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Enamel matrix derivative monotherapy versus combination therapy with bone grafts for periodontal intrabony defects: An updated review

Akira Hasuike [a,b,*], Taito Watanabe [a,c], Akemu Hirooka [d], Shingi Arai [a], Hideyasu Akutagawa [a], Naoto Yoshinuma [a,b], Shuichi Sato [a,b]

[a] Department of Periodontology, Nihon University School of Dentistry, 1-8-13 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8310, Japan
[b] Dental Research Center, Nihon University School of Dentistry, 1-8-13 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8310, Japan
[c] Division of Applied Oral Sciences, Nihon University Graduate School of Dentistry, 1-8-13 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8310, Japan
[d] Sweden Dental Clinic, Japan

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ABSTRACT

This systematic review evaluated the effectiveness of combining enamel matrix derivative (EMD) with various bone grafts in periodontal regenerative surgery, specifically targeting intrabony defects. Randomized controlled trials with 12-month follow-ups were included. Clinical outcomes assessed included clinical attachment level, probing depth, gingival recession, and radiographic defect fill. Meta-analysis showed that adding bone grafts to EMD does not provide additional benefits in periodontal tissue examination, with improvement observed only in radiographic defect fill. Subgroup analyses examined the impact of different bone graft types, revealing that alloplastic bone grafts are effective in radiographic defect fill. The risk of bias assessment indicated a moderate risk across studies, with challenges in blinding owing to the nature of the surgical treatment. Furthermore, a minimal intervention surgical approach may not require additional bone grafts for optimal periodontal regeneration. These findings contribute to the ongoing dialogue in the field and guide clinicians toward evidence-based decisions for optimal periodontal outcomes, emphasizing the judicious use of bone grafts.

1. Introduction

Periodontitis is an inflammatory condition characterized by progressive loss of attachment and bone [1]. The primary objective of periodontal treatment is to reorganize functional tissue by regenerating lost attachment and bone [2,3]. Periodontal bone defects are categorized as suprabony or infrabony, with infrabony defects further subdivided into intrabony defects and craters [4]. Intrabony defects, which contain space isolated by bony walls, represent the main target of periodontal regenerative therapy. According to the European Federation of Periodontology clinical guidelines, teeth with residual deep pockets associated with intrabony defects $\geq$ 3 mm should be treated with periodontal regenerative therapy [5]. Various regenerative methods involving scaffolds, membranes, growth factors, and biologics have been proposed and have demonstrated regenerative effects, leading to improved clinical outcomes compared to open flap debridement [6].

Enamel matrix derivative (EMD) is a widely recognized biomaterial used for periodontal regeneration [7]. It contains amelogenin derived from the Hertwig epithelial root sheath of developing porcine tooth buds [8]. EMD influences the behavior of various cell types and effectively enhances the recovery of hard and soft tissues while reducing inflammation [7]. The efficacy of EMD was first demonstrated in 1997 in a study comparing it to open flap debridement for intraosseous defects [9,10]. A human histology study has shown that EMD promotes periodontal healing by facilitating the formation of acellular cementum, periodontal ligament, and alveolar bone in an experimental defect [9]. Over the past two decades, EMD has ushered in a new era of periodontal tissue engineering [7]. A recent systematic review reported a significant gain in clinical attachment level (CAL) (1.31 mm [95 % confidence interval [CI]: 0.95–1.73]) [11].

Although effective for periodontal regeneration, EMD may not be suitable for all bone defects owing to its gel-like consistency. Its limited ability to create space can impact its regenerative potential, particularly in non-contained defects. In such cases, combining EMD with bone grafts can prevent flap collapse and provide a secure space for periodontal regeneration. Bone grafts act as fillers and scaffolds that enhance bone formation and accelerate wound healing. They include autografts, allografts, xenografts, and alloplastic materials. Autogenous bone grafts,

* Corresponding author at: Department of Periodontology, Nihon University School of Dentistry, 1-8-13, Kanda Surugadai, Chiyoda-ku, Tokyo 101-8310, Japan.
E-mail address: hasuike.akira@nihon-u.ac.jp (A. Hasuike).

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harvested from the patient, are traditionally considered the gold standard because of their high osteogenic capacity, but harvesting involves an additional procedure and can lead to donor site complications. Conversely, allografts, xenografts, and alloplastic grafts eliminate the need for secondary procedures and mitigate donor-site issues. In periodontal surgery, empirical evidence supports true periodontal regeneration of periodontal ligament, cementum, and bone with allografts [12] and xenografts [13]. However, although alloplastic grafts such as hydroxyapatite [14] and tricalcium phosphate (TCP) [15] enhance clinical parameters effectively, they show limited histological evidence of regeneration. A previous systematic review examined histologic evidence from 10 studies on the effects of alloplastic biomaterials in regenerative periodontal surgery for human intrabony defects [16]. The results generally indicated healing characterized by the formation of a long junctional epithelium and connective tissue encapsulation of graft particles. Periodontal regeneration or cementum formation was mostly restricted to the apical regions of the defects, with minimal and infrequent bone formation around the graft particles. None of the studies reported complete defect resolution, and inflammation levels remained consistently low. Other previous review highlighted numerous clinical investigations into the effects of combining these bone graft materials with EMD [17].

Several previous reviews have synthesized this evidence on the effectiveness of EMD combination therapy through meta-analyses [18–20]. The most recent systematic reviews on the synergistic effects of bone grafts and EMD, compared to EMD monotherapy, were published in 2011 [18] and 2014 [19]. Systematic reviews require regular updates to reflect the most current knowledge. Therefore, an updated review of this clinical topic is warranted. Additionally, earlier reviews included clinical studies with varying follow-up periods ranging from 6 to 24 months, and meta-analyses incorporating data from diverse observational periods present significant challenges for users. While clinical studies on this topic often report findings at 6 and 12 months, evaluations at 6 months may be too brief for meaningful clinical assessment. Longer follow-up periods allow for a more comprehensive assessment of treatment efficacy, considering factors such as tissue maturation and the stability of regenerative outcomes. Machtei recommends a minimum follow-up period of 12 months to adequately evaluate the true regenerative potential and clinical benefits of periodontal therapies [21]. Therefore, this review aims to update previous reviews on clinical comparisons of EMD monotherapy versus combination therapy with bone grafts at 12 months.

2. Materials and methods

2.1. Focused question

This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [22]. The study protocol was prospectively registered in the PROSPERO database (registration number: CRD42021281155). The research questions were framed in the PICOT format:

(P) Participants: Adult human patients with periodontitis, residual pockets, and infrabony defects after initial periodontal treatment.

(I) Intervention: Periodontal regenerative surgery with EMD and any bone graft type.

(C) Comparisons: Periodontal regenerative surgery with EMD alone.

