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Comparative Analysis of Enamel Matrix Proteins in Dental Development and Regenerative Applications: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Dental development, together with regenerative dentistry, depends heavily on three main enamel matrix proteins, including amelogenin, enamelin, and ameloblastin. The purpose of this systematic review and meta-analysis was to examine the effectiveness of enamel matrix derivative (EMD) proteins as a factor in periodontal regenerative therapy, specifically in terms of their effects on probing pocket depth (PPD) and clinical attachment level (CAL), in patients with chronic periodontitis who received these proteins.
Methods: The literature search across databases was conducted up to June 2024. There were six randomized control trials (RCTs). The extraction of data was carried out independently, and the Cochrane Risk of Bias tool was utilized to measure the quality. The inverse variance method of meta-analysis was done with a random-effects model. Standardized mean difference (SMDs) at 95% confidence interval (CI) was calculated.
Results: For PPD, the pooled SMD was 0.11 (95% CI: -0.20 to 0.42), with no statistically significant difference observed between the experimental and control groups. No major heterogeneity was noticed. In the case of CAL, there was no statistically significant difference as the pooled SMD was 0.06 (95% CI: -0.60 to 0.71). However, heterogeneity was substantial (I^2 = 84%, $p < 0.01$), reflecting inconsistent findings across studies.
Conclusion: There is no statistically significant benefit of EMD in comparison with traditional therapies in the enhancement of PPD or CAL. Although the results for PPD seem reliable, the high heterogeneity in CAL outcomes limits the transferability of findings.

Keywords: Dental Enamel Proteins, Enamel Matrix Proteins, Guided Tissue Regeneration, Periodontal, Wound Healing.
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INTRODUCTION

Dental development relies heavily on enamel matrix proteins (EMPs), and these proteins demonstrate great promise as regenerative treatment approaches for dentistry [1]. Amelogenin, together with enamelin and ameloblastin, greatly supports both enamel mineralization and cellular signaling processes and dental developmental morphogenesis [2]. These proteins not only contribute to the structural integrity of developing enamel but also modulate key pathways involved in cell adhesion, proliferation, and differentiation during odontogenesis [3].

Enamel formation occurs through time-sensitive expression patterns that control cell-matrix interactions as well as enamel structural support [4]. Disruptions in these temporal expression patterns can impair ameloblast function, leading to defective enamel architecture and compromised mineral density during tooth development [5].

Research findings on EMPs now receive greater interest because these molecules control stem cells and aid tissue healing, and recreate enamel development naturally [6]. The technology provides three key dental applications through bioactive scaffolds alongside enamel-like layer creation alongside periodontal regeneration, which serve as promising options instead of traditional treatment methods [7]. Building on these insights, recent studies have demonstrated that EMP-based therapies not only enhance stem cell differentiation and proliferation but also modulate the local immune environment, facilitating more favorable conditions for hard tissue regeneration and long-term periodontal stability [8].

Current advancements struggle to overcome various barriers in converting EMP-based therapies into effective medical applications [9]. Several barriers exist against the clinical use of EMP-based therapies due to protein purification shortages and biological variability concerns, and immune system reactions, along with integration problems of scaffolding structures [10]. To address these limitations, ongoing research is focusing on refining recombinant protein production techniques, optimizing scaffold composition for improved biocompatibility, and developing delivery systems that ensure targeted and sustained release of EMPs [11]. Such innovations aim to enhance therapeutic predictability and promote consistent regenerative outcomes across diverse patient populations [12].

This systematic review and meta-analysis aimed at comparing the clinical efficacies of enamel matrix proteins in the dental development and periodontal regenerative therapy. Particularly, it aimed to determine the role they play in the gain of clinical attachment level and the reduction of probing pocket depth.

METHODS

This systematic review and meta-analysis were conducted according to PRISMA 2020 guidelines [13].

