (7.4)	Test: 10/7 Control: 4/15	NR	Smokers (not specifying quantity of cigarettes): Test: 10 (76.9%) Control: 8 (66.7%)	Tooth loss due to periodontitis: Test: 61.5% Control: 50%	AstraTech test: 1 Control: 1 All other subjects had received Branemark machined surfaced implants	NR
NR	14/8	NR	Smokers were equally distributed among groups (<10 cigarettes a day)	NR	Branemark: Test: 1, Control:0, Camlog: Test: 1, Control: 1, ITI: Test: 2, Control: 1, KSI: Test: 1, Control: 1, MTX: Test: 3, Control:4, Tapered screw vent: Test: 2, Control: 1, ZL-Duraplant: Test: 1, Control: 1	NR

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TABLE 2 Case definition and treatment protocols.

Author, year	Peri-implantitis disease definition/case definition	Treatment protocol		
		Test	Control	Supportive therapy
Regidor et al., 2023[19]	BOP/Sup + PD ≥7 mm + RBL ≥3 mm for more than a year Defect configuration (according to the classification by Monje et al.[24]): Contained (II/IIIc): Test: 45.5%, Control: 19% Non-contained (II/IIIb): Test: 55.5%, Control: 81%	Supra/submucosal debridement 4 weeks prior to surgery with plastic ultrasonic scalers + air polishing with erythritol powder containing 0.3% CHX Access flap + debridement with curettes + decontamination with NiTi brush + saline rinsing + xenogeneic bone filler + cross-linked collagen membrane + fixing pin Non-submerged healing 0.12% CHX/0.05% cetylpyridinium chloride rinsing for 2 weeks + amoxicillin 750 mg 2 tablets/day for 10 days (starting 3 days before surgery)	Supra/submucosal debridement 4 weeks prior to surgery with plastic ultrasonic scalers + air polishing with erythritol powder containing 0.3% CHX Access flap + debridement with curettes + decontamination with NiTi brush + saline rinsing + xenogeneic bone filler Non-submerged healing 0.12% CHX/0.05% cetylpyridinium chloride rinsing for 2 weeks + amoxicillin 750 mg 2 tablets/day for 10 days (starting 3 days before surgery)	Maintenance therapy including oral hygiene instruction and professional plaque removal using plastic ultrasonic scalers and air polishing scheduled at 4, 6 weeks and at 6, 12 months
Monje et al., 2022[18]	BOP/Sup + PD ≥6 mm + RBL ≥3 mm apical of the most coronal portion of the intraosseous part of the implant Defect configuration (according to the classification by Monje et al.[24]) Ib: 15 (31.3%) Ic: 14 (29.2%) IIIb: 14 (29.2%) IIIc: 5 (10.4%)	Supra/submucosal debridement 5 to 6 weeks prior to surgery with ultrasonic device + mechanical debridement + air polishing with erythritol powder + irrigation with 0.12% CHX Access flap + debridement with curettes + implantoplasty when necessary, performed at supracrestal or 1-to-2-wall defects with carbide bur + decontamination with NiTi brush + H2O2 (3%) 2 min. + saline irrigation + infra-osseous defect fill with demineralized (fibers) and mineralized (particles) cortical allograft + cross-linked collagen membrane Non-submerged healing 0.12% CHX mouth rinsing and chitosan gel for 2 weeks + amoxicillin 750 mg 2 tablets/day for 7 days + ibuprofen 600 mg 1 tablet every 5–6 h	Supra/submucosal debridement 5 to 6 weeks prior to surgery with ultrasonic device + mechanical debridement + air polishing with erythritol powder + irrigation with 0.12% CHX Access flap + debridement with curettes + implantoplasty when necessary, performed at supracrestal or 1-to-2-wall defects with carbide bur + decontamination with NiTi brush + H2O2 (3%) 2 min. + saline irrigation + infra-osseous defect fill with demineralized (fibers) and mineralized (particles) cortical allograft Non-submerged healing 0.12% CHX mouth rinsing and chitosan gel for 2 weeks + amoxicillin 750 mg 2 tablets/day for 7 days + ibuprofen 600 mg 1 tablet every 5–6 h	During the first 2 months, professional-administered oral hygiene every 2/3 weeks; thereafter every 3–/4-months maintenance therapy.
Isler et al., 2018, 2022[20,38]	PD of ≥5 mm + BOP and/or SUP + two-, three-, or four-wall intrabony defects ≥3 mm Two-wall defects: 22 (43.14%) Three-wall defects: 12 (23.52%) Four-wall defects: 17 (33.33%)	Supra/submucosal debridement 4–6 weeks prior to intervention Access flap + debridement with titanium curettes + saline irrigation + xenogenic bone filler particles + CGF membrane Submerged healing 0.12% CHX mouth rinse + amoxicillin 500 mg + metronidazole 500 mg + flurbiprofen 100 mg	Supra/submucosal mechanical debridement 4–6 weeks prior to intervention Access flap + debridement with titanium curettes + saline irrigation + xenogenic bone filler particles + collagen membrane Submerged healing 0.12% CHX mouth rinse + amoxicillin 500 mg + metronidazole 500 mg + flurbiprofen 100 mg	Supragingival plaque removal every third month. Subgingival debridement + saline irrigation when necessary, except surgical site until 1-year postoperatively. Later, patients were enrolled in individualized supportive care.

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TABLE 2 (Continued)

Author, year	Peri-implantitis disease definition/case definition	Treatment protocol		Supportive therapy
		Test	Control	
Aghazadeh et al., 2012, 2022[23,39]	PD ≥5 mm + BOP/SUP + RBL ≥2 mm + angular peri-implant bone defect ≥3 mm 3-wall defects Group 1: 29.7% implants Group 2: 44% implants 4-wall defects Group 1: 13%–5% implants Groups 2: 12% implants	Supra/submucosal debridement prior to intervention Access flap + mechanical debridement with titanium instruments +3% H_2O_2 + saline irrigation + autogenous bone graft + collagen membrane Non-submerged healing Azithromycin 250 mg + 0.1% CHX mouth rinse + ibuprofen 400 mg	Supra/submucosal debridement prior to intervention Access flap + mechanical debridement with titanium instruments +3% H_2O_2 + saline irrigation + xenogenic bone filler particles + collagen membrane Non-submerged healing Azithromycin 250 mg + 0.1% CHX mouth rinse + ibuprofen 400 mg	Supragingival plaque removal and oral hygiene instructions after 6 weeks, then, every 3 months
Roos-Jansaker et al., 2007, 2011, 2014[22,40,41]	BOP and/or SUP + bone loss of ≥3 threads (≥1.8 mm) following the first year of healing One-wall defects: 14.6% Two-wall defects: 29.2% Three-wall defects: 43.8% Four-wall defects: 10.4% Non-classified defects: 2.1%	Amoxicillin 375 mg + metronidazole 400 mg prior to intervention Access flap + mechanical debridement +3% H_2O_2 + saline irrigation+ xenogenic bone filler particles + resorbable polymer membrane Non-submerged healing 0.1% CHX mouth rinse + ibuprofen 400 mg	Amoxicillin 375 mg + metronidazole 400 mg prior to intervention Access flap + mechanical debridement +3% H_2O_2 + saline irrigation + xenogenic bone filler particles Non-submerged healing 0.1% CHX mouth rinse + ibuprofen 400 mg	Supragingival plaque removal and oral hygiene instruction after 6 weeks, then every 3 months.
Schwarz et al., 2006, 2008, 2009[21,42,43]	PD of >6 mm + intrabony defect >3 mm.	Supra/submucosal debridement +0.2% CHX mouth rinse/subgingival gel prior to intervention Access flap + mechanical debridement with plastic curettes + synthetic bone Non-submerged healing 0.2% CHX mouth rinse	Supra/submucosal debridement +0.2% CHX mouth rinse/subgingival gel prior to intervention Access flap + mechanical debridement with plastic curettes + xenogenic bone filler particles + collagen membrane Non-submerged healing 0.2% CHX mouth rinse	Supragingival plaque removal and oral hygiene instruction after 1, 3, 6, 12, 18, 24, 30, 36, 42, and 48 months