(O) Outcomes: CAL gain.

Change in probing depth (PD).

Change in gingival recession (REC).

Radiographic defect fill.

(T) Timeframe: 12-month follow-up.

2.2. Eligibility criteria

Only randomized controlled trials (RCTs) that met the PICOT format were included. The exclusion criteria were as follows: (I) narrative reviews, studies based on questionnaires or interview guidelines, editorials, and opinion pieces; (II) case reports, case series, observational studies, retrospective studies, and clinical studies without randomization; (III) studies with only histological data; (IV) studies on furcation defects or supra-osseous defects; and (V) studies comparing EMD + bone grafts versus bone grafts alone.

2.3. Search strategy

RCTs were electronically searched across multiple databases, including MEDLINE PubMed (up to October 1, 2021), Web of Science (up to October 1, 2021), Embase (up to October 1, 2021), and CENTRAL (up to October 1, 2021).

The search strategy for MEDLINE PubMed included a combination of Medical Subject Heading (MeSH) terms and full-text search terms, as follows: (((“periodontal pock-et”[MeSH Terms] OR “periodontal regeneration”[All Fields] OR “periodont*”[All Fields] OR “intrabony defect”[Text Word] OR “infrabony defect”[Text Word] OR “intra bony defect*”[All Fields] OR “infra bony defect*”[All Fields] OR “intra-osseus”[Text Word]) AND (“enamel matrix proteins”[Supplementary Concept] OR “emdogain*”[All Fields] OR “enamel matrix derivative*”[All Fields] OR “enamel matrix protein*”[All Fields] OR “dental enamel protein*”[All Fields] OR “enamel protein*”[All Fields]) AND (“Bone Substitutes”[MeSH Terms] OR “Bone Substitutes”[Supplementary Concept] OR “bone substitute”[Text Word] OR “bone graft”[Text Word] OR “Bone Transplantation”[MeSH Terms] OR “Calcium Phosphates”[MeSH Terms] OR “autogenous bone”[Text Word] OR “deproteinized bovine bone mineral”[Text Word] OR “bone mineral”[Text Word] OR “xenograft”[Text Word] OR “alloplastic”[Text Word] OR “allogenic”[Text Word]) AND (((“randomized controlled trial”[Publication Type] OR (“con”[All Fields] AND “trolled”[All Fields] AND “clinical trial”[Publication Type]) OR “randomized”[Title/Abstract] OR “Prospective Studies”[MeSH Terms] OR “Follow-Up Studies”[MeSH Terms] OR “clinical trials as topic”[MeSH Terms] OR “randomly”[Title/Abstract] OR “trial”[Title]) NOT (“animals”[MeSH Terms] NOT “humans”[MeSH Terms])) OR (“meta-analysis”[Publication Type] OR “meta-analysis”[Title/Abstract] OR “cochrane database syst rev”[Journal] OR “systematic review”[Title/Abstract]))) NOT “case report”[Title]) NOT “dental implantation, endosseous”[MeSH Terms].

Search terms for other databases are detailed in Table S1 in the Supplementary Materials.

The reference lists of selected studies and previously published systematic reviews underwent thorough manual scrutiny by two examiners to identify cross-references and potentially eligible studies or ancillary publications. To ensure up-to-date evidence, our search was updated by querying PubMed on January 18, 2024, using the same search terms as those in the initial search. Two reviewers examined the full texts of potential articles, and eligibility for inclusion in this review was confirmed through consensus discussion. Disagreement were resolved after consulting an independent reviewer. For studies that met the inclusion criteria, two authors independently extracted the main author names, year of publication, study design, patient demographics (mean age and sex ratio), number and morphology of defects, types of bone grafts used in the treatment group, follow up period, and data on CAL, PD, REC, and radiographic outcomes.

2.4. Data extraction and subgroup analysis

Data extraction for each included study was conducted by three independent reviewers. They systematically gathered key information for each trial, including the first author’s name, year of publication, study design, patient demographics (mean age and sex ratio), total number of intrabony defects in each group, types of intrabony defects, bone grafts used in the treatment group, length of follow-up, and continuous

