



Enamel Matrix Derivatives (EMD) Alone Versus EMD Combined with Bone Grafting in Periodontal Intrabony Defects: An Umbrella Review

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Abstract

Objectives: The aim of this umbrella review was to evaluate whether the combination of enamel matrix derivatives (EMD) with bone grafts provides additional clinical benefits compared with the use of EMD alone in the treatment of periodontal intrabony defects.

Materials and Methods: An umbrella review was conducted according to PRIOR and PRISMA 2020 recommendations. A comprehensive search was performed in PubMed/MEDLINE, Cochrane Library, ScienceDirect, Google Scholar, and Mendeley Search for systematic reviews published between 2009 and 2025. Reviews comparing EMD alone versus EMD combined with bone grafts in human intrabony periodontal defects were included. Methodological quality was assessed using AMSTAR 2, and risk of bias was evaluated using the ROBIS tool.

Results: Six systematic reviews, with or without meta-analysis, were included. Overall, the findings suggested a slight advantage for the combination therapy (EMD + bone graft), particularly regarding clinical attachment level gain and probing pocket depth reduction. However, the observed differences were quantitatively modest and heterogeneous across studies. Methodological appraisal revealed very low overall confidence and a high risk of bias in most included reviews.

Conclusions: The adjunctive use of bone grafts with EMD may provide limited additional clinical benefits compared with EMD alone in periodontal intrabony defects. Nevertheless, the current evidence remains methodologically weak, requiring cautious interpretation.

Clinical Relevance: Although EMD combined with bone grafts may enhance regenerative outcomes in some clinical situations, the magnitude of benefit appears limited, and treatment decisions should be individualized according to defect morphology and clinical context.

Keywords: Enamel Matrix Derivatives; Bone Grafting; Periodontal Regeneration; Intrabony Defects; Periodontitis; Umbrella Review

Introduction

Periodontitis is a chronic inflammatory disease characterized by the progressive destruction of tooth-supporting tissues, including alveolar bone, periodontal ligament, and root cementum. Intrabony defects represent one of its most challenging clinical manifestations due to their variable morphology.

Periodontal regeneration aims to restore these lost structures by promoting the formation of a new functional attachment. In this context, enamel matrix derivatives (EMD) have significantly transformed regenerative strategies by stimulating cementum formation and periodontal ligament organization. In parallel, bone grafting biomaterials provide mechanical support by stabilizing the blood clot and maintaining space for regeneration.

The combination of EMD with bone grafting is based on a biologically plausible rationale, integrating biological stimulation with structural support. However, despite numerous studies and systematic reviews, findings remain heterogeneous, with some reporting significant benefits and others suggesting only marginal clinical relevance.

To date, no umbrella review has comprehensively synthesized this evidence while assessing its methodological robustness. Therefore, the aim of this study was to evaluate, through an umbrella review, the clinical effectiveness of EMD used alone compared with EMD combined with bone grafting in the treatment of periodontal intrabony defects.

Materials and Methods

Study design

This study was conducted as an umbrella review (overview of systematic reviews), aiming to synthesize and critically analyze evidence from systematic reviews, with or without meta-analysis, on a specific clinical topic.

The objective was to evaluate the clinical effectiveness of enamel matrix derivatives (EMD) used alone compared with EMD combined with bone grafting in the treatment of periodontal intrabony defects.

Only published systematic reviews were included, without direct inclusion of primary clinical trials, allowing a hierarchical overview of the available evidence and identification of consistencies, discrepancies, and methodological limitations.

The study was conducted and reported in accordance with the PRIOR 2022 checklist [1].

Study period

The study was conducted between July 2025 and April 2026, including protocol registration (INPLASY2025120103), literature search, study selection, methodological assessment (AMSTAR 2 and ROBIS), and data synthesis.

The publication period of included reviews ranged from January 2009 to September 2025.

Search strategy

A systematic and reproducible literature search was performed to identify relevant systematic reviews on EMD alone or combined with bone grafting in intrabony defects.

The following databases were searched: PubMed/MEDLINE, Cochrane Library, ScienceDirect, and Google Scholar. Additional searches were conducted using Mendeley and by screening reference lists of included studies.

The search strategy combined free-text terms, MeSH terms, and Boolean operators, adapted to each database.

Eligibility criteria

Inclusion criteria

Systematic reviews meeting the following criteria were included:

- Systematic reviews with or without meta-analysis published between January 2009 and September 2025;
- Studies involving patients with periodontal intrabony defects;
- Reviews comparing enamel matrix derivatives (EMD) alone versus EMD combined with bone grafting;
- Reviews based on human clinical studies with a minimum follow-up of 6 months;
- Articles published in English or French.

Exclusion criteria

The following were excluded:

- Primary studies (e.g., randomized controlled trials, cohort studies, case reports);
- Narrative or non-systematic reviews (e.g., scoping reviews, editorials);
- In vitro, animal, or peri-implantitis studies;
- Reviews without a direct comparison between EMD alone and EMD combined with bone grafting;
- Studies with follow-up <6 months or outside the scope of periodontal intrabony defect regeneration.