Abbreviations: BOP, bleeding on probing; CGF, concentrated growth factors; CHX, chlorhexidine; PD, probing depth; SUP, suppuration.

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2.4 | Study selection

During the first literature selection stage, according to the defined inclusion criteria, titles, and abstracts of all identified studies were screened for eligibility by two independent reviewers (A.R. and E.C). In the second stage, the full texts of potentially eligible articles were reviewed and evaluated according to the aforementioned exclusion criteria. Any disagreement was resolved by discussion, and whenever necessary, a third reviewer was consulted (F.S.). The level of inter-examiner agreement for the first and second literature-selection stages were calculated by Cohen's kappa scores.

2.5 | Risk of bias in individual studies

The Cochrane Collaboration's tool was implemented for the assessment of the risk of bias (RoB 2.0) in RCTs.[13] The Risk of Bias In

TABLE 3 Primary and secondary treatment outcomes.

Author, year	Treatment approach	PD changes	Bleeding score changes	Sup	Plaque index
Regidor et al., 2023[19]	Group 1 (test): Xeno + M Group 2 (control): Xeno	Group 1: Baseline – 9.4 ± 2.2 12 months – 5.1 ± 0.68 Group 2: Baseline – 8.8 ± 2.0 12 months – 4.6 ± 1.2 Inter-group comparison: $p > 0.05$	BOP (%) Group 1: Baseline – 94.0 ± 22.2 12 months – 25.0 ± 37.3 Group 2: Baseline – 93.2 ± 23.4 12 months – 26.2 ± 35.8 Inter-group comparison: $p > 0.05$	SUP (%) Group 1: Baseline – 48.8 ± 47.1 12 months – 0.0 ± 0.0 Group 2: Baseline – 21.6 ± 39.6 12 months – 1.2 ± 5.6 Inter-group comparison: $p > 0.05$	NR
Monje et al., 2022	Group 1 (test): Allog + CM Group 2 (control): Allog bone alone	Group 1: Baseline – 6.53 ± 1.09 12 months – 3.13 ± 0.68 Group 2: Baseline – 7.04 ± 1.42 12 months – 3.01 ± 0.71 Inter-group comparison: $p = 0.292$	NR	Group 1: Baseline – 0.57 ± 0.68 12 months – 0.01 ± 0.07 Group 2: Baseline – 0.60 ± 0.59 12 months – 0.03 ± 0.17 Inter-group comparison: $p = 0.876$	Modified PI Group 1: Baseline – 0.66 ± 0.69 12 months – 0.04 ± 0.10 Group 2: Baseline – 0.34 ± 0.64 12 months – 0.08 ± 0.18 Inter-group comparison: $p = 0.09$
Isler et al., 2018, 2022	Group 1 (test): Xeno + CGF Group 2 (control): Xeno + M	Group 1: Baseline – 5.9 ± 1.42 12 months – 3.71 ± 1.09 $p < 0.001$ 36 months – 3.8 ± 1.41 Group 2: Baseline – 5.41 ± 1.16 12 months – 2.70 ± 0.80 $p < 0.001$ 36 months – 3.28 ± 1.27 Inter-group comparison at 12 months: $p = 0.001$ Inter-group comparison: $p = 0.007$	BOP (%) Group 1: Baseline – 97.12 ± 12.8 12 months – 35.58 ± 30.14 $p < 0.001$ 36 months – 40.38 ± 33.22 Group 2: Baseline – 97.12 ± 8.15 12 months – 29.81 ± 30.02 $p < 0.001$ 36 months – 35.58 ± 33.3 BI Group 1: Baseline – 1.11 ± 0.23 36 months – 0.37 ± 0.54 Group 2: Baseline – 1.08 ± 0.27 36 months – 0.32 ± 0.49 Inter-group comparison at 12 months: $p = 0.503$ Inter-group comparison: $p = 0.969$	NR	Group 1: Baseline – 0.96 ± 0.89 12 months – 0.67 ± 0.35 $p = 0.072$ 36 months – 0.59 ± 0.5 Group 2: Baseline – 1.12 ± 0.4 12 months – 0.45 ± 0.44 $p < 0.001$ 36 months – 0.52 ± 0.45 Inter-group comparison at 12 months: $p = 0.051$ Inter-group comparison: $p = 0.609$

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Non-randomized Studies of Interventions (ROBINS-I) tool was employed for CCTs and prospective comparative clinical studies.[14]

2.6 | Data collection

Data extraction templates were generated including the following information:

2.6.1 | General information

Study design, follow-up period, setting (i.e., private practice or university), number of treated patients and implants/implant functioning time; implant location; patient-related information, including age, gender, smoking status, periodontal status; implant and prosthesis-related information, including implant design, type of prosthetic restauration, fixation type (i.e., fixed or cemented) (Table 1).