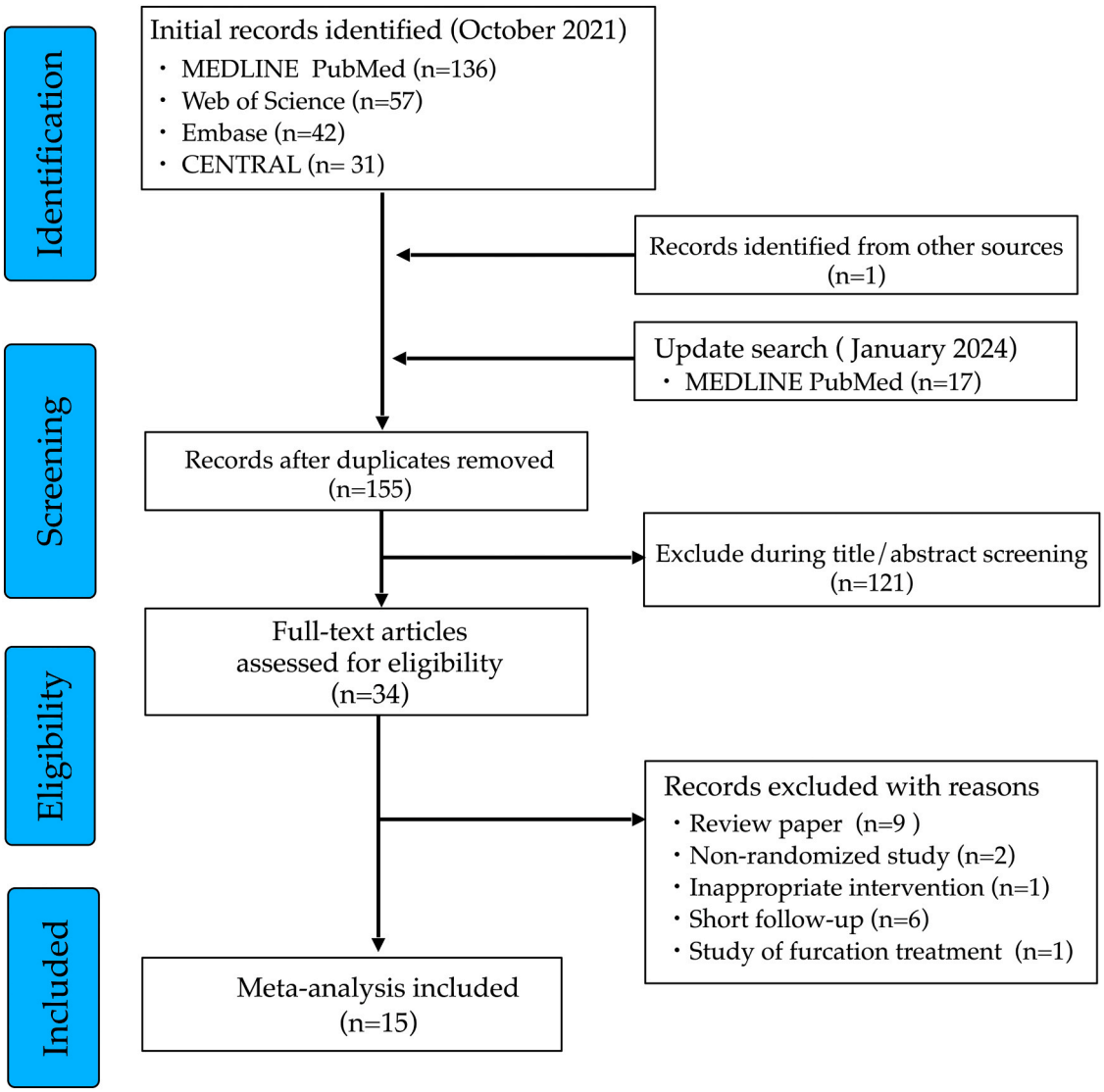


Fig. 1. Flowchart of the review process.

outcome results (mean and standard deviations [SDs]). When case papers presented standard error (SE) or 95% CI with the mean of each outcome, SD was estimated through calculation. For baseline-end continuous outcomes not reported in the article, absolute differences and SDs were computed for both the test and control groups [23]. Additionally, we conducted a subgroup meta-analysis to assess the influence of bone graft type on the pooled estimates, categorized as autogenous, allograft, xenograft, and alloplastic.

2.5. Assessment of risk of bias

As this study involved comparative interventions, the methodological quality of the included RCTs was evaluated using Cochrane's risk of bias assessment tool. Two investigators independently assessed the methodological quality of these included studies.

2.6. Statistical methods

The statistical analysis in this study was conducted using RevMan

Table 1
Characteristics of included studies of autogenous bone graft.

Study	Study design	Intrabony defects	Treatment groups	Defects, No.	Bone grafts	Patient age (y)	Patients (%, female)	Follow-up (months)
Guida et al. [27] 2007	Parallel	1 or 2 wall	EMD EMD + AB*	14 14	Cortical bone from the buccal plate by bone scraper	46.3 ± 8.7	27 (51.8%)	6 and 12
Yilmaz et al. [30] 2010	Parallel	2 or 1–3 walls	EMD EMD + AB*	20 20	Cortico-cancellous bone from the retromolar area using a trephine bur	30–50	40 (60%)	12

*AB: autogenous bone graft

Table 2
Characteristics of included studies of allograft.

Study	Study design	Intrabony defects	Treatment groups	Defects, No.	Bone grafts	Patient age (y)	Patients (%, female)	Follow-up (months)
Ogihara et al.[35] 2014	Parallel	2 or 3 walls, or combination	EMD EMD + FDBA* EMD + DFDBA†	23 23 23	Oragraft‡	54 ± 4 53 ± 11 56 ± 9	69 (79.7%)	12 and 36

* FDBA: freeze-dried bone allograft

† DFDBA: demineralized freeze-dried bone allograft

‡ Oragraft: OraGraft, LifeNet Health

Table 3
Characteristics of included studies of xenograft.

Study	Study design	Intrabony defects	Treatment groups	Defects, No.	Bone grafts	Patient age (y)	Patients (%, female)	Follow-up (months)
Zucchelli et al.[24] 2003	Parallel	1 or 2 or 1–2 wall	EMD EMD + DBBM*	30 30	BioOss‡	45.8 ± 6.8 47.2 ± 5.3	60 (56.67%)	12
Cortellini et al.[31] 2011	Parallel	2 or 3 walls, or combination	M-MIST† EMD EMD + DBBM*	15 15 15	BioOss‡	48.9 ± 7.9 47.2 ± 8.5 53.5 ± 11.9	45 (46.7%)	12
Rodriguez et al.[38] 2022	Parallel	1 or 1–3 or 2–3 or 1–2 or 1–2–3 walls	EMD EMD + DBBM*	12 12	Cerabone§	46.5 ± 10.47 50.33 ± 9.02	24 (37.5%)	12

* DBBM: deproteinized bovine mineral

† M-MIST: modified minimally invasive surgical technique

‡ BioOss: Bio-Oss, Geistlich, Wolhusen, Switzerland

§ Cerabone: CeraBone, Botiss

Table 4
Characteristics of included studies of alloplastic bone graft.

Study	Study design	Intrabony defects	Treatment groups	Defects, No.	Bone grafts	Patient age (y)	Patients (%, female)	Follow-up (months)
Jepsen et al.[29,32,37] 2008, 2011, 2016	Parallel	1 or 2 or 1–2 wall	EMD EMD + AP*	35 38	BoneCeramic‡	45.8 ± 6.8 47.2 ± 5.3	73 (31.5%)	12
Pietruska et al.[33] 2012	Parallel	1–2 or 2 or 3 walls	EMD EMD + AP*	12 12	BoneCeramic‡	34–62	24 (58.3%)	12 and 48
De Leonardis et al.[34] 2013	Split-mouth	1 or 2 wall	Flap debridement EMD EMD + AP*	34 34 34	BoneCeramic‡	45.3 ± 5.9	36 (58.3%)	12 and 24
Losada et al.[37] 2016	Parallel	1 or 2 wall	EMD EMD + AP*	25 21	BoneCeramic‡	50.20 ± 9.48 54.90 ± 10.77	36 (37.0%)	6 and 12
Sculean et al.[25,28] 2005, 2007	Parallel	1–2 or 2 or 3 walls	EMD EMD + AP*	15 15	Bioactive glass	47.5 ± 7.7 47.2 ± 12.9	30 (53.3%)	12 and 48
Bokan et al.[26] 2006	Parallel	1–2 or 2–3 walls	Flap debridement EMD EMD + AP*	18 19 19	Cerasorb§	55.0 ± 8.4 56.6 ± 9.4 59.7 ± 7.6	56 (51.8%)	12

† AP: Alloplastic bone

‡ BoneCeramic: Straumann bone ceramic

§ Cerasorb: Cerasorb M

5.4.1. The meta-analysis assessed the mean difference between groups, with 95% CIs. Statistical significance was set at $p < 0.05$. Heterogeneity was evaluated using the chi-square test and I^2 statistic. Owing to high heterogeneity previously observed in systematic reviews [18,19], a random-effects model was employed for the meta-analysis in this review.