Literature search methodology

- Study selection was performed independently by two reviewers (M.T., B.E.), with disagreements resolved by discussion or consultation with a third reviewer (E.Z.). The selection process was reported using a PRISMA 2020 flow diagram [6].
- A systematic search was conducted across PubMed/MEDLINE, Cochrane Library, ScienceDirect, and Google Scholar, supplemented by Mendeley and manual reference screening.
- The PubMed search combined a broad strategy to maximize sensitivity and a narrow strategy to improve specificity by restricting searches to title/abstract fields and systematic reviews.
- Search strategies across databases used combinations of keywords related to enamel matrix derivatives (EMD), bone grafting, periodontal intrabony defects, and study design (systematic reviews and meta-analyses), combined with Boolean operators (AND, OR).
- Search filters were applied when appropriate to refine results according to study design and relevance.

Study selection process

All identified references were imported into Zotero®, and duplicates were removed prior to screening.

Study selection was conducted in a stepwise manner according to predefined eligibility criteria:

Title screening: Irrelevant records were excluded based on titles.

- **Abstract screening:** Remaining records were assessed for eligibility based on study design, population, intervention, and comparison.
- **Full-text screening:** Potentially eligible articles were reviewed in full to confirm inclusion and document reasons for exclusion.

Critical analysis of included systematic reviews

- The methodological quality of the included systematic reviews was assessed using the AMSTAR 2 tool [3].
- AMSTAR 2 is a validated instrument comprising 16 items designed to evaluate the methodological quality of systematic reviews, with response options of “Yes”, “Partial Yes”, and “No”.
- The assessment was performed independently by two reviewers (M.T., B.E.), with disagreements resolved by consensus.
- The overall confidence in each review was determined based on the seven critical domains of AMSTAR 2: protocol registration, adequacy of the search strategy, justification of excluded studies, risk of bias assessment, appropriateness of meta-analytical methods, consideration of risk of bias in interpretation, and assessment of publication bias.
- Based on these criteria, reviews were classified into four levels of confidence: high, moderate, low, or critically low.

Data extraction and narrative synthesis

A narrative synthesis was conducted to summarize and compare the findings of the included systematic reviews.

Extracted data included study characteristics (author, year, search period), number and type of included studies, samples sizes, interventions, quality assessment tools, analytical methods, main outcomes, and clinical implications.

Results

Study identification

A total of 1,402 records were identified through database searches. After duplicate removal, 618 unique records remained for screening.

Detailed results of the search strategy are presented in Figure 1–6.

Study selection

After title screening of 618 records, only 14 articles were considered potentially relevant. Following abstract screening, 5 articles were excluded. Full-text evaluation led to the exclusion of 3 reviews due to inappropriate design or lack of direct comparison between EMD alone and EMD combined with bone grafting (Table 1).

At the end of the selection process, six systematic reviews, with or without meta-analysis, were included in the final dataset.

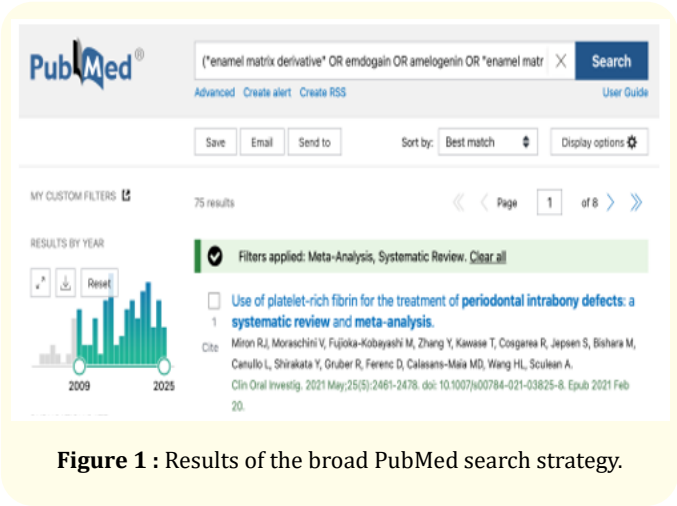


Figure 1 : Results of the broad PubMed search strategy.

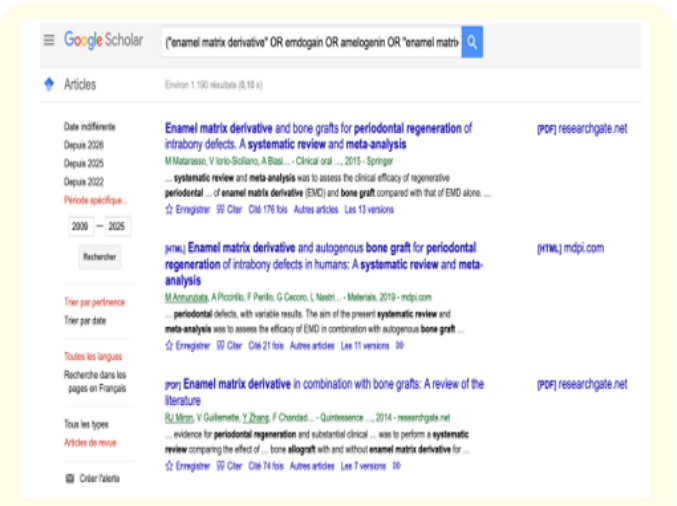


Figure 4: Results of the Google Scholar search strategy.