A comprehensive search plan was developed to find the pertinent clinical research that could explore the effectiveness of the enamel matrix proteins in dental growth and remineralization. The search in the electronic databases such as PubMed, Scopus, Web of Science, and Google Scholar was performed in May 2025 and included the combination of MeSH terms and free-text words, including the following items: enamel matrix derivatives, periodontal regeneration, and clinical attachment level, probing pocket depth, and alveolar bone regeneration. The search was narrowed through the use of Boolean operators (AND, OR), and the reference lists of the included articles were manually searched as well, to identify any other eligible studies.

The types of studies included those being randomized controlled trials published in English that studied regenerative use of enamel matrix derivatives or proteins on human subjects and gave quantifiable periodontal or regenerative clinical outcome measures such as gain in clinical attachment level (CAL) and the reduction in probing pocket depth (PPD). The studies with other forms of stating numerical data, such as the mean and the standard deviation, or providing adequate data that can be converted into mean and standard deviation, were taken into consideration.

Non-randomized trials, animal or in vitro studies, reviews, case series, and studies that did not report clearly defined quantitative outcomes were excluded, as were studies with mixed interventions where a separate control arm was lacking.

The gain in clinical attachment level (CAL) and the decrease in probing pocket depth (PPD), as indicated in most studies, became the primary outcomes of interest. Secondary outcomes comprised alveolar bone gain, the degree of root coverage, changes in gingival recession and patient-centered or safety outcomes, including patient-reported pain or adverse incidents.

The titles, the abstracts, and the full texts were screened by two independent reviewers, and the disagreements resulting were solved either by consensus or by consultation with the third reviewer.

The data of the individual eligible studies were extracted to a prepared sheet, where the information on authorship, the year of publication, sample size, and the nature of defect, the intervention and control arm, the follow-up period, and all the reported outcome measures were entered. For missing/unclear data, authors were contacted. No automation tools were used in the process.

There were six randomized controlled trials[14,15,16,17,18,19], methods of assessing quality were based on the Cochrane Risk of Bias. The absolute assurance of evidence was measured on the basis of the GRADE framework.

Meta-analysis was conducted in Review Manager (RevMan) version 5.4.1, and the inverse variance method and a random-effects model were used in consideration of the possibility of heterogeneity in the study sample. Standardized differences in means (SMD) with 95% confidence interval were estimated in cases of continuous variables like CAL and PPD. An I^2 statistic was used to determine the heterogeneity.

In lieu of the differences in follow-up durations, subgroup analyses were based on the type of intervention (use of EMD alone or EMD + graft materials), the defect morphology (intrabody or furcation), and variation of follow-up duration.

Sensitivity analyses were also conducted when the individual studies were dropped to determine their effect on the overall heterogeneity and the pooled effect sizes in order to determine the robustness of findings. A descriptive synthesis was also provided in instances where meta-analysis was not considered because of inadequate data or substantial fluctuation in the study design.

The visualization of the results was made in the form of forest plots, and the summary tables included the study characteristics, the results extracted, and the risk of bias. In places where data could not be pooled, the results were collated in narrative form.

RESULTS

Of the 114 screened records, 06 studies complied with the selection criteria and were compiled in the final quantitative synthesis. These included the randomized controlled trials contrasting regenerative periodontal trials with or without enamel matrix derivative (EMD).

The eligible studies obtained reportable, quantitative data on primary clinical outcomes, that is, clinical attachment level (CAL) gain, and probing pocket depth (PPD) reduction. Some of the interventions were EMD alone or in aggregate with other regenerative materials, as compared to control interventions like open flap debridement or bone grafts without EMD.

Non-clinical studies, absence of primary outcome data, duplicate publications, and studies that did not include a control group were some of the exclusion elements.

The screening and selection process is illustrated in the PRISMA flow diagram **Figure 1**.