3. Results

3.1. Search results

Initially, 136 articles were identified through a MEDLINE PubMed search. Subsequently, 57 articles were sourced from Web of Science, 42 from Embase, and 31 from CENTRAL. One more article was found and included during the manual search of reference lists from the initially identified articles. In January 2024, a PubMed search was conducted to review the latest evidence on the topic, resulting in the screening and assessment of 155 eligible articles. Full-text assessments were conducted on 34 articles, and ultimately, 15 articles from 12 studies were included in this review and meta-analysis [24–38]. A flowchart detailing the review process is shown in Fig. 1. A comprehensive overview of excluded studies and reasons for the exclusion is shown in Table S1 in the Supplementary Materials [11,17–19,39–53].

Among the 12 studies included, 2 specifically investigated the impact of autogenous bone grafts with EMD application (Table 1) [27,30]. Another study conducted a comparative analysis involving three treatment arms: EMD +freeze-dried bone allograft (FDBA), EMD + demineralized FDBA, and EMD alone (Table 2) [35].

Three studies focused on examining the effects of bone xenografts, all utilizing deproteinized bovine mineral (DBBM), with two utilizing the same commercial product (Bio-Oss) (Table 3) [24,31,38]. Among these, two studies used a minimally invasive surgical technique (MIST) with DBBM and EMD, a modified minimally invasive surgical technique (M-MIST) [31], and a non-incised papilla surgical approach [38] for

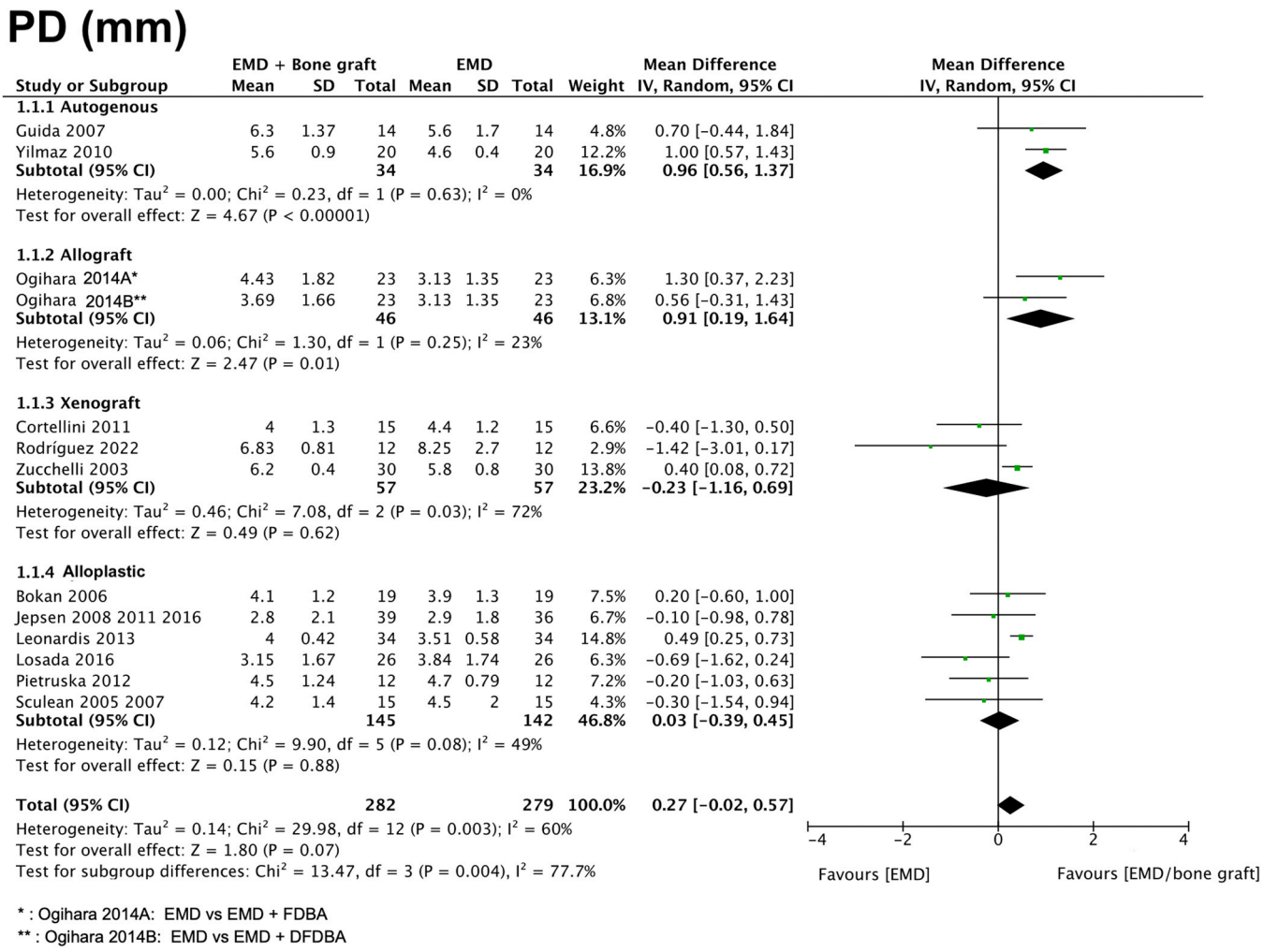


Fig. 2. Forest plot of probing depth (PD) reduction in mm.

periodontal regenerative surgery. Alloplastic bone research emerged as the most prevalent, comprising nine articles from six distinct research projects (Table 4) [25,26,28,29,32–34,36,37]. One of these projects involved a split-mouth RCT [33]. Among the six studies, four utilized a commercial biphasic calcium phosphate product (Straumann Bone-Ceramic), which contains 60% hydroxyapatite and 40% beta-tricalcium phosphate (β-TCP). Another study used β-TCP material (Cerasorb, Curasan) [26], and the remaining one employed bioactive glass [25,28].

3.2. Clinical periodontal tissue examinations

This section summarizes the clinical changes in PD, CAL, and REC. All included trials reported PD reduction (Fig. 2). Pooled estimates in a random-effects model showed that using EMD in combination with bone grafts resulted in a 0.27 mm greater reduction in PD (95% CI: −0.02–0.57) than using EMD alone. However, this difference was not statistically significant, and there was substantial heterogeneity among the trials (I^2 = 60%). Subgroup analysis indicated that combination therapy with autogenous and allograft bone grafts showed a statistically significant difference compared to EMD monotherapy. Trials involving xenografts showed a statistically significant difference in a trial employing EMD + DBBM in conventional flap surgery [24], whereas those employing MIST did not demonstrate significant differences [31,38]. Changes in CAL were also assessed in all included trials (Fig. 3). Pooled estimates using a random-effects model indicated that combining EMD with bone grafts resulted in a slightly greater CAL gain of 0.05 mm (95% CI: −0.39–0.50) compared to using EMD alone. However, no statistically significant difference was observed between the two treatment groups, and notable heterogeneity was observed among the trials (I^2 = 75%). In the subgroup analysis, only combination therapy with allograft bone grafts showed a statistically significant improvement. Similar to the PD results, a statistically significant difference was observed in a trial employing conventional flap surgery [24], whereas trials using MIST did not show significant differences [31,38]. Changes in REC were observed in 10 of the 12 studies (Fig. 4). Pooled estimates in a random-effects model showed that EMD monotherapy had 0.16 mm (95% CI: −0.03–0.35) more REC than combination therapy. However, no statistically significant difference was observed between the two treatment groups, with moderate heterogeneity observed among the included trials (I^2 = 44%). Subgroup analyses did not show statistically significant differences.