RBL	RDF	Soft tissue level changes	Disease resolution/treatment success, definition of success	Implant/prosthesis survival, complications
Group 1: Baseline – 6.8 ± 1.9 12 months – 5.3 ± 2.3 Group 2: Baseline – 5.3 ± 1.8 12 months – 4.2 ± 2.4 Inter-group comparison: $p > 0.05$	NR	Group 1: Baseline – 0.9 ± 1.1 12 months – 1.1 ± 1.2 Group 2: Baseline – 0.9 ± 1.3 12 months – 0.9 ± 1.3 Inter-group comparison: $p = 0.470$	No implant loss + absence of BOP or Sup + PD ≤5 mm + soft tissue recession on buccal aspect ≤1 mm Group 1: 36.8% of implants Group 2: 45.0% of implants	Group 1: 100% Implant survival Group 2: 100% Implant survival Group 1: Soft tissue dehiscence: 19% of implants Exposure of membrane: 9.5% of implants Exposure of bone substitute: 4.8% of implants
Group 1: Baseline – 4.58 ± 1.45 12 months – 2.85 ± 1.61 Group 2: Baseline – 4.65 ± 1.18 12 months – 2.92 ± 1.35 Inter-group comparison: $p = 0.774$	NR	Group 1: Baseline – 0.71 ± 0.86 12 months – 1.04 ± 0.81 Group 2: Baseline – 0.42 ± 1.21 12 months – 1.54 ± 0.93 Inter-group comparison: $p = 0.470$	Lack or 1 spot of BOP or Sup + PD ≤5 mm + no radiographic bone loss within the standard error ≥1 mm Group 1: 75.1% Group 2: 79.2% Inter-group comparison: $p = 0.737$	Group 1: 100% Implant survival Group 2: 100% Implant survival
Group 1: Baseline – 4.1 ± 1.56 12 months – 2.51 ± 1.45 $p < 0.001$ 36 months – 2.76 ± 1.56 Group 2: Baseline – 3.66 ± 1.02 12 months – 1.67 ± 0.76 $p < 0.001$ 36 months – 1.99 ± 0.76 Inter-group comparison at 12 months: $p = 0.015$ Inter-group comparison: $p < 0.001$	NR	MR Group 1: Baseline – 0.04 ± 0.2 12 months – 0.25 ± 0.39 $p = 0.007$ 36 months – 0.38 ± 0.48 Group 2: Baseline – 0.06 ± 0.2 12 months – 0.27 ± 0.44 $p = 0.026$ 36 months – 0.46 ± 0.55 Inter-group comparison at 12 months: $p = 0.925$ Inter-group comparison: $p = 0.313$	Absence of additional bone loss + PD ≤5 mm, + no BOP or Sup Group 1: 26.9% Group 2: 34.6% Inter-group comparison: $p = 0.249$ Absence of additional bone + PD ≤5 mm Group 1: 53.8% Group 2: 61.5% Inter-group comparison: $p = 0.390$ Absence of additional bone loss Group 1: 73.1% Group 2: 84.6% Inter-group comparison: $p = 0.382$	Group 1: 92.86% Implant survival Group 2: 96.55% Implant survival Surgical therapy had to be repeated on 2 implants in Group 1 and 1 implant in Group 2 due to severe inflammation with suppuration. 3 implants in Group 2 (11.5%) exhibited slight membrane exposure. After 5-years: Group 1: 9 (34.6%) implants were diagnosed as healthy, 12 (46.2%) were diagnosed with peri-implant mucositis, and 5 (19.2%) implants showed recurrence of peri-implantitis. Group 2: 5 (20%) implants were diagnosed as healthy, 11 (40%) implants had peri-implant mucositis, 9 (36%) implants were diagnosed with a recurrence of peri-implantitis.

(Continues)

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TABLE 3 (Continued)

Author, year	Treatment approach	PD changes	Bleeding score changes	Sup	Plaque index
Aghazadeh et al., 2012, 2022	Group 1 (test): Xeno + M Group 2 (control): Auto + CM	Group 1: Baseline – 6.2 ± 1.4 12 months – 3.3 ± 0.2 Group 2: Baseline – 6 ± 1.3 12 months – 3.8 ± 0.2 Inter-group comparison: $p = 0.01$ PD change baseline-5 years Group 1: 2.8 ± 1.7 mm Group 2: 1.7 ± 1.8 mm Inter-group comparison: $p = 0.001$	BOP (%) 12 months Group 1: Baseline – 79.4 ± 28.9 12 months – 26.7 ± 4.7 Group 2: Baseline – 87.5 ± 20.1 12 months – 48.4 ± 5.4 Inter-group comparison: $p > 0.05$ BOP changes baseline-5 years Group 1: 50.6 ± 44.9% Group 2: 55.6 ± 32.8% Inter-group comparison: $p > 0.05$	Sup (%) Group 1: Baseline – 25 ± 32 12 months – 1.2 ± 1.4 Group 2: Baseline – 12.5 ± 21.5 12 months – 2 ± 1.6 Inter-group comparison: $p = 0.01$	Plaque (%) Group 1: Baseline – 13 ± 23.7 12 months – 4.1 ± 3.1 Group 2: Baseline – 21.4 ± 25.4 12 months – 18.7 ± 3.6 Inter-group comparison: $p > 0.05$
Roos-Jansaker et al., 2007, 2011, 2014[22,40,41]	Group 1 (test): Xeno + M Group 2 (control): Xeno	Group 1: Baseline – 5.6 ± 1.9 12 months – 3.1 ± 2.0 p <60 months – 3 ± 2.4 Group 2: Baseline – 6 ± 2.2 12 months – 3.4 ± 1.7 p < 60 months – 3.3 ± 2 Inter-group comparison at 12 months: $p = 0.56$ Inter-group comparison: $p = 0.60$	NR	Sup (%) Group 1: Baseline – 19.9 60 months – 0 Group 2: Baseline – 22.7 60 months – 0 Inter-group comparison:	NR
Schwarz et al., 2006, 2008, 2009[21,42,43]	Group 1 (test): Synth bone alone Group 2 (control): Xeno + M	Group 1: Baseline – 6.9 ± 0.6 12 months – 4.9 ± 0.8 36 months – 5.8 ± 0.7 Group 2: Baseline – 12 months – 4.4 ± 0.6 7.1 ± 0.7 36 months – 4.6 ± 0.9	BOP (%) Group 1: Baseline – 80 12 months – 36 36 months – 48 Group 2: Baseline – 70 12 months – 29 36 months – 28	NR	Group 1: Baseline – 0.6 ± 0.5 12 months – 0.8 ± 0.6 36 months – 1.1 ± 0.3 Group 2: Baseline – 0.8 ± 0.4 12 months – 0.9 ± 0.5 36 months – 1 ± 0.6

Abbreviations: AB, antibiotic; Allog bone alone, allograft embedded in decalcified matrix; Autog, autologous bone filler; CGF, concentrated growth factor membrane; CM, collagen membrane; M, synthetic or collagen membrane; PD, probing pocket depth; RBL, radiographic bone level; RDF, radiographic defect fill; Sup, suppuration; Synth bone alone, synthetic bone filler; Xeno bone alone, xenogenic bone filler embedded in collagen matrix.

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RBL	RDF	Soft tissue level changes	Disease resolution/treatment success, definition of success	Implant/prosthesis survival, complications
Group 1: Baseline – 5.9 ± 2.3 12 months – 4.2 ± 0.3 Group 2: Baseline – 5.6 ± 2.2 12 months – 5.8 ± 0.3 Inter-group comparison: $p > 0.05$	Group 1: 1.1 ± 0.3 Group 2: 0.2 ± 0.3 Inter-group comparison: $p = 0.05$ RBL change baseline-5 years Group 1: 1.6 ± 1.8 mm Group 2: −0.7 ± 1.5 mm Inter-group comparison: $p = 0.001$	NR	PD ≤5 mm + no BOP + no SUP + gain or no loss of alveolar bone 12 months Group 1: 20.5% implants Group 2: 11.1% implants 5 years Group 1: 78.3% implants Group 2: 36% implants Inter-group comparison: 12 months: $p > 0.05$ 5-years: $p < 0.001$ PD ≤5 mm + max one site with BOP + no SUP + gain or no loss of alveolar bone 12 months Group 1: 38.5% implants Group 2: 13.9% implants Inter-group comparison: $p < 0.05$ No PD ≥5 mm + no BOP + no SUP + bone gain ≥1.0 mm 5 years Group 1: 54% implants Group 2: 20% implants Inter-group comparison: $p < 0.05$	12 months Group 1: 100% Implant survival Group 2: 100% Implant survival 5 years Two implants fractured in each group
NR	At 12 months Group 1: 1.6 ± 1.2 Group 2: 1.3 ± 1.4 Inter-group comparison at 12 months: $p = 0.44$ Group 1: 1.5 ± 1.2 Group 2: 1.1 ± 1.2 Inter-group comparison: $p = 0.24$	MR Group 1: Baseline – 1.3 ± 1.5 12 months – 1.6 ± 1.5 60 months – 1.3 ± 1.7 Group 2: Baseline – 1.4 ± 3.9 12 months – 1.7 ± 2.1 60 months – 2 ± 1.8 Inter-group comparison at 12 months: $p = 0.89$ Inter-group comparison: $p = 0.50$	RDF ≥25% + PD ≤5 mm + BOP score ≤1 51.1% RDF ≥25% + PD ≤5 mm 62.2% RDF ≥25% 66.7%	100% Implant survival One (2.2%) implant demonstrated progressive peri-implantitis (i.e., bone loss ≥1.0 mm)
NR	NR	MR Group 1: Baseline – 0.4 ± 0.2 12 months – 0.8 ± 0.4 36 months – 0.9 ± 0.4 Group 2: Baseline – 0.4 ± 0.3 12 months – 0.7 ± 0.5 36 months – 0.9 ± 0.2	NR	Group 1: 100% Implant survival Group 2: 90.1% Implant survival One implant in Group 2 had to be discontinued from the study due to severe suppuration. The patient was repeatedly treated with a surgical regenerative approach.