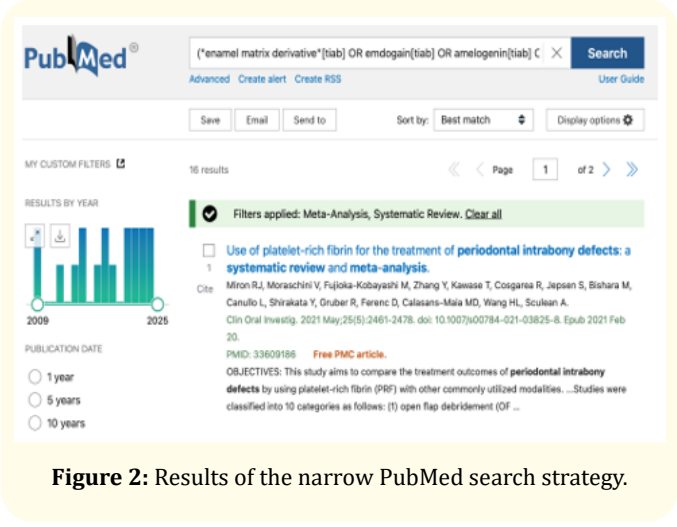


Figure 2: Results of the narrow PubMed search strategy.

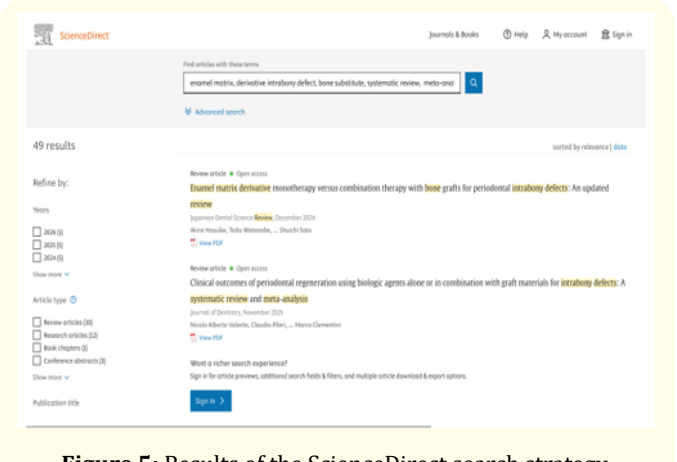


Figure 5: Results of the ScienceDirect search strategy.

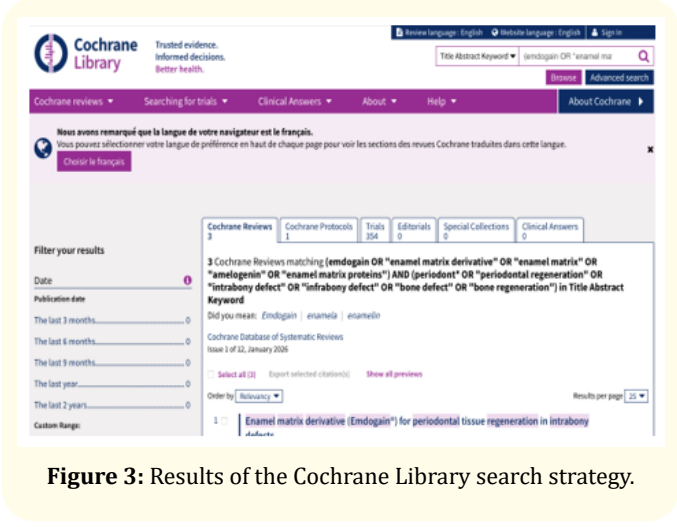


Figure 3: Results of the Cochrane Library search strategy.

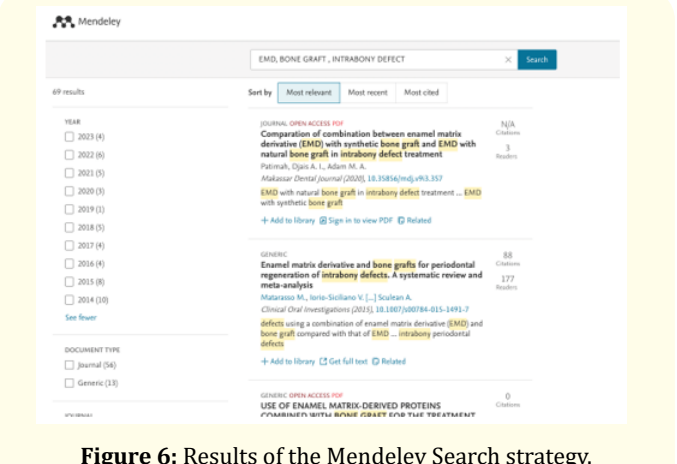


Figure 6: Results of the Mendeley Search strategy.

Author (year)	Title	Reason for exclusion
Koop., <i>et al.</i> 2012	Periodontal Regeneration with Enamel Matrix Derivative in Reconstructive Periodontal Therapy	Systematic review evaluating the effectiveness of EMD in various regenerative indications, without a structured direct comparison between EMD alone and EMD combined with bone grafting in intrabony defects. Heterogeneity of interventions and absence of a targeted comparative analysis corresponding to the PICO question.
Kao., <i>et al.</i> 2015	Periodontal Regeneration – Intrabony Defects	Review derived from an AAP workshop including multiple regenerative approaches (GTR, biomaterials, EMD, and combination therapies). Does not constitute a specific comparison between EMD alone versus EMD combined with bone grafting and includes interventions outside the scope defined by the inclusion criteria.
Bud., <i>et al.</i> 2025	Bony Defect Regeneration in Periodontitis	Review focused on the use of enamel matrix derivative proteins across different clinical contexts. Absence of a direct comparison between EMD alone and EMD combined with bone grafting in human intrabony defects; therefore, it does not strictly meet the comparative framework defined in the umbrella review.