3.3. Radiographic examinations

Six studies conducted radiographic examinations to measure improvements in defect depth in millimeters (mm) (Fig. 5a). One study also assessed the enhancement of defect area in percentage (%) (Fig. 5b) [31]. Pooled estimates using a random-effects model indicated that combining EMD with bone grafts resulted in a 0.80 mm increase in bone defect depth compared to EMD alone, with a statistically significant difference. There was no heterogeneity observed among the included trials (I^2 = 3%). In subgroup analysis, combination therapy involving alloplastic bone grafts showed a significant treatment effect, demonstrating a 0.88 mm difference (95% CI: 0.62–1.14) compared to EMD

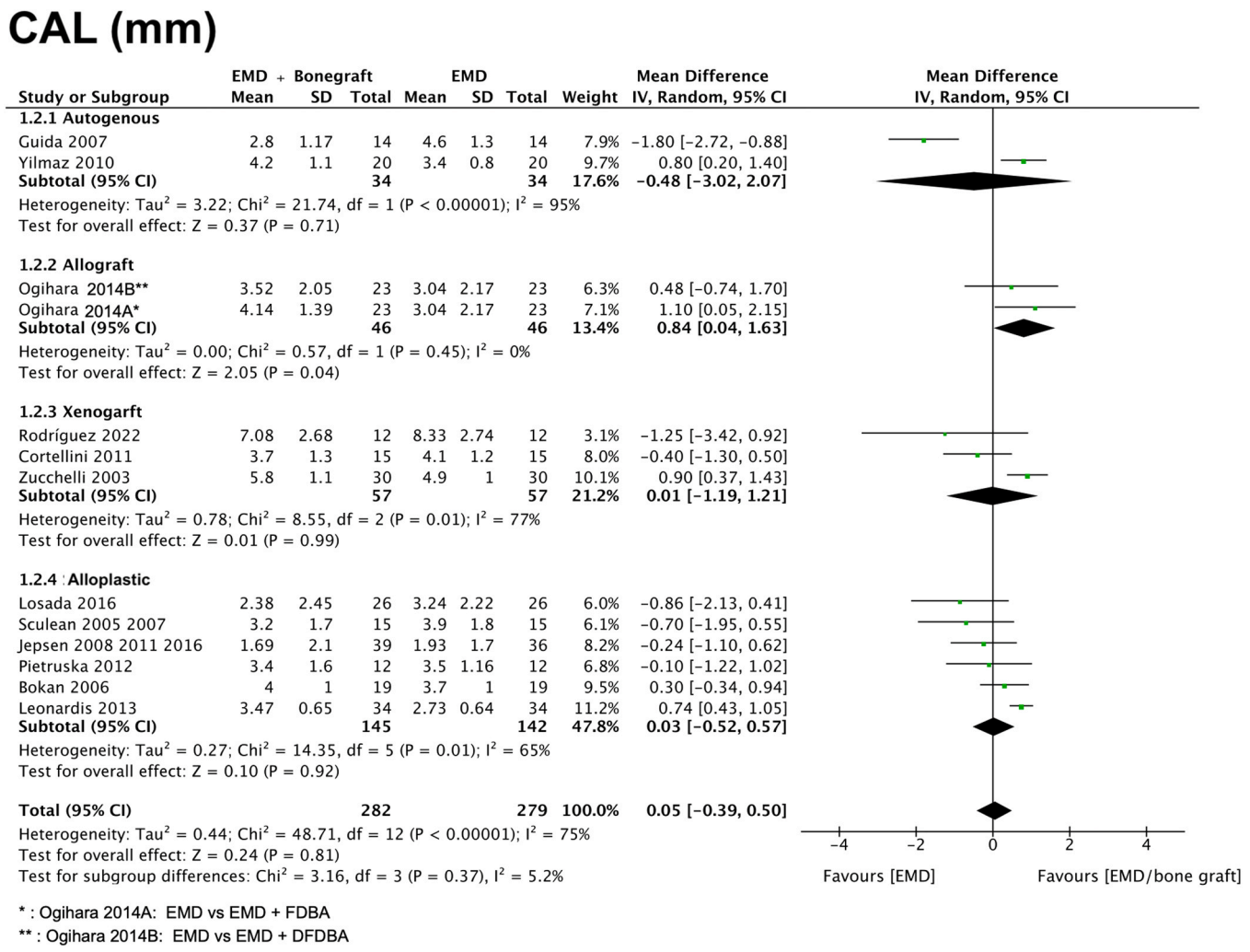


Fig. 3. Forest plot of clinical attachment level (CAL) gain in mm.

monotherapy. The combined M-MIST + EMD approach did not show additional benefits over EMD monotherapy in defect depth (Fig. 5a). Similar results were observed in bone defect fill with area percent (Fig. 5b).

3.4. Risk of bias assessment

The Cochrane Collaboration tool was used to evaluate the risk of bias in the articles included in this review (Fig. 6). While most items received a rating of "low risk of bias," the lack of information regarding blinding for participants and personnel resulted in an "unclear" assessment for this item across all studies. Owing to the nature of dental treatment, blinding in this context was challenging. Studies that used coin toss randomization were rated as having a high risk of bias for both randomization and allocation concealment. In summary, the aggregated evidence suggested a moderate risk of bias.

4. Discussion

This updated systematic review assessed the 12-month efficacy of combination therapy based on a meta-analysis of current RCTs. The limited number of relevant articles evaluating 12-month postoperative outcomes may challenge discerning differences in efficacy between EMD alone and combination therapy, but a meta-analysis synthesizing multiple studies should be a reasonable approach. The findings indicated that while periodontal tissue evaluations, including PD, CAL, and REC, showed no significant differences between EMD monotherapy and combination therapy, incorporating bone grafts enhanced radiographic filling of bone defects.