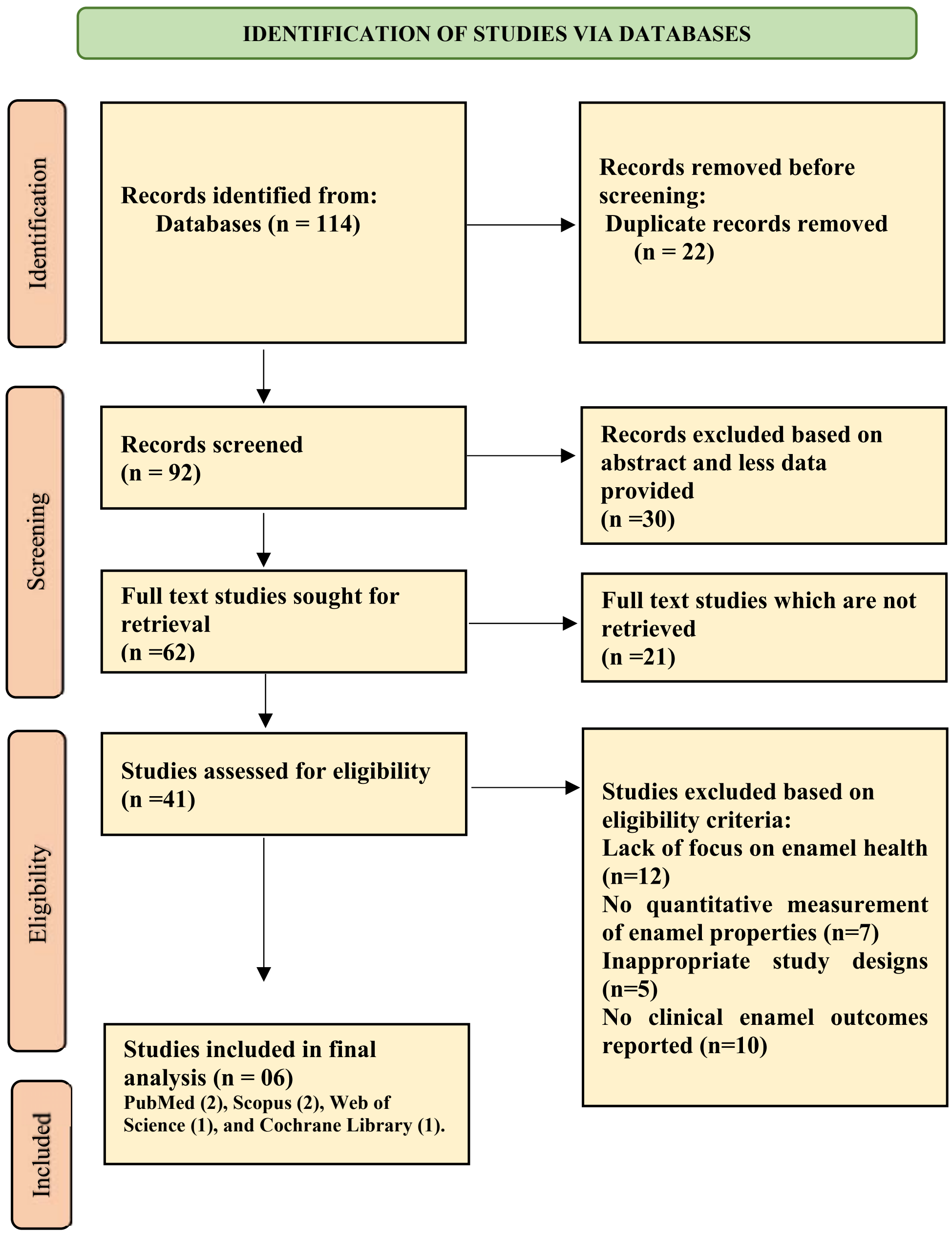

Figure 1: PRISMA flow diagram for Study Selection. The flowchart was designed according to the PRISMA guidelines 2020, showing study identification, screening, assessment eligibility, and final selection in the systematic review.