Table 1: Excluded systematic reviews and reasons for exclusion.

The study selection process is illustrated in a PRISMA 2020 flow diagram (Figure 7).

Characteristics of included systematic reviews

A total of six systematic reviews, with or without meta-analysis, were included in the present umbrella review (Table 2).

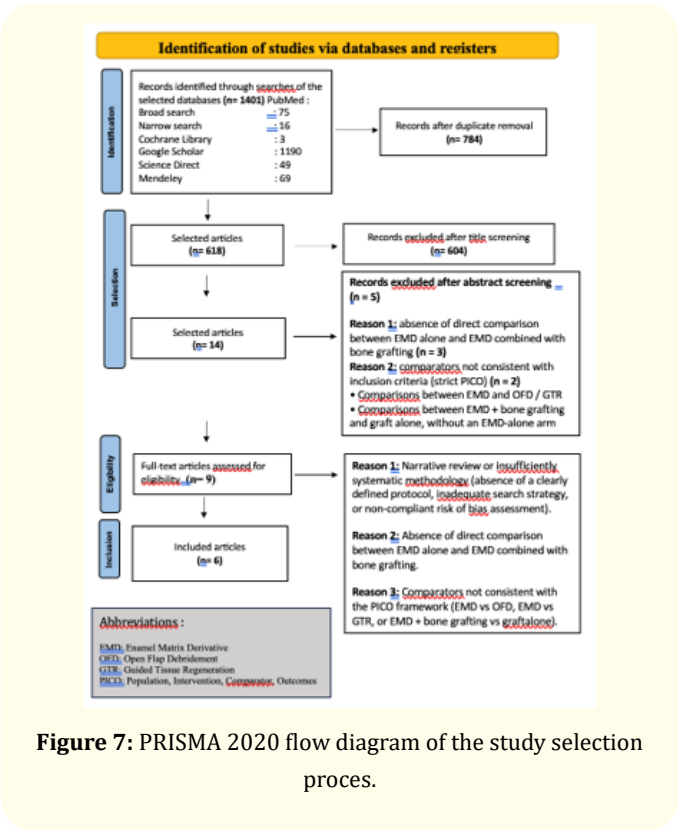


Figure 7: PRISMA 2020 flow diagram of the study selection proces.

Authors	Year	Title of Systematic Re-view	Journal
Tu., <i>et al.</i> (2010) [7]	2010	Do bone grafts or barrier membranes provide additional treatment effects for infrabony lesions treated with enamel matrix derivatives? A network meta-analysis of randomized-controlled trials	Journal of Clinical Periodontology
Li., <i>et al.</i> (2012) [8]	2012	The efficacy of enamel matrix derivative in the treatment of periodontal intrabony defects: a meta-analysis	Journal of the American Dental Association
Matarasso., <i>et al.</i> (2015) [9]	2015	Enamel matrix derivative and bone grafts for periodontal regeneration of intrabony defects: a systematic review and meta-analysis	Clinical Oral Investigations

Liu., <i>et al.</i> (2017) [10]	2017	Effect of enamel matrix derivative combined with bone grafts in the treatment of periodontal intrabony defects: a systematic review and meta-analysis	International Journal of Periodontics and Restorative Dentistry
Annunziata., <i>et al.</i> (2019) [11]	2019	Enamel matrix derivative combined with autogenous bone graft in the treatment of periodontal intrabony defects: a systematic review and meta-analysis	Materials (Basel)
Hasuike., <i>et al.</i> (2024) [12]	2024	Clinical outcomes of enamel matrix derivative alone versus in combination with bone grafts in periodontal intrabony defects: a systematic review and meta-analysis	Japanese Dental Science Review

Table 2: Included systematic reviews.

The included reviews reported a defined search period, although timeframes and databases varied across studies. While no explicit language restrictions were reported in the reviews, all included studies were in English. We noted a substantial variability in graft types, clinical outcomes, and statistical methods.

The main characteristics of the included systematic reviews are summarized in Tables 3 and 4, which present the bibliometric and PICO features of the studies, respectively.

Methodological quality assessment of included systematic reviews (AMSTAR 2)

The methodological quality of the included systematic reviews was assessed using the AMSTAR 2 tool [3]. Assessments were performed independently by two reviewers (M.T., B.E.), and disagreements were resolved by consensus (Table 5).