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Interventions: Peri-implantitis definition, treatment protocols in test and control groups, supportive therapy (Table 2).

Primary and secondary outcomes: Changes in clinical and radiographic parameters (BI/BOP, PD, SUP, PI, RBL, RDF, and Rec), disease resolution or treatment success, and loss of implant/implant-supported prosthesis (Table 3).

2.7 | Data analyses

To conduct a network meta-analysis (NMA), the treatment effects between different treatment arms were estimated for each study separately as differences in means (MD) and standard error (SE) using a commercially available software program (Comprehensive Meta-Analysis V3; Biostat). Implant was considered as a statistical unit.

To investigate the effectiveness of various interventions, a random-effects NMA was performed using the R package Netmeta.[15] As autogenous bone is considered the gold standard for bone-reconstruction procedures,[16] the GBR-supported approach employing the application of autogenous bone and collagen membrane (Auto+CM) was set as a reference treatment for the NMA estimations for mean BOP, mean PD, mean RBL, and mean Rec. Additionally, for the changes in the mean PI, mean BOP, mean PD, mean RBL, and mean Rec, NMA estimations were assessed using the xenogenic bone filler and a barrier membrane (Xeno+M) as a reference treatment, because this treatment approach was the most common comparator available for all parameters. Standardized mean differences (SMD) and confidence intervals (95% CI) between the reference treatment and various treatment approaches were estimated for the primary and secondary outcomes. Statistical heterogeneity among studies was explored by the I^2 index.[17] Funnel plots were created to assess publication bias. Results were considered significant if $p < 0.05$.

3 | RESULTS

The flowchart of the literature search is presented in Figure 1. The electronic literature search yielded 1470 articles (Medline via PubMed: 953, Embase: 517). After screening the titles and abstracts, 57 articles were selected for full-text analysis (kappa score >0.75). Of those, 45 articles were excluded for various reasons, of which the most frequent were implementation of non-GBR-supported reconstructive treatment approaches (10 RCTs, six prospective studies), studies with one treatment arm (15 prospective studies), and enrollment of less than six patients per treatment arm (2 prospective studies; Table S1).

Ultimately, four RCTs (six publications) and two prospective comparative clinical studies (six publications) met the inclusion criteria and were eligible for further analysis (kappa score >0.95; Table 1).

3.1 | Study characteristics

The follow-up periods among the included studies varied from 12 months (two RCTs)[18,19] to 3 years (1 RCT),[20] 4 years (1 prospective study),[21] and 5 years (one prospective study and one RCT)[22,23] (Table 1). Two 2-arm studies compared different GBR-supported treatment approaches,[20,23] and four studies assessed the efficacy of the GBR-supported treatment protocol versus the application of bone substitute alone (i.e., synthetic particulated bone filler,[21,22] allogenic cortical bone embedded in demineralized fibers,[22] or xenogenic bone embedded in collagen matrix[19]).

Patients in all but two studies were treated in a university setting. Among the three studies reporting on the patients' periodontal status, 44%–95.2% of the enrolled population were patients with a history of periodontitis,[20,22,23] whereas two studies excluded patients with active periodontal disease.[18,19] As indicated in five studies, smokers constituted 9.3%–76.9% of the treated patient sample, whereas in one study,[18] current smokers were excluded (Table 1).

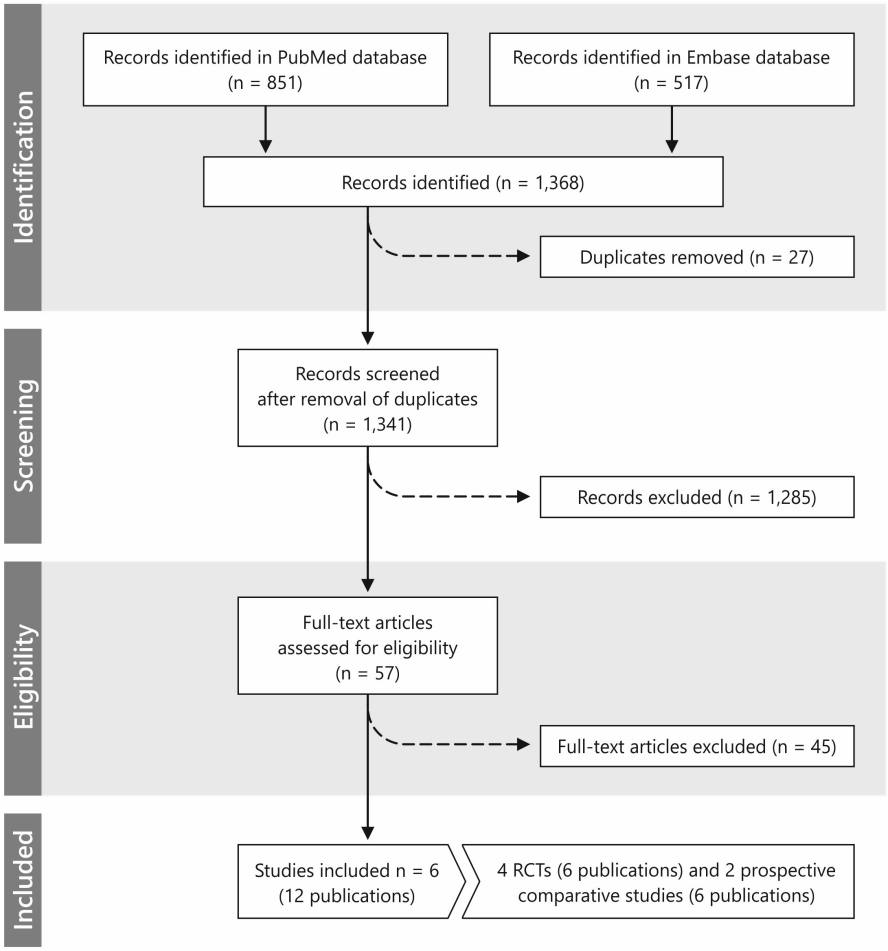
All studies defined peri-implantitis as the presence of BOP and/or SUP and the presence of RBL (Table 2). The reference points (i.e., baseline radiographs) and threshold values used to identify RBL were either not specified or varied among the studies. The threshold values applied for the PD measurements were ≥5 mm (three studies), ≥6 mm (two studies), or ≥7 mm (one study). As specified in five studies, cases to be treated with a GBR-supported approach should feature an intrabony-contained defect configuration with a depth of at least 3 mm.[18–21,23] Based on the data provided in three studies, most of the treated peri-implantitis sites featured intrabony defects surrounded by either two walls (29.2%–43.14%) or three walls (23.52%–44%), whereas four-wall intrabony defects were present just in the minority of the cases (10.4%–33.33%).[20,22,23] Two RCTs included either 2–3 wall defects (according to Monje et al.,[24] type I/III b: 41.6%–67.4% of the defects) or circumferential four-wall defects (type I/III c: 32.6%–41.6% of the defects) with or without a supracrestal defect compartment.[18,19] In fact, in one RTC assessing the need for a barrier membrane following the reconstructive peri-implantitis therapy, the defect configurations were unequally distributed between the test and control groups (i.e., contained four-wall defects GBR treatment: 19%; non-GBR treatment: 45.5%).[19]