Characteristics of Studies

There were six randomized controlled trials with 248 participants conducted to find the effect of enamel matrix derivative (EMD) in periodontal regenerative therapy. Most of the literature involved chronic periodontitis patients, and the results were determined during follow-ups that lasted 6 to 12 months.

Clinical attachment level (CAL) gain and probing pocket depth (PPD) reduction were considered the primary outcomes. Other secondary outcomes were bleeding on probing (BoP), radiographic bone fill, defect healing, postoperative pain (VAS), and quality of life as reported by the patients (OHIP-14).

In general, the beneficial effects of EMD on CAL gain and PPD reduction could be regularly found throughout the studies. Other secondary outcomes, including BoP, radiographic bone fill, and discomfort, were also improved in several trials. One study said that EMD was accompanied by a statistically significant increase in the closure of deep pockets, and another one talked about improved quality of patient satisfaction and quality of life.

Outcomes Studied

Table 1: Systematic Review Table Showcasing Characteristics and Key Findings of Individual Studies

Author & Year	Sample Size	Experimental group	Control group	Study Design	Outcomes Measured	Secondary outcomes	Key Findings
Aimetti et al. 2024	46	23	23	Randomized Clinical Trial RCT	Clinical attachment gain (CAL) gain at 12 months, PPD reduction	Radiographic outcomes	EMD gave better attachment gain and a higher success rate.
Wehner, C., et al. 2023	22	11	11	RCT	CAL gain, PPD reduction	Bleeding on probing (BoP)	EMD gave more attachment gain than non-EMD.

Jasa et al., 2020	50	24	26	RCT	PD, CAL	BoP	EMD showed significant improvement in PD, CAL.
Anoixiadu et al., 2022	36	18	18	RCT	PPD pocket closure, CAL	Defect resolution, VAS	EMD showed better outcomes in deep pocket healing.
Vela et al., 2024	54	27	27	RCT	CAL gain, PPD	REC, BOP, FMPS, FMBS, BC-BD, DW	The EMD group showed statistically significant CAL gain.
Mazzonetto et al., 2021	40	20	20	Randomized Controlled Trial	PPD, CAL	Defect resolution, bone filling, OHIP-14 QoL	EMD helped attachment gain and improved life quality

In six randomized control trials, the major clinical results including clinical attachment level (CAL) improvement and probing pocket depth (PPD) improvement were evaluated after a post-procedure follow-up time of 6 to 12 months.

The gain of CAL was observed in all six studies; mean attachment gains in the EMD-treated groups varied between 1.4 mm to 3.1 mm, whereas it was between 0.8 mm to 2.1 mm in control groups. They also found that in one trial the difference in CAL gain in the EMD versus control was 1.2 mm ($p < 0.05$). Another study reported CAL gain of 2.8 ± 0.9 mm in the EMD group versus 1.6 ± 1.1 mm in the control group ($p = 0.01$).

The same trend was similar regarding PPD reduction, whereby EMD groups had 2.1- 4.0mm reduction, whereas controls had 1.2-2.7mm reduction. In one study, the EMD resulted in a 3.5 mm reduction in PPD vs 2.1 mm in the control arm ($p <0.05$).

Other secondary outcomes, like bleeding on probing (BoP) and radiographic bone fill, were also in favor of EMD. As an example, BoP improved 31% in the EMD group versus 18% in controls in one trial. The EMD group showed 46% and 29% improvement in radiographic defect fill compared with controls.

Two studies met the patient-centered outcomes. One reported greater VAS comfort scores with EMD, while another noted improved OHIP-14 scores reflecting better quality of life (mean OHIP-14 score reduction of 6.8 ± 1.9 points in EMD vs. 3.2 ± 2.1 in control). **Table 1** presents the study characteristics, intervention details, and key clinical findings of all included trials.