Authors	Year/Journal	Country	Type of Review	Search Period	Number of Included Studies	Study Design	Quality Assessment Tool	Comparison	Type of Grafts Evaluated	Follow-up
Tu., <i>et al.</i> [7]	2010/ Journal of Clinical Periodontology	UK/Europe	Network meta-analysis (NMA)	1996–2008	28	RCTs	NR	EMD vs EMD + BG	Mixed (autogenous, xenogeneic, alloplastic, membranes)	≥ 6 months
Li., <i>et al.</i> [8]	2012/Journal of the American Dental Association (JADA)	China/Asia	Meta-analysis (MA)	1950 – Sept 30, 2011	11	RCTs	Internal criteria derived from Cochrane Handbook	EMD vs EMD + BG	Mixed (autogenous, xenogeneic, alloplastic)	≥ 6 months
Matarasso., <i>et al.</i> [9]	2015/Clinical Oral Investigations	Italy–Switzerland/ Europe	Systematic review and meta-analysis	Up to Feb 2014	12	RCTs + CCTs	Cochrane Collaboration Risk of Bias Tool	EMD vs EMD + BG	Mixed (autogenous, xenogeneic, alloplastic)	6–24 months

Liu., <i>et al.</i> [10]	2017/International Journal of Periodontics and Restorative Dentistry (IJPRD)	China/Asia	Systematic review and meta-analysis	Up to Nov 2015	9	RCTs	Cochrane-based internal criteria	EMD vs EMD + BG	Alloplastic only	≥ 6 months
Annunziata., <i>et al.</i> [11]	2019/Materials (Basel)	Italy/Europe	Systematic review and meta-analysis	Up to Feb 2019	3	RCTs	Modified Van der Weijden., <i>et al.</i> (2009) criteria	EMD vs EMD + BG	Autogenous only	≥ 6 months
Hasuike., <i>et al.</i> [12]	2024/Japanese Dental Science Review	Japan/Asia	Systematic review and meta-analysis	Up to Jan 2024	15	RCTs	Cochrane Risk of Bias Tool (RoB)	EMD vs EMD + BG	Mixed (autogenous, allogeneic, xenogeneic, alloplastic)	12 months

Table 3: Bibliometric characteristics of included systematic reviews.

Abbreviations:

NMA: Network Meta-Analysis; SR: Systematic Review; MA: Meta-Analysis; RCTs: Randomized Controlled Trials; CCTs: Controlled Clinical Trials; NR: Not Reported; EMD: Enamel Matrix Derivative; BG: Bone Graft.

Systematic Review	Population	Intervention (Exposure)	Comparison	Outcomes	Conclusion
Tu., <i>et al.</i> (2010) [7]	Patients with periodontitis presenting periodontal intrabony defects, included in randomized controlled trials evaluating periodontal regenerative approaches	Surgical regenerative treatment of intrabony defects using enamel matrix derivatives (EMD)	Surgical regenerative treatment using EMD combined with bone grafting	Clinical and radiographic outcomes: clinical attachment level (CAL) gain, probing depth (PD) reduction, and bone fill	The combination of EMD with bone grafting may provide additional clinical benefits compared with EMD alone; however, the magnitude of this effect remains modest and varies depending on treatment modalities
Li., <i>et al.</i> (2012) [8]	Patients with periodontitis presenting intrabony defects, included in randomized controlled trials evaluating regenerative approaches	Surgical regenerative treatment using EMD combined with bone grafting	Use of EMD alone without bone grafting	Clinical and radiographic outcomes: CAL gain, PD reduction, and bone fill	The combination of EMD with bone grafting shows a statistically significant but clinically limited advantage over EMD alone, with heterogeneous results across included studies

Matarasso, <i>et al.</i> (2015) [9]	Patients with periodontitis presenting intrabony defects, included in interventional clinical studies	Surgical regenerative treatment using EMD combined with bone grafting	Treatment using EMD alone without bone grafting	Clinical and radiographic outcomes: CAL gain, PD reduction, and bone fill	The combination of EMD with bone grafting may improve certain periodontal clinical parameters compared with EMD alone; however, the magnitude of benefit remains limited and results should be interpreted cautiously due to methodological heterogeneity
Liu, <i>et al.</i> (2017) [10]	Patients with periodontitis presenting intrabony defects, included in randomized controlled trials evaluating regenerative treatments	Surgical regenerative treatment using EMD combined with alloplastic materials	Use of EMD alone without alloplastic materials	Clinical and radiographic outcomes: CAL gain, PD reduction, and bone fill	The combination of EMD with alloplastic materials may provide additional clinical benefits compared with EMD alone; however, the effect size remains limited and results should be interpreted with caution due to study heterogeneity
Annunziata, <i>et al.</i> (2019) [11]	Patients with periodontitis presenting intrabony defects, included in randomized controlled trials	Surgical regenerative treatment using EMD combined with autogenous bone graft	Treatment using EMD alone without autogenous graft	Clinical and radiographic outcomes: CAL gain, PD reduction, and bone fill	The combination of EMD with autogenous bone graft may improve certain clinical parameters, particularly CAL gain; however, results should be interpreted cautiously due to the limited number of included studies and methodological limitations
Hasuike, <i>et al.</i> (2024) [12]	Patients with periodontitis presenting intrabony defects, included in randomized controlled trials evaluating regenerative approaches	Surgical regenerative treatment using EMD combined with bone grafting	Use of EMD alone without bone grafting	Clinical and radiographic outcomes: CAL gain, PD reduction, and bone fill	The combination of EMD with bone grafting may provide additional clinical benefits compared with EMD alone; however, the magnitude of this effect remains modest and conclusions should be interpreted with caution due to methodological heterogeneity and study limitations

Table 4: PICO characteristics of included systematic reviews.