The introduction of various bone graft materials, such as autogenous, allograft, xenograft, and alloplastic options, underscores the dynamic nature of clinical interventions in EMD combination therapy. Subsequently, subgroup analyses based on bone graft types revealed distinct outcomes in radiographic defect fill. Autogenous bone has an osteoconductive effect, serving as a scaffold for osteoblasts to produce new bone, and may also possess osteogenic properties, promoting the proliferation and differentiation of osteoprogenitor cells [54,55]. While autogenous bone has been considered the gold standard for bone replacement, the results of this meta-analysis demonstrated that the efficacy of combined treatment (EMD and autogenous bone graft) is limited only for reducing PD. For other outcomes, no superior effect of combined therapy was observed, and the CIs for each outcome were large. These findings are attributed to imprecision stemming from the limited number of included bone defects. In this review, we included only two trials involving autogenous bone grafts [27,30], reflecting the scarcity of evidence on this topic and necessitating tentative conclusion regarding the efficacy of autogenous bone. Alloplastic bone exhibited some effectiveness in defect fill, whereas the other three types did not demonstrate discernible impact. Specifically, a commercial alloplastic bone material containing 60% hydroxyapatite and 40% β-TCP (Straumann® BoneCeramic) showed positive results in defect fill [34,37], likely due to the low resorption characteristic of hydroxyapatite. While

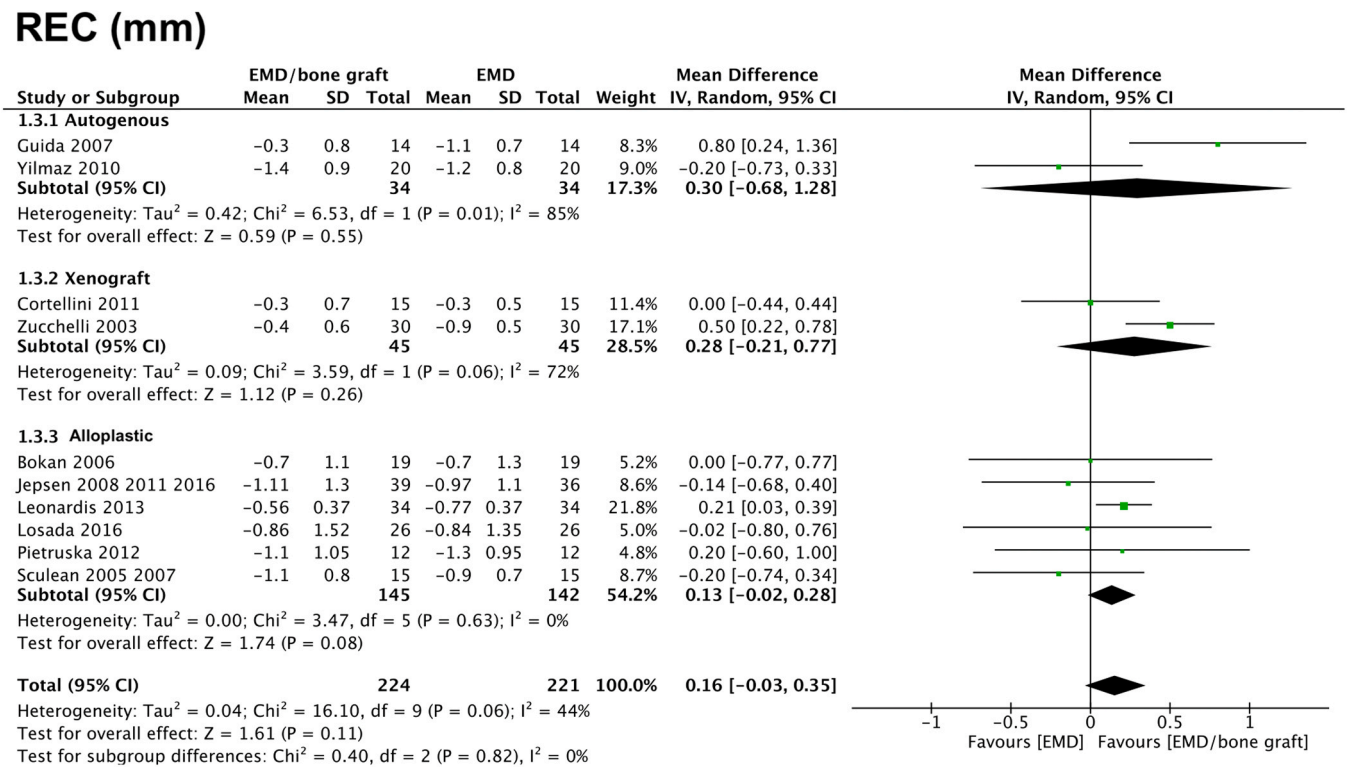


Fig. 4. Forest plot of gingival recession (REC) increase in mm.