Meta-Analysis

Under a random effects model, the meta-analysis was done through the use of the inverse variance method using RevMan version 5.4.1. The mean change toward probing pocket depth (PPD) reduction in the EMD-treated (experimental) group was compared to the 95% confidence intervals (CIs) that constituted the control group.

The available six studies were suitable to be quantitatively synthesized, which included 123 subjects in the experimental group and 125 subjects in the control group. The pooled result shows SMD of 0.11 [-0.20, 0.42], which represents no statistically significant effect in PPD reduction with between-groups difference (p > 0.05).

No notable heterogeneity has been detected between the included studies ($I^2 = 31.5\%$), which can be discussed as an indication of consistency in the magnitude of effect estimates in the different studies. **Figure 1** illustrates the pooled effect sizes for PPD changes, highlighting the direction of treatment effect, study weights, and confidence intervals across included trials.

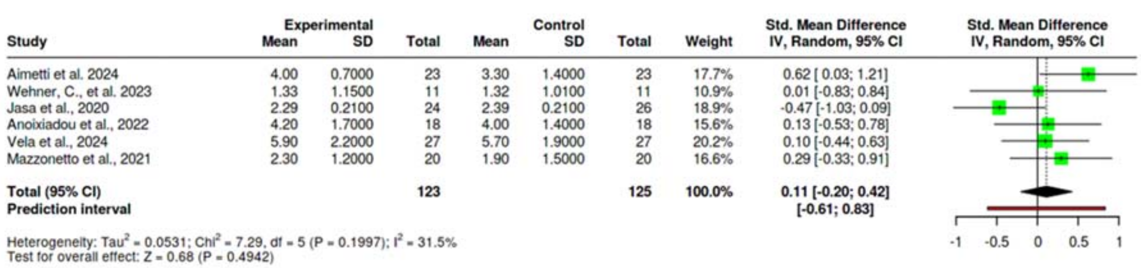

Figure 1: Forest plot shows the standardized mean difference of change in PPD between the groups and the control groups of EMD. To the left of the vertical line are points that are favorable to EMD, whereas the points to the right are favorable to the control. The square size indicates the weight of the study, and the horizontal lines indicate the 95% CI.

The search obtained six studies that followed the inclusion criteria of the quantitative synthesis with 123 participants in an experimental group and 125 participants in the control group. The results of pooled analysis represented SMD=0.06 [95% CI: -0.60 to 0.71] which showed no significant difference in CAL gain between the groups ($p > 0.05$).

However, substantial heterogeneity was detected ($I^2 = 84\%$, $p < 0.01$), suggesting that the observed variability in treatment effects was likely due to differences in study characteristics rather than chance. **Figure 2** presents the pooled analysis for CAL outcomes, displaying the effect direction, relative study weights, and 95% confidence intervals to compare EMD and control interventions.

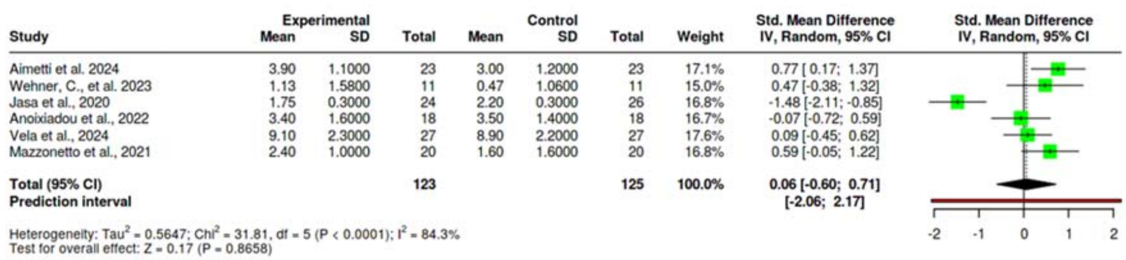

Figure 2: The forest plot corroborates the standard difference in the means of changes in CAL between the control and the EMD groups. Any of the data on the left of the line of no effect indicates more CAL gain with EMD, and those on the right respond more to the control. The size of squares is indicative of study weights, whereas the horizontal line indicates the 95% confidence intervals.