Systematic Review	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Overall Quality
Tu, <i>et al.</i> (2010) [7]	Y	N	N	N	Y	Y	N	Y	PY	N	Y	Y	Y	Y	N	Y	Critically low
Li, <i>et al.</i> (2012) [8]	Y	PY	N	N	Y	Y	Y	Y	PY	N	Y	N	Y	Y	N	Y	Critically low
Matarasso, <i>et al.</i> (2015) [9]	Y	PY	N	N	Y	Y	N	Y	PY	N	N	Y	Y	Y	N	Y	Critically low
Liu, <i>et al.</i> (2017) [10]	Y	PY	N	N	N	Y	N	Y	PY	N	Y	N	N	Y	N	Y	Critically low
Annunziata, <i>et al.</i> (2019) [11]	Y	PY	N	N	N	Y	Y	Y	N	N	Y	N	N	N	N	Y	Critically low
Hasuike, <i>et al.</i> (2024) [12]	Y	PY	N	N	Y	Y	Y	Y	PY	N	Y	N	N	N	N	Y	Critically low

Table 5: Methodological quality assessment of the included systematic reviews according to AMSTAR 2.

Abbreviations:
Y: Yes
N: No
PY: Partial Yes.

Individual study analysis

A detailed critical analysis of the included systematic reviews was performed using AMSTAR 2, focusing on key methodological strengths and limitations across critical domains (Table 5).

Tu YK., et al. (2010) [7]

This review demonstrated some methodological strengths, including the use of appropriate statistical methods (Item 11) and partial assessment of risk of bias with consideration in result interpretation (Items 9 and 13).

However, several critical limitations were identified, notably the absence of protocol registration (Item 2), an incomplete search strategy (Item 4), lack of transparency regarding excluded studies (Item 7), and no assessment of publication bias (Item 15). These shortcomings are particularly concerning in the context of a network meta-analysis, where unaccounted bias may lead to overestimation of treatment effects.

Overall confidence: critically low.

Li X., et al. (2012) [8]

This review showed some methodological strengths, including predefined (but unregistered) protocol, independent study selection and data extraction, appropriate statistical analysis, and consideration of risk of bias in result interpretation (Items 2, 5, 6, 11, and 13).

Nevertheless, key limitations were identified, notably an incomplete search strategy (Item 4), absence of publication bias assessment (Item 15), and partial risk of bias evaluation (Item 9), which may affect the validity of the findings.

Overall confidence: critically low.

Matarasso S., et al. (2015) [9]

This review showed some methodological strengths, including adherence to PRISMA guidelines, use of a predefined (but unregistered) protocol, appropriate statistical analysis, and consideration of risk of bias in interpretation (Items 2, 11, and 13).

However, key limitations were identified, notably an incomplete search strategy (Item 4), lack of transparency regarding excluded studies (Item 7), partial risk of bias assessment (Item 9), and

absence of publication bias evaluation (Item 15), which may affect the validity of the findings.

Overall confidence: critically low.

Liu Y., et al. (2017) [10]

The main methodological strength was the use of appropriate statistical methods for meta-analysis (Item 11).

However, a number of critical limitations were observed, including an inadequately described and unregistered protocol (Item 2), an incomplete search strategy (Item 4), lack of transparency regarding excluded studies (Item 7), partial risk of bias assessment (Item 9), absence of risk of bias consideration in interpretation (Item 13), and no evaluation of publication bias (Item 15). These shortcomings substantially affect the validity of the findings.

Overall confidence: critically low.

Annunziata M., et al. (2019) [11]

This review showed some methodological strengths, including appropriate statistical analysis, clear reporting of included and excluded studies, and a partially predefined protocol based on PICO criteria (Items 11, 7, and 2).

However, several critical limitations were identified, notably an incomplete search strategy (Item 4), absence of risk of bias assessment (Item 9), lack of consideration of bias in result interpretation (Item 13), and no evaluation of publication bias (Item 15). These methodological weaknesses considerably reduce the reliability of the findings.

Overall confidence: critically low.

Hasuike H., et al. (2024) [12]

Several methodological strengths were identified, including protocol registration (Item 2), appropriate statistical analysis (Item 11), and transparent reporting of excluded studies (Item 7).

However, key limitations were identified, notably an incomplete search strategy (Item 4), partial risk of bias assessment (Item 9), lack of bias consideration in interpretation (Item 13), and absence of publication bias evaluation (Item 15). This significant weakness may affect the validity of the results.

Overall confidence: critically low.

This review nevertheless appears to be the most methodologically robust among those included in the present analysis, notably due to prior protocol registration and greater transparency in the study selection process.

Overall Synthesis of AMSTAR 2 assessment

All included systematic reviews were rated as having critically low confidence according to AMSTAR 2, due to recurrent weaknesses in key domains, including lack of protocol registration, incomplete search strategies, absence of publication bias assessment, and inadequate consideration of risk of bias in result interpretation.

These methodological limitations compromise the validity and reliability of the findings. Although some reviews demonstrated strengths, particularly in statistical analysis, these were insufficient to offset deficiencies in critical domains.

These findings highlight the need for more rigorous systematic reviews, including protocol registration, comprehensive search strategies, and systematic assessment and integration of bias in the interpretation of results.

To complement the methodological assessment, the ROBIS tool was also used, with results presented in Table 6.