As indicated in three studies, the majority of treated implants were modified surfaced,[18,19,21] whereas 49%–97% of included implants in two studies exhibited machined surfaces.[22,23] One study did not specify implant surface characteristics.[20] Based on the information provided in four studies, the mean implant functioning time prior to peri-implantitis treatment ranged between 3.6 and 11.5 years.[19–22]

All but one study reported on initial nonsurgical interventions prior to surgical therapy, including oral hygiene instructions and sub- and/or supra-mucosal instrumentation (Table 2). With respect to the protocols implemented for implant surface decontamination, the majority of the studies used a combination of mechanical debridement

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FIGURE 1 Literature search flowchart.



with titanium or plastic curettes and irrigation with physiological solution with[22,23,25] or without[20] adjunctive application of hydrogen peroxide (3%). Two studies used titanium brushes for mechanical removal of the biofilm from implant surfaces alone or with subsequent irrigation with hydrogen peroxide (3%) and saline.[18,19] In one RCT, uncontained defect components (i.e., supracrestal or 2–3 wall defects) were additionally treated with implantoplasty performed employing a carbide bur.[18]

The GBR-supported treatment approaches included the following protocols: (1) use of a particulated xenogenic bone filler and concentrated growth factor membrane (Xeno + CGF; one study/one arm), (2) a particulated xenogenic bone or embedded in collagen matrix with either collagen membrane (four arms) or synthetic resorbable membrane (one arm) (Xeno + M; in total five studies/five arms), (3) Autog + CM (one study/one arm), and (4) mineralized allogeneic cortical bone embedded in demineralized fibers and cross-linked collagen membrane (Allog + CM; one study/one arm). The non-GBR-supported treatment protocols included the following approaches: (1) use of synthetic particulated bone (Synth; 1 study, one arm), (2) mineralized allogeneic cortical bone embedded in demineralized fibers (Allog; one study, one arm), and (3) particulated xenogenic bone or embedded in collagen matrix (Xeno; two studies/two arms) (Table 2).

In five studies, the treated implant sites underwent a transmucosal healing with[18,19,23] or without[21,22] adjunctive prescription systemic antibiotics, whereas in one remaining study, implants were submerged for 4 months without the use of systemic antibiotics. All studies reported on patients' enrollment in regular maintenance programs following the surgery.

3.2 | Risk of bias

Based on the RoB 2.0 tool, three RCTs were judged to be at a low risk of bias,[18,20,23] and one RCT had an overall unclear risk of bias due to the missing outcome data (Domain 3).[19] One prospective study was found to be at a serious risk of bias,[22] and the remaining one study was judged to be at moderate risk of bias.[21] The concerns were mainly related with the presence of confounding variables, selection of participants, and measurement of the outcomes (Figure S1a,b).

3.3 | Data synthesis

One RCT reporting on Allog and Allog + CM treatment protocols was not connected to the network graph,[18] and therefore, could not be included into the NMA. Finally, five studies reporting on three GBR (i.e., Xeno + CGF [one arm], Xeno + M [five arms] and Autog + CM [one arm]) and two non-GBR (i.e., Synth [one arm]

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and Xeno [two arms]) approaches were included in the NMA estimations. Considering the varying follow-up periods across the studies (1–5 years), the NMA was conducted based on the 1-year outcome of each study.

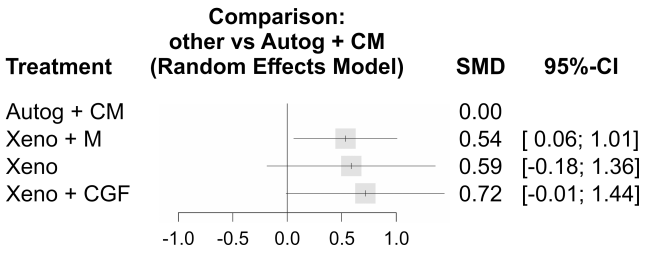


FIGURE 2 Forest plot for the standardized mean differences for bleeding on probing (BOP) between different GBR and non-GBR-supported treatment approaches when compared with autogenous bone and collagen membrane (Autog + CM).

3.3.1 | Primary outcomes

Based on the NMA estimations, the use of Xeno + M resulted in significantly higher mean BOP reduction compared to Auto + CM (SMD: 0.54 [95% CI: 0.06; 1.01], $p = 0.0265$), whereas no differences were found compared to the Xeno and Xeno + CGF groups (SMD: 0.59 [95% CI: −0.18; 1.36], $p = 0.1355$ and SMD: 0.72 [95% CI: −0.01; 1.44], $p = 0.06$, respectively; Figure 2, Table 4). Similarly, once the Xeno + M was set as a reference treatment, the Autog + CM treatment showed a significantly lower mean BOP reduction (SMD: −0.54 [95% CI: −1.01; −0.06], $p = 0.0265$; Figure 3), whereas no differences

TABLE 4 Standardized mean differences (SMD) and confidence intervals (95% CI) between the reference treatment and various treatment approaches for the primary and secondary outcomes.