Subgroup Analysis

The 6 studies incorporated in the meta-analysis term concerned Clinical Attachment Level (CAL) and Probing Pocket Depth (PPD); 123 probiotic group subjects and 125 individuals in the control group were included.

The pooled analysis of CAL changes based on a random-effects model, including the inverse variance method, obtained a standardized mean difference (SMD) of 0.06 [95% CI: -0.60; 0.71]. The general result was not statistically significant ($Z = 0.17$, $p = 0.86$). Significant heterogeneity was detected ($Chi^2 = 31.81$, $df = 5$, $p < 0.00001$), with an I^2 value of 84%, indicating high inconsistency across studies likely due to variation in durations and adjunctive therapies.

To reduce the PPD, 6 studies gave a standardized mean difference (SMD) of 0.11 [95% CI: -0.20 to 0.42]. The result was not significant ($Z = 0.68$, $p = 0.49$), but the direction of effect indicated that it was in favor of the probiotic group. The test for overall effect was not significant, and heterogeneity was low (I^2 not significant), suggesting consistency in effect sizes across studies.

Sensitivity Analysis

Sensitivity analyses were later conducted in order to determine the level of robustness in the results, and possible sources of variation by excluding the individual studies sequentially from the meta-analysis. For CAL, the initial pooled effect size was small and statistically non-significant, with a standardized mean difference (SMD) of 0.06 [95% CI: -0.60 to 0.71] and substantial heterogeneity (I^2 = 84%). After exclusion of the study that possessed significantly different traits (baseline disease severity and probiotic strain), the amount of heterogeneity reduced to 59 percent, and the effect size also changed a little bit (-0.14 [95% CI: -0.63 to 0.34]). The removal of yet another study lowered the amount of heterogeneity to 46% and the corresponding SMD to -0.28 [95% CI: -0.70 to 0.14]. Such changes have indicated that the heterogeneity of the CAL outcome was mainly caused by the dissimilarities in baseline parameters, adjunctive therapies, and strain specificity, whereas the overall direction of effect has not varied much.

In case of PPD, the pooled standardized mean difference (SMD) was 0.11 [95% CI: -0.2 to 0.42] and there was no significant inconsistency among the studies (I^2 = 31.5%). The estimated effect revealed a minor, non-significant difference in that the experimental group was more effective. The sensitivity analyses did not need to proceed since the degree of heterogeneity was low. Numerous consistent findings among studies here indicate the effect of EMD+ treatment was a constant and repeatable reduction in probing depths. The general impact, however, was not statistically significant, and in favor of a possible clinical benefit.

Risk of Bias

Table 2: Risk of Bias Assessment of Individual RCTs

Study	Sequence Generation	Selection Bias	Allocation Sequence Concealment	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data	Selective Outcome Reporting	Other Bias
Aimetti et al. 2024	+	+	+	±	+	+	+	+
Wehner, C., et al. 2023	+	+	±	+	+	+	+	+
Jasa et al., 2020	+	+	+	+	+	+	+	+

Anoixiadou et al., 2022	+	+	+	+	+	+	+	+
Vela et al., 2024	+	+	±	+	+	+	+	+
Mazzonetto et al., 2021	+	+	+	+	+	+	+	+

"+" indicates a low risk of bias, "±" indicates an unclear or moderate risk of bias, and"-" indicates a high risk of bias.

All the studies included were randomized controlled trials (RCT), and their methodological quality was determined according to Cochrane Risk of Bias Tool.

Apparently, in most trials, the risk of bias was low in the important domains such as generation sequence, allocation concealment, and outcome assessment. Such factors were properly presented and used in almost every research topic with a sound internal validity. Nevertheless, in several studies, performance bias, namely blinding of the performers and staff, was evaluated as unclear, either due to a lack of reporting or due to a lack of conduct. Besides, there was a problem of selective reporting of outcome in two studies, and one trial presented moderate risk, having incomplete outcome data.