Systematic Review	Domain 1: Eligibility Criteria	Domain 2: Identification and Selection	Domain 3: Data Collection and Risk of Bias in Primary Studies	Domain 4: Synthesis and Presentation	Overall Risk of Bias
Tu., <i>et al.</i> (2010) [7]	Low	High	High	High	High
Li., <i>et al.</i> (2012) [8]	Low	High	Unclear	High	High
Matarasso., <i>et al.</i> (2015) [9]	Low	High	Unclear	High	High
Liu., <i>et al.</i> (2017) [10]	Low	High	High	High	High
Annunziata., <i>et al.</i> (2019) [11]	Low	High	High	High	High
Hasuike., <i>et al.</i> (2024) [12]	Low	High	Unclear	High	High

Table 6: Risk of bias assessment of the included systematic reviews using the ROBIS tool.

Risk of bias assessment (ROBIS)

Overall, all included systematic reviews were judged to be at high risk of bias according to the ROBIS tool [4]. While most reviews showed low risk in Domain 1 (eligibility criteria), substantial concerns were identified in Domains 2, 3, and 4, particularly regarding study selection, data collection and risk of bias assessment in primary studies, and the synthesis and presentation of results (Table 6).

These findings are consistent with the AMSTAR 2 assessment, reinforcing concerns about the methodological robustness and reliability of the available evidence.

Discussion

Before analyzing clinical outcomes, the findings of this umbrella review should be interpreted within the biological and biomechanical framework of periodontal regeneration.

Periodontal regeneration is a multifactorial process influenced by site biology, clot stability, defect morphology, and patient-related factors [13]. Enamel matrix derivatives (EMD) act as biological modulators by promoting periodontal ligament cell activity and new attachment formation [14-16]. In contrast, bone grafts mainly provide mechanical support through clot stabilization and space maintenance [13,17].

Thus, the combination of EMD with bone grafting reflects a complementary approach, integrating biological stimulation with structural support. However, this does not necessarily imply a consistent synergistic effect, as the benefit of grafting largely depends on defect morphology. Contained three-wall defects may respond well to EMD alone, whereas non-contained one- or two-wall defects may benefit from additional mechanical support.

Moreover, bone grafting involves increased biological, surgical, and financial costs, which should be considered when evaluating the overall benefit–risk ratio.

Accordingly, a key question arises: “Does the combination of EMD with bone grafting provide a clinically meaningful advantage over EMD alone, or is the observed benefit modest and context-dependent?”

Analysis of clinical outcomes

Clinical Attachment Level (CAL) Gain

CAL gain is a key parameter for assessing periodontal regeneration, reflecting functional attachment restoration [15,16].

Most selected meta-analyses (Tu., *et al.* [7], Li., *et al.* [8], Matarasso., *et al.* [9], Annunziata., *et al.* [11], and Hasuike., *et al.* [12]) reported a statistically significant additional CAL gain with EMD combined with bone grafting. This gain generally ranged from 0.5 to 1.0 mm, with substantial variability. In contrast, Liu., *et al.* [10] reported inconsistent or non-significant differences.

This variability is largely explained by differences in defect morphology, baseline defect depth, surgical techniques, and biomaterials. Contained three-wall defects may achieve favorable outcomes even with EMD alone, whereas non-contained defects may benefit more from grafting.

Overall, the available evidence suggests a modest and context-dependent benefit rather than a consistent clinical advantage.

Analysis of probing pocket depth (PPD) Reduction

PPD reduction is a key clinical parameter reflecting both inflammation resolution and periodontal tissue improvement.

Three studies (Tu., *et al.* [7], Li., *et al.* [8], and Matarasso., *et al.* [9]) reported a statistically significant additional reduction with EMD combined with bone grafting, generally ranging from 0.5 to 1.0 mm. Similar findings were reported by Hasuike., *et al.* [12], although with considerable heterogeneity among the selected clinical trials. In contrast, Annunziata., *et al.* [11] and Liu., *et al.* [10] found limited or non-significant differences.

This variability is mainly explained by differences in baseline pocket depth, treatment protocols, and measurement techniques. Importantly, PPD reduction is strongly influenced by initial pocket depth, which may introduce interpretation bias.

Moreover, PPD is a non-specific parameter affected by factors such as inflammation reduction, soft tissue changes, and probing variability, and does not necessarily reflect true periodontal regeneration.

Overall, although statistically significant, the additional PPD reduction remains modest and clinically limited, suggesting no consistent superiority of the combined approach.

Analysis of bone gain

Bone gain is a complex outcome to interpret, as radiographic bone fill does not necessarily reflect true periodontal regeneration.

A number of studies suggest a trend in favor of EMD combined with bone grafting, with increased radiographic bone fill reported in several reviews (Matarasso., *et al.* [9], Annunziata., *et al.* [11], and Hasuike., *et al.* [12]). However, other reviews (Liu., *et al.* [10], Tu., *et al.* [7], and Li., *et al.* [8]) reported inconsistent or non-significant differences.

This variability is largely explained by differences in imaging techniques, measurement methods, biomaterials, and baseline defect characteristics. In addition, the lack of standardized assessment methods and absence of histological validation limit the reliability of these findings.

Importantly, radiographic bone fill may reflect biomaterial presence rather than true functional regeneration, potentially leading to overestimation of treatment effects.

Overall, despite a favorable radiographic trend, the evidence remains heterogeneous and does not support a clear biological or functional superiority of the combined approach.