Outcome measure	Comparison	SMD	95%CI	*p*
BOP (reference [Autog + CM])	[Autog + CM] vs. [Xeno + CGF]	0.72	−0.01; 1.44	0.0527
	[Autog + CM] vs. [Xeno + M]	0.54	0.06; 1.01	0.0265
	[Autog + CM] vs. [Xeno]	0.59	−0.18; 1.36	0.13655
BOP (reference [Xeno + M])	[Xeno + M] vs. [Autog + CM]	−0.54	−1.01; −0.06	0.0265
	[Xeno + M] vs. [Xeno]	0.05	−0.56; 0.66	0.8719
	[Xeno + M] vs. [Xeno + CGF]	0.18	−0.37; 0.73	0.5203
PD (reference [Autog + CM])	[Autog + CM] vs. [Xeno + CGF]	0.84	0.12; 1.56	0.0227
	[Autog + CM] vs. [Xeno + M]	0.52	0.05; 0.99	0.0303
	[Autog + CM] vs. [Synth]	1.27	0.22; 2.32	0.018
	[Autog + CM] vs. [Xeno]	0.51	−0.10; 1.11	0.1019
PD (reference [Xeno + M])	[Xeno + M] vs. [Xeno + CGF]	0.32	−0.23; 0.87	0.2531
	[Xeno + M] vs. [Autog + CM]	−0.52	−0.99; −0.05	0.0303
	[Xeno + M] vs. [Synth]	0.75	−0.19; 1.69	0.1182
	[Xeno + M] vs. [Xeno]	−0.01	−0.40; 0.37	0.9405
PI (reference [Xeno + M])	[Xeno + M] vs. [Synth]	0.14	−0.76; 1.04	0.7609
	[Xeno + M] vs. [Xeno + CGF]	1.52	0.89; 2.15	<0.0001
RBL (reference [Autog + CM])	[Autog + CM] vs. [Xeno + CGF]	1.07	0.38; 1.76	0.003
	[Autog + CM] vs. [Xeno + M]	0.84	0.35; 1.33	0.0008
	[Autog + CM] [Xeno]	0.98	0.20; 1.76	0.014
RBL (reference [Xeno + M])	[Xeno + M] vs. [Xeno + CGF]	0.23	−0.26; 0.72	0.3576
	[Xeno + M] vs. [Autog + CM]	−0.84	−1.33; −0.35	0.0008
	[Xeno + M] vs. [Xeno]	0.14	−0.47; 0.75	0.6515
Rec (reference [Autog + CM])	[Autog + CM] vs. [Xeno + CGF]	1.07	0.38; 1.76	0.003
	[Autog + CM] vs. [Xeno + M]	0.84	0.35; 1.33	0.0008
	[Autog + CM] vs. [Xeno]	0.98	0.20; 1.76	0.003
Rec (reference [Xeno + M])	[Xeno + M] vs. [Xeno + CGF]	0.23	−0.26; 0.72	0.3576
	[Xeno + M] vs. [Autog + CM]	−0.84	−1.33; −0.35	0.0008
	[Xeno + M] vs. [Xeno]	0.14	−0.47; 0.75	0.6515

Note: Rec: soft tissue level changes; Xeno + CGF: xenogenic bone + concentrated growth factor membrane; Xeno + M: xenogenic bone + synthetic or collagen membrane; Autog + CM: autogenous bone + collagen membrane; Synth: synthetic bone; Xeno: xenogenic bone.

Abbreviations: BOP, bleeding on probing; PD, probing depth; PI, plaque index; RBL, radiographic bone level.

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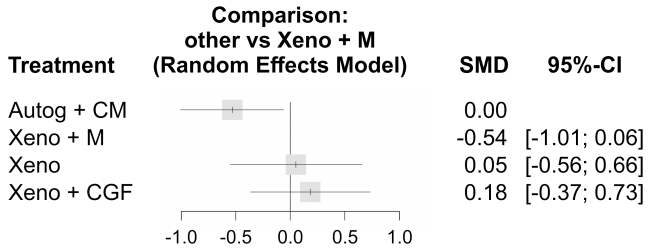


FIGURE 3 Forest plot for the standardized mean differences for BOP between different GBR and non-GBR-supported treatment approaches when compared with xenogenic bone + barrier membrane (Xeno + M).

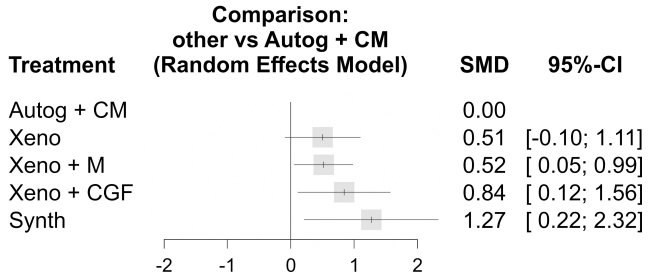


FIGURE 4 Forest plot for the standardized mean differences for probing depth (PD) between different GBR and non-GBR-supported treatment approaches when compared with autogenous bone and collagen membrane (Autog + CM).

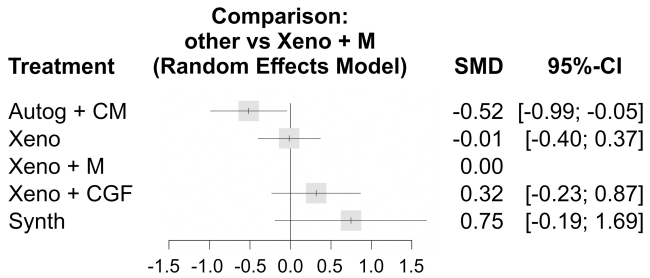


FIGURE 5 Forest plot for the standardized mean differences for PD between different GBR and non-GBR-supported treatment approaches when compared with xenogenic bone + barrier membrane (Xeno + M).

were found between the Xeno + M and Xeno or Xeno + CGF treatments. Funnel plots and a network are presented in Figures S2a,b and S3a, respectively.

With respect to the changes in mean PD values with the Auto + CM as a reference treatment, except for the Xeno group, all remaining treatment approaches (i.e., Xeno + M and Xeno + CGF, Synth) showed a significantly greater mean PD reduction (Figure 4). Likewise, when the Xeno + M was set as the reference treatment, the Autog + CM showed a significantly lower improvement in PD values (SMD: −0.52 mm [95% CI: −0.99; −0.05], $p = 0.0303$), whereas no differences were estimated between Xeno + M and the remaining groups (i.e., Xeno, Xeno + CGF and Synth; Figure 5, Table 4). Funnel plots and a network are presented in Figures S2c,d and S3b.

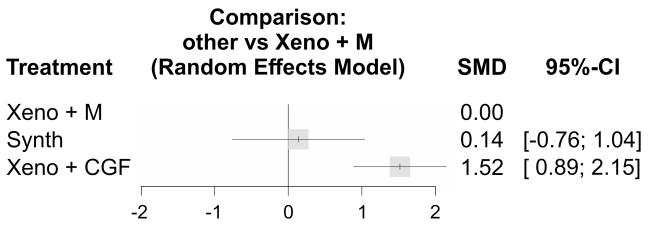


FIGURE 6 Forest plot for the standardized mean differences for plaque index (PI) between different GBR and non-GBR-supported treatment approaches when compared with use of xenogenic bone and barrier membrane (Xeno + M).

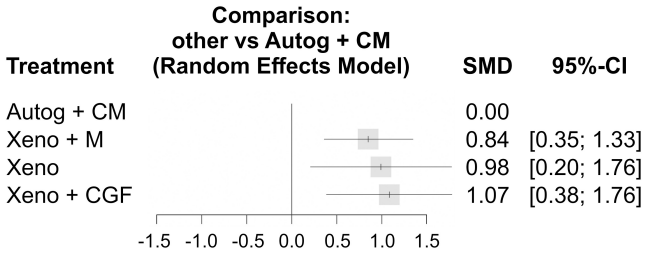


FIGURE 7 Forest plot for the standardized mean differences for radiographic bone levels (RBL) between different GBR and non-GBR-supported treatment approaches when compared with autogenous bone and collagen membrane (Autog + CM).