Regardless of these few concerns, no trials were considered to be at high risk of bias in general. The overall quality of methods was moderate according to GRADE, which added credence to the validity and reliability of the synthesized evidence. Future investigations ought to increase transparency in the presentation of blinding protocols and make the data of the outcome complete in order to strengthen methodological clarity even further. **Table 2** presents the risk of bias assessment for each included randomized controlled trial, outlining the methodological quality and potential sources of bias across key domains.

DISCUSSION

Enamel matrix proteins (EMPs) have emerged as biologically active agents capable of mimicking key events in natural tooth development and tissue regeneration [20]. Originally identified for their role in enamel biomineralization, EMPs are now being extensively investigated for their therapeutic potential in periodontal and peri-implant regenerative procedures due to their capacity to modulate cellular behavior, including proliferation, migration, and differentiation of periodontal ligament cells and osteoblasts [21,22]. Preclinical studies have shown that EMPs enhance wound healing and matrix deposition by stimulating the release of growth factors and cytokines, laying the foundation for their clinical translation [23].

Enamel matrix proteins (EMPs), including enamel matrix derivative (EMD), yield various beneficial effects for both periodontal tissue and peri-implant tissue regeneration [24]. EMD activates periodontal healing processes according to randomized controlled trials demonstrating both CAL increases and PD decreases, and new bone development due to its effect on cells of the periodontal ligament and cementum oblata [25]. Building on preclinical evidence, clinical investigations have further validated the regenerative capabilities of enamel matrix derivative (EMD), a commercially available formulation of EMPs [26]. EMD is applied topically during periodontal surgeries, where it modulates the local microenvironment to promote tissue regeneration [27].

The application of EMD delivers clearer therapeutic benefits to patients who have intrabody defects because their outcomes show better improvement than standard treatments alone. [28]. By influencing the behavior of key cell types such as periodontal ligament fibroblasts, cement oblasts, and osteoblasts, EMD facilitates the reconstruction of lost periodontal support through the stimulation of cementum, alveolar bone, and periodontal ligament formation [29]. EMD stimulates biological pathways through its activation of wound-healing functions such as new blood vessel growth, cell multiplication, and release of protein factor [30].

The available data demonstrate that EMD benefits the healing process of soft tissues and controls inflammatory reactions, particularly through combined applications with surgical methods, including guided tissue regeneration (GTR) and open flap debridement (OFD) [31]. Its adjunctive use with guided tissue regeneration (GTR) or open flap debridement (OFD) enhances clinical outcomes by accelerating soft tissue maturation and modulating pro-inflammatory cytokine expression [32]. These mechanisms contribute to more predictable healing, improved attachment gain, and reduced postoperative inflammation, thereby reinforcing the utility of EMD in comprehensive periodontal regenerative protocols [33].

The diverse clinical outcomes are, however, affected by confounding elements that affect the results, such as the characteristics of the defects and their relationship to patient age, smoking behavior, and oral hygiene compliance [34,35]. The effectiveness studies show that EMD produces better results in patients with three-wall defects and non-smokers, indicating potential specific uses in clinical practice [36].

The current evidence about regenerative outcomes remains limited due to insufficient subgroup categorization between genetic predisposition and healing capacity, along with baseline inflammatory conditions. The benefits of using EMD in treating peri-implantitis and enamel remineralization require further exploration to establish its effectiveness for these applications [37,38].

Research must continue to test the validity of initial results while determining how much EMD treatment costs patients and healthcare systems, how well people feel about the results, and how stable the regenerations remain over time for different types of populations [39]. The combination of molecular biomarkers with histological examination enhances both clinical applications as well as advances in mechanistic understanding [40].

The reliability, along with the generalizability of the obtained results