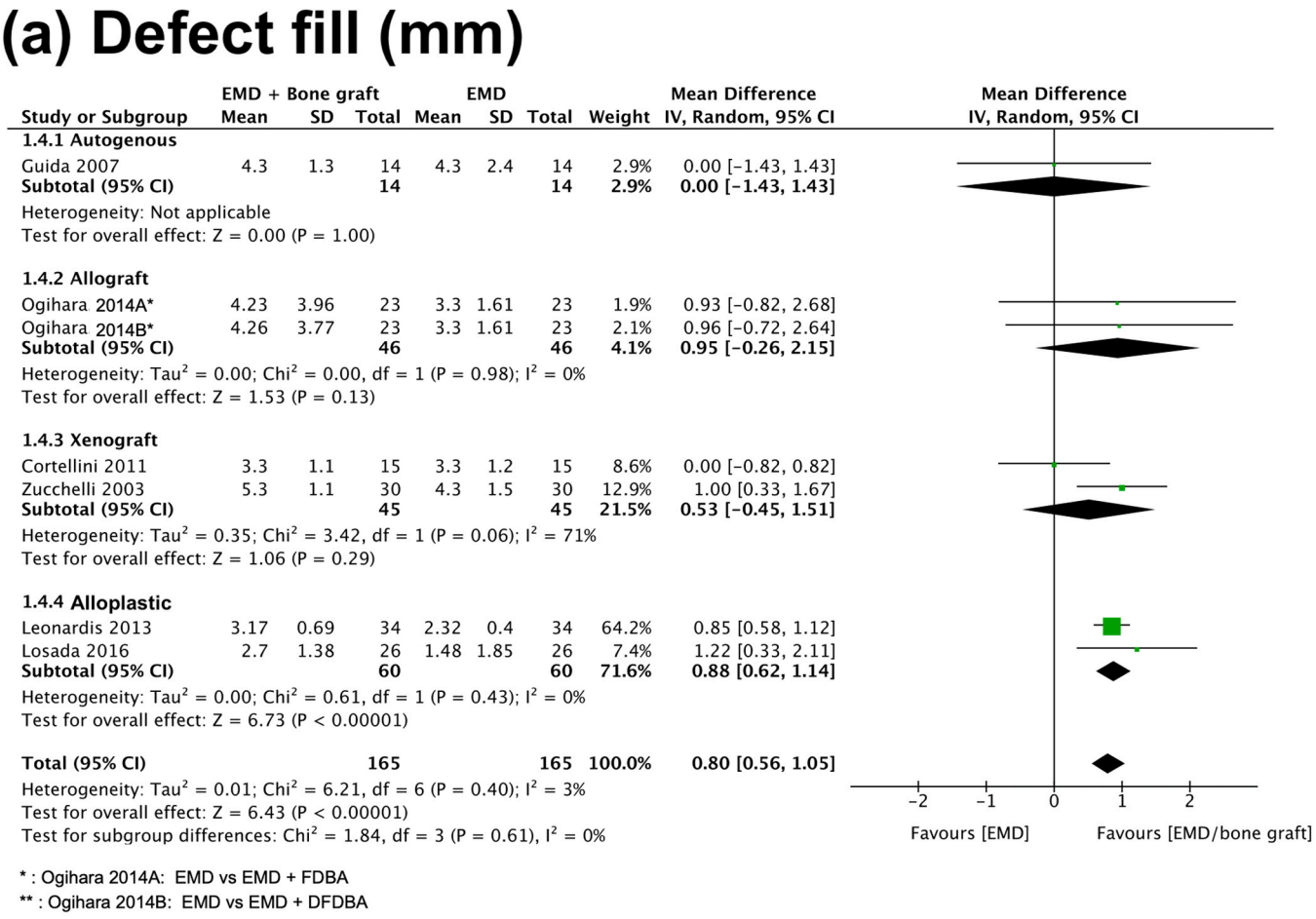
the primary objective of combination therapy is to preserve space for regeneration, clinicians sometimes combine bone grafts with EMD to prevent post-healing gingival recession. They contend that bone grafts can act as a rigid barrier, which prevents the collapse of interdental soft tissues into the intrabony defect before their integration and eventual replacement by new bone. This approach is believed to mitigate soft tissue margin recession. However, our pooled results did not confirm the effectiveness of this combined approach in preventing gingival recession.

Previous reviews provided a foundation for comprehending the effectiveness of EMD combination therapy [18,19]. However, the temporal gap since the last comprehensive review necessitates an update to capture the latest evidence. By synthesizing data from studies conducted until January 2024, this review offers a contemporary perspective, meeting the demand for regularly updated systematic reviews in the field. Another methodological difference between previous systematic reviews and this is the follow-up duration. Previous systematic reviews included studies with varying follow-up periods [18,19]. While a 6-month period aligns with the biological viewpoint of achieving active wound healing, clinicians often find this duration insufficient for thorough reevaluation. Conversely, longer follow-ups may lead to patient withdrawal. Considering these factors, we opted for a 12-month follow-up period, deemed most suitable for a comprehensive evaluation. Hence, the observed heterogeneity in this meta-analysis stemmed from variables such as bone defect morphology, severity, flap design, and surgical technique, with the observation period exerting a minimal impact.

Despite the superior outcomes demonstrated by alloplastic materials, it is crucial to acknowledge the potential biological complications associated with their use. Previous reports have documented root resorptions following hydroxyapatite grafts [56,57], alongside instances of ankylosis and infection associated with non-resorbable hydroxyapatite, suggesting that non-resorbable materials may be etiological factors for recurrent periodontitis [58,59]. Therefore, emphasizing the adoption of resorbable bone materials capable of replacing woven bone over time is crucial. However, some studies suggest that slowly resorbing biomaterials may delay, interfere with, or even obstruct bone formation [60,61] and periodontal wound healing/regeneration [62], compromising space provision due to their slow biodegradation rates. The biodegradation of implanted biomaterials may interfere with local bone formation and maintenance. Therefore, a comprehensive understanding of the potential complications associated with different bone graft materials is essential for making informed clinical decisions and achieving optimal patient outcomes.

Systematic reviews of RCTs provide high-certainty evidence, yet their applicability in clinical settings can be limited towing to significant indirectness. Occasionally, findings from alternative study designs, such as cohort studies, may offer more applicable relevance, albeit with higher inherent risk of bias. In 2023, Matsuura et al. conducted a 3-year cohort study evaluating the efficacy of combining autogenous bone grafts with EMD for treating intrabony defects, specifically focusing on the defect angles [63]. The findings aligned with those of this review, indicating that bone grafts did not significantly enhance clinical outcomes compared to EMD monotherapy. Nevertheless, in cases where the bone defect angle exceeded 40°, bone grafts notably augmented the reduction in radiographic bone defect depth. This study underscores specific scenarios where combining bone grafts with EMD may enhance effectiveness, suggesting a tailored approach to periodontal regenerative therapy based on the bone defect angle. Currently, detailed evidence regarding the impact of nuanced bone morphology on treatment outcomes is limited. Further studies are essential to validate these preliminary findings.

In the evaluation of xenograft, the trial employing EMD + DBBM in conventional flap surgery demonstrated statistical differences in PD, CAL, and REC [24], whereas trials with MIST did not demonstrate any significant differences [31,38]. Recently, novel minimally invasive periodontal regenerative techniques have emerged, emphasizing the complete preservation of marginal tissue to achieve and sustain primary closure above the applied regenerative material during critical healing phases. The designed flaps aim for passive primary closure and excellent



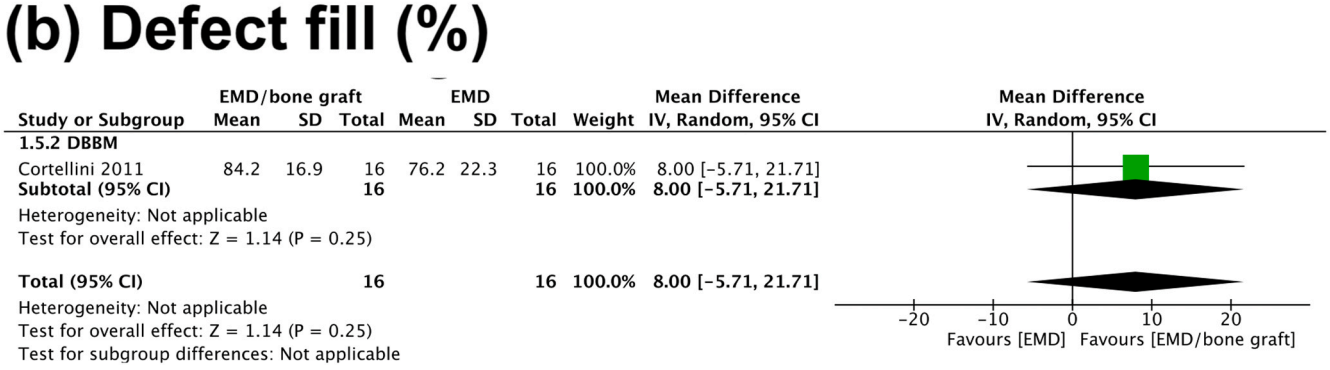


Fig. 5. Forest plot of radiographic examination: (a) Defect fill in millimeters. (b) Defect fill in percentage.

wound stability, potentially eliminating the need for additional bone grafts, even in complex non-contained bone defects when EMD is used.