Methodological analysis

Analysis of primary studies

The interpretation of findings from the included systematic reviews must be considered in light of the primary studies on which they are based, as their validity depends on study quality and comparability [22].

A major limitation is the substantial clinical heterogeneity across studies, involving differences in populations, interventions, and outcome assessments [23]. In particular, defect morphology, one of the main prognostic factors, is often inconsistently reported despite its strong influence on regenerative outcomes.

Contained three-wall defects generally show more predictable results, whereas non-contained defects may benefit from additional mechanical support. This suggests that the observed advantages of combined therapy may reflect defect selection rather than true treatment superiority.

Further heterogeneity arises from variations in surgical techniques (conventional versus minimally invasive), biomaterials used, and follow-up duration, all of which can significantly influence outcomes. In addition, differences in measurement methods may introduce bias, particularly for CAL and PPD assessments.

Overall, these sources of heterogeneity limit the comparability of studies and may influence the reported treatment effects.

Analysis of systematic reviews

The critical evaluation of the included systematic reviews using AMSTAR 2 [3] and ROBIS [4,5] revealed recurrent methodological weaknesses that may affect the validity and robustness of the findings.

Most reviews lacked protocol registration [31], comprehensive search strategies including grey literature [22], assessment of publication bias, and adequate consideration of the risk of bias of primary studies in result interpretation [32]. These limitations affected several critical AMSTAR 2 domains (Items 2, 4, 9, 13, and 15), leading to overall low to critically low confidence, while ROBIS consistently indicated a high risk of bias.

Among these issues, the absence of publication bias assessment is particularly concerning, as it may lead to overestimation of treatment effects, especially when statistically significant studies are preferentially published [22,33,34]. This limitation is especially relevant in the present context, where observed effects are small and may therefore be easily overestimated.

Furthermore, the lack of systematic integration of risk of bias in the interpretation of findings reduces the reliability of conclusions and may lead to misleading interpretations [32].

Overall, these methodological limitations substantially reduce confidence in the available evidence and support a cautious interpretation of the reported findings.

Should the results be discarded in light of methodological limitations?

Although most included systematic reviews were rated as having critically low confidence, this does not imply that their findings should be discarded. Rather, it indicates that the estimated effects are uncertain and potentially influenced by bias [3,35].

Despite these limitations, a certain consistency across meta-analyses suggests a possible therapeutic signal in favor of the combined approach, although insufficient to support strong conclusions. Importantly, these limitations primarily concern the methodology of the reviews rather than the intrinsic validity of all primary studies.

Therefore, a binary interpretation should be avoided. Instead, the findings should be interpreted critically, considering their consistency, biological plausibility, and level of certainty.

Taken together, the available evidence should not be rejected but cautiously interpreted within the context of its methodological limitations.

Strengths, limitations, and future perspectives

Strengths

- This umbrella review provides a comprehensive and hierarchical synthesis of systematic reviews comparing EMD alone versus EMD combined with bone grafting.
- Methodological rigor was ensured through prior protocol registration [31], adherence to PRIOR guidelines [1], and the combined use of AMSTAR 2 [3] and ROBIS [4] for quality and bias assessment.
- In addition, a systematic search across multiple databases optimized both sensitivity and specificity, strengthening the reliability of the evidence synthesis [37].

Limitations

- The main limitation lies in the dependence on the methodological quality of the included reviews, most of which were rated as having critically low confidence [3,4,20].
- Potential overlap of primary studies across reviews may have led to data redundancy [38].

- Furthermore, substantial clinical heterogeneity related to defect morphology, biomaterials, surgical techniques, and follow-up duration limits the generalizability of the findings [13,15].
- Finally, language restriction may have introduced selection bias [39].

Future perspectives

Despite these limitations, this review highlights a modest but consistent trend favoring the combined approach, although with low certainty [19,32].

Future research should focus on:

- Well-designed and standardized randomized clinical trials [15]
- High-quality systematic reviews with protocol registration and bias assessment [22,31,33,35]
- Stratified analyses based on defect characteristics and patient-related factors

Advances in biomaterials and tissue engineering may further improve personalized regenerative approaches [14,16].

Conclusion

Current evidence does not support the systematic superiority of the combined approach but rather suggests a modest and context-dependent effect influenced by defect morphology, mechanical stability, and patient-related factors. On the other hand, these reviews should not be rejected, but interpreted with caution in light of their methodological limitations.

Therefore, clinical decision-making should rely on an individualized approach integrating biological principles, clinical context, and the benefit–risk ratio.

Future research should focus on well-designed and standardized clinical trials, as well as high-quality systematic reviews, to strengthen the evidence base.

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Registration

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Data Availability

No new datasets were generated or analyzed during the current study. This umbrella review was based exclusively on data from previously published studies.

Author Contributions

M.T. contributed to the study conception and design, literature search, study selection, data extraction, methodological assessment, data analysis, and manuscript drafting. B.E.H. contributed to study supervision, methodological guidance, interpretation of the findings, and critical revision of the manuscript. J.K. contributed to study supervision, interpretation of the findings, and critical revision of the manuscript. All authors reviewed and approved the final manuscript.

Competing Interests

The authors declare that they have no competing interests.

Ethics Approval

Ethical approval was not required for this study because it is an umbrella review based exclusively on previously published literature.

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