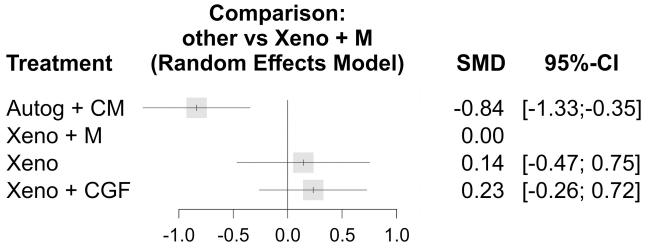


FIGURE 8 Forest plot for the standardized mean differences RBL between different GBR and non-GBR-supported treatment approaches when compared with use of xenogenic bone and barrier membrane (Xeno + M).

3.3.2 | Secondary outcomes

In terms of the mean PI value changes, compared to the Xeno + M group, Xeno + CGF showed significantly higher PI reduction (SMD: 1.52 [95% CI: 0.89; 2.15], $p < 0.001$; Figure 6; Figures S2e and S3c), while no differences were found between Xeno + M and Synth (SMD: 0.14 [95% CI: −0.76; 1.04], $p = 0.761$).

The GBR and non-GBR approaches employing xenogenic bone (Xeno, Xeno + CM and Xeno + CGF) resulted in significantly greater mean RBL compared to Autog + CM (Figure 7; Figures S2f and S3d). When the Xeno + M was set as a reference treatment, only the Autog + CM treatment showed significantly inferior mean RBL values (SMD: −0.84 mm [95% CI: −1.33; −0.35], $p = 0.0008$; Figure 8; Figure S2g).

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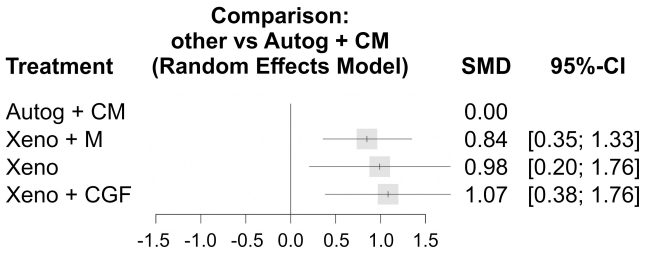


FIGURE 9 Forest plot for the standardized mean differences for soft tissue recession (Rec) between different GBR and non-GBR-supported treatment approaches when compared with autogenous bone and collagen membrane (Autog + CM).

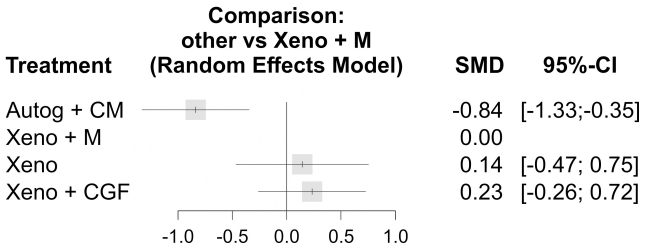


FIGURE 10 Forest plot for the standardized mean differences for Rec between different GBR and non-GBR-supported treatment approaches when compared with xenogenic bone + barrier membrane (Xeno + M).

With respect to the extent of Rec, GBR and non-GBR treatment approaches employing xenogenic bone (Xeno, Xeno + CM and Xeno + CGF) led to significantly less pronounced Rec compared to the Auto + CM group (Figure 9; Figures S2h and S3e). The NMA estimation using Xeno + M as a reference likewise showed that the Autog + CM was the only treatment leading to significantly greater Rec (SMD: −0.84 mm [95% CI: −1.33; −0.35], $p = 0.0.0008$; Figure 10; Figure S2i).

3.4 | Implant survival, treatment success and complications

The survival of implants treated with GBR-supported approaches ranged from 90.1% to 100% (Table 3). For the implants treated with non-GBR treatment protocols, the corresponding survival rates varied between 92.86% and 100%.

Based on a similar definition, treatment success after 12 months to 5 years was obtained for 11.1%–78.3% of the implants treated with GBR-supported reconstructive approaches[18–20,23] and 36.8%–79.2% of the implants treated with bone filler alone (Table 3).[18,19] One RCT after 5 years reported on a significantly more frequently obtained treatment success (i.e., no bone loss, PD > 5 mm, or SUP; max. one site with BOP) at implant sites treated with Xeno + CM compared to sites treated with Autog + CM (78.3% and 36%, respectively; $p < 0.001$).[23] The differences between the groups remained significant when the success criteria was complemented by "a gain in bone levels ≥ 1.0 mm" (Xeno + CM: 54% of implants; Autog + CM: 20% of implants; $p < 0.05$).[23]

Postoperative exposure of the collagen membrane (Xeno + CM group; 11.5% of implants) was reported for the implant sites treated with the GBR approach undergoing submerged healing.[20] One RCT comparing GBR versus non-GBR treatment approaches indicated the occurrence of soft tissue dehiscence (19%), exposure of collagen membrane (9.5%), and exposure of the bone substitute (4.8%) only at the implant sites treated with the GBR approach following non-submerged healing.[19] Persistent inflammation requiring repeated surgical interventions following GBR-supported treatment was reported in two studies.[20,21] After 3 years, 20%–34.6% of the implant sites treated with GBR approaches (i.e., Xeno + CM or Xeno + CGF) demonstrated peri-implant tissue health, whereas the majority of the treated implants were diagnosed with either peri-implant mucositis (40%–46.2% of implants) or recurrent peri-implantitis (19.2%–36.9%).[20]

4 | DISCUSSION

This analysis was aimed at evaluating the long-term (≥12 months) clinical efficacy of GBR-supported reconstructive surgical therapy at peri-implantitis-related bone defects. To the authors' best knowledge, this is the first analysis specifically focusing on the GBR-supported therapeutic approaches in managing bone defects at peri-implantitis sites.

Based on the network meta-analysis estimations that were limited to a 12-month follow-up period, GBR approaches employing xenogenic bone (i.e., Xeno+ and Xeno+ CGF) led to greater resolution of inflammation, as depicted a greater reduction in BOP and PD values compared to the GBR approaches using autogenous bone (Autog + CM). Furthermore, the use of a xenogenic bone substitute alone (Xeno) or along with collagen or growth factor membranes (Xeno + CM and Xeno + CGF) resulted in considerably lower postoperative soft tissue recession and significantly higher RBL values compared to GBR protocols using autogenous bone (Autog + CM). Given these findings, it appears that from the clinical perspective, a GBR- or non-GBR-supported approach implementing xenogenic bone substitutes may lead to enhanced therapeutic end points in terms of clinical and radiographic outcomes compared to GBR employing autogenous bone, which has been shown to undergo fast postoperative resorption.[26,27]

Considering the potential added benefit of the adjunctive use of a barrier membrane, this analysis pointed to improved changes in mean BOP and PD values once either collagen (for BOP changes) or growth factor membranes (for PD values) were applied over the xenogenic bone filler compared with the Autog + CM treatment. Furthermore, significantly lower PI reduction was obtained at implant sites treated with Synth compared to those treated with the GBR approach employing Xeno + M. Our findings contradict those obtained in one recent network meta-analysis, which, based on in the four included RCTs, found no additive benefits of a CM applied over xenogenic bone substitutes (particulated or collagen-embedded) in terms of