Tu et al. conducted a network meta-analysis (NMA) of RCTs to assess whether combining EMD with other regenerative materials produces superior outcomes compared to using EMD alone [45]. NMA represents an advancement over traditional meta-analyses by exploring multiple treatments comprehensively rather than solely comparing relevant treatment alternatives pairwise. Their literature search included studies published until December 2008, focusing on changes in PD, CAL, and defect depth as measured outcomes. Our findings generally aligned with their results, which presented both NWA and conventional meta-analyses. The analysis provided limited evidence supporting the additional benefits of combining EMD with other regenerative materials. Notably, combination with DBBM exhibited the most significant treatment effects when examined separately. However, it is crucial to acknowledge the significant limitations of NMA, particularly regarding the assumption of transitivity. This assumption validates indirect comparisons using a shared comparator, and if compromised, it can introduce bias, potentially skewing analytical outcomes. Recognizing and addressing this limitation is essential for accurately interpreting NMA results. Given the heterogeneity of surgical interventions in periodontal research, NMA should not be indiscriminately applied to periodontal clinical questions at this stage.

This study had some limitations. First, inconsistencies in study design and surgical procedures among the included trials could introduce risk factors for conceptual heterogeneity. Second, there was a moderate risk of bias across the studies. Blinding and allocation concealment were particularly challenging owing to the nature of the

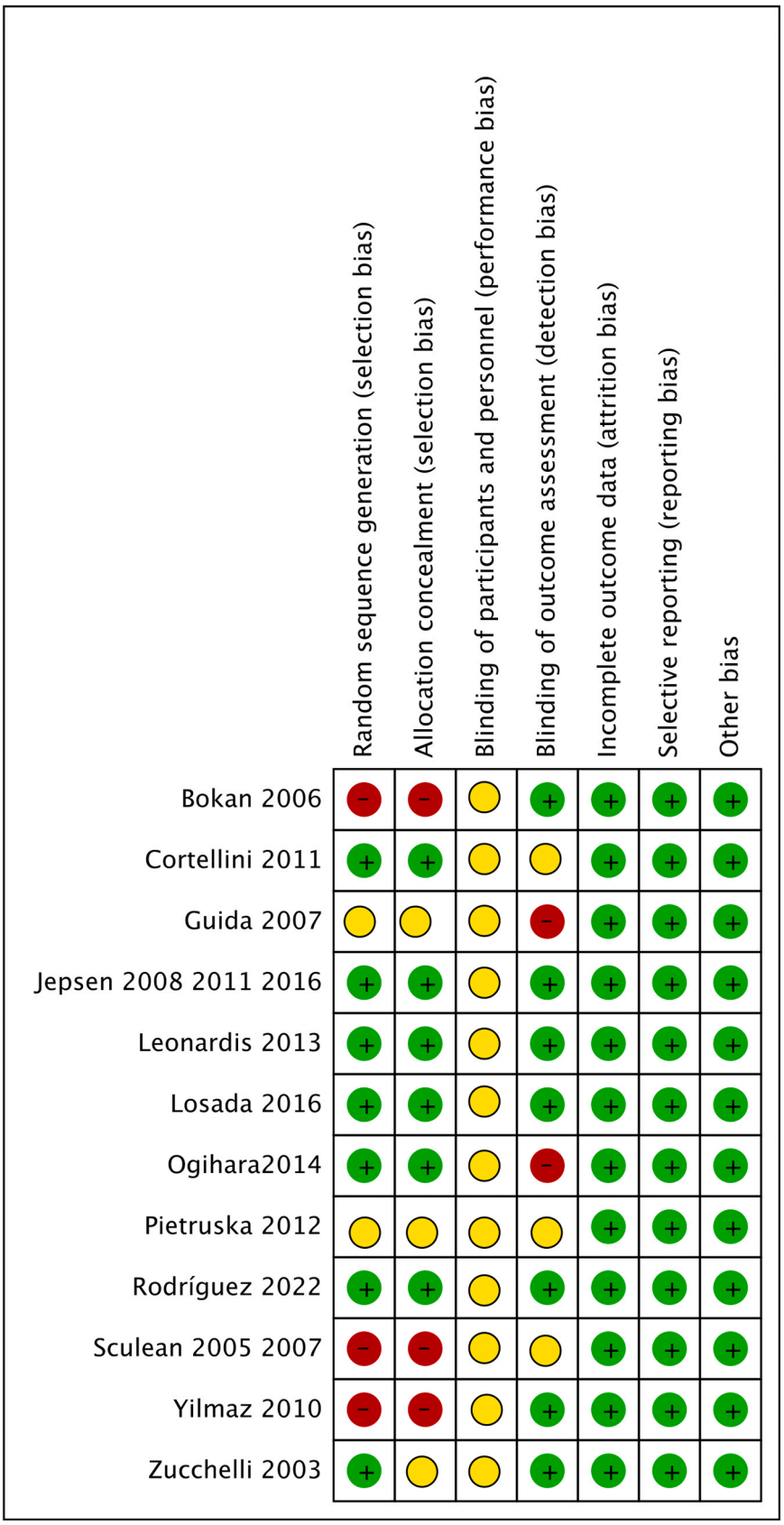


Fig. 6. Risk of bias of the studies included in this review: the green symbol represented a low risk of bias, whereas the yellow symbol represented a high risk of bias.

surgical treatment, potentially introducing inherent bias into our analysis. It is difficult to blind the adjunct use of grafting material, which may result in a high risk of performance bias. Lastly, the authors provided limited information regarding the defect configuration, such as the number of defect walls, defect depth, and radiographic angulation. To address these challenges, future research should prioritize standardized methodologies to enhance the overall robustness of the evidence base.

5. Conclusion

This systematic review indicates that adding bone grafts to EMD does not provide additional benefits in periodontal tissue examination, with improvement observed only in radiographic defect fill. This finding contributes to ongoing discussions in the field and guides clinicians toward evidence-based decisions for achieving optimal periodontal outcomes, emphasizing the judicious use of bone grafts.

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Conflict of interests

None.

Data Availability

The data was extracted from the already published RCTs and therefore the directly accessible through the meta-analysis in this review.

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None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jdsr.2024.08.001.

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