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PD and BOP changes (WMD 2.2%, $p=0.865$, and WMD 0.3 mm; $p=0.689$, respectively).[10] The present results do not further align with the results of previous RCTs that failed to identify the benefits of a barrier membrane (synthetic or collagen) positioned over synthetic, allogeneic, or xenogeneic bone substitutes on the outcomes of reconstructive therapy of peri-implantitis.[18,19,22] In fact, one RCT reported significantly higher patient postoperative pain scores 2 weeks after the treatment (median values: 20.0 vs. 5.0) and significantly increased treatment time (48.3 min vs. 38.3 min) in patients treated with a GBR approach (Xeno + M) compared to those treated with bone filler alone (Xeno).[19] In addition, more postoperative complications, such as soft tissue dehiscence or exposure of membrane or bone filler, were observed in the GBR group (Xeno + M) compared to the non-GBR group (i.e., Xeno).[19] The contradiction of the findings related to the benefits of a barrier membrane obtained in this data synthesis and previous results may be at least partially associated with the Xeno + M treatment being the most commonly employed reconstructive protocols that enclosed five treatment arms, whereas the remaining therapeutic approaches were based on either one (Xeno + CGF; Autog + CM, Synth) or two (Xeno) arms. It needs to be also noted that although in the Xeno + M group GBR treatments employed collagen or synthetic membranes, as reported in the former experimental in-vivo study, the GBR using either natural collagen or synthetic membranes over xenogenic bone lead to similar treatment outcomes of the chronic peri-implant dehiscence-type defetcs.[28]

One critical factor that might have greatly contributed to the lack of significant clinical differences obtained between GBR and non-GBR-supported treatment approaches (i.e., Non-R and bone alone treatments) could be the various defect configurations included in the studies. The guidelines provided by the 15th European Workshop on Periodontology indicated that the presence of a contained intrabony defect configuration is a prerequisite for the selection of reconstructive peri-implantitis treatment approaches.[9] As specified in four studies, most of the treated peri-implantitis sites featured a non-contained (i.e., 2–3 wall) defect configuration, whereas in only one RCT, the majority of the peri-implantitis sites (58.4%) present a circumferential four-wall defect configuration.[24] In fact, as reported by one analysis, four-wall defects showed 6.0–7.0 times higher odds ratios (ORs) for a successful outcome of the treatment (i.e., absence of additional bone loss + PD ≤ 5 mm) compared to three- and two-wall defects, respectively.[20] In line are the results of previous clinical studies that pointed to greater PD reduction and RDF following the use of a GBR-supported reconstruction protocol in peri-implantitis cases featuring circumferential-type defects compared to those lacking buccal and/or lingual walls.[29,30] In this context, for instance, when interpreting the findings of the aforementioned RCT comparing the GBR and non-GBR therapeutic approaches, the defect configurations were unequally distributed between the test (GBR) and the control (non-GBR) groups, with more favorable contained defect configurations (i.e., four-wall defects) being treated with the non-GBR approach (Xeno + M: 45.5%, Xeno: 19.0%), which may be the reason for the lack of observed differences between the test and the control groups. Subsequently, it might be speculated that the barrier membrane effect may be dependent on the defect configuration, with greater benefits provided at non-contained defects (i.e., 2–3 wall defects). However, in this analysis, none of the studies specified the treatment outcomes with respect to the defect configurations, which made it impossible to assess the defect morphology's influence on the therapeutic outcomes of peri-implantitis.

Although implant survival rates were high and comparable across the included studies on GBR- and non-GBR-supported treatment modalities, the treatment success defined as a composite outcome varied greatly (GBR approach: 11.1%–75.1% of implants; non-GBR approach: 36.5%–79.2% of implants).[18,19] In fact, the highest treatment success rates (defined as no BOP/Sup, PD ≤ 5 mm, and no further bone loss ≥1 mm) over a 12-month period were reported in one RCT, in which the majority of peri-implantitis sites featured a circumferential four-wall defect configuration (58.4%), thus suggesting that defect morphology may be a crucial factor for the therapy's success.[18] In the latter study, the authors found a direct association between disease resolution and low preoperative PI values (OR = 0.13; $p=0.006$) as well as a wider band of keratinized mucosa (OR = 2.10; $p=0.035$).[18] Nonetheless, while substantial clinical evidence supports the important role of keratinized mucosa in maintaining peri-implant tissue health and stability,[31] its influence on peri-implantitis treatment outcomes remains controversial.[32]

When interpreting the findings of this analysis, it is important to highlight the limited number of studies feasible for inclusion in the analyses with low to moderate risk of bias. In fact, the computation of heterogeneity for the assessed outcomes was not feasible, as no data distribution such as normal distribution, Poisson etc. could be fitted. The analysis was based on three GBR and two non-GBR treatment protocols employing xenogenic, autogenous, or synthetic bone, whereas one RCT employing allogenic bone could not be included in the NMA estimations. Furthermore, only two treatment approaches (Xeno + M and Xeno) included at least two treatment arms, while the remaining approaches included one treatment arm, thus, the outcomes of this analysis should be interpreted with caution. Due to that limitation, the authors did not report the outcomes of indirect comparison in the NMA. Also, during the study selection process, we did not consider patients' general health, though emerging data show that systemic patient health correlates with peri-implant tissue health status and might also influence treatment outcomes.[33,34] In addition, it should be stressed that the findings of this data analysis are valid for outcomes limited to 12 months as a longer term assessment was not possible due to a paucity of clinical data.

Along these lines, it is worthwhile to note that implant surface characteristics appear to influence the outcomes of surgical peri-implantitis treatment, with less predictable outcomes of reconstructive therapy obtained for moderately rough-surfaced implants compared to rough-surfaced implants.[35] Furthermore, more favorable nonreconstructive peri-implantitis treatment outcomes and reduced risk for disease recurrence following therapy were reported for implants with nonmodified surfaces compared to modified-surfaced implants.[36,37] In this analysis, except for two studies, most of the treated implants had modified surfaces, whereas one study

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did not specify implant surface characteristics. Therefore, it was not feasible to verify the extent to which implant surface characteristics might have affected the treatment outcome following either GBR or non-GBR-supported approaches. In addition, included studies employed various implant surface decontamination protocols, different postoperative healing modes (i.e., submerged and non-submerged) with or without adjunctive systemic antibiotics, representing variability across the studies, and thus not allowing to assess the extent to which the outcomes of this analysis might have been influenced by the aforementioned factors.

Considering the present findings, it can be concluded that GBR-supported reconstructive therapy for peri-implantitis-related bone defects implementing xenogenic bone substitutes may lead to superior clinical outcomes in terms of resolution of bleeding scores, probing pocket reduction, improved radiographic bone levels, and soft tissue height maintenance compared to GBR treatment with autogenous bone. In terms of inflammation resolution, determined by reduction in bleeding on probing and probing depth values, the GBR approaches using xenogenic bone showed superiority over the respective non-GBR treatments.

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CONFLICT OF INTEREST STATEMENT

The authors do not report any conflicts of interest related to this study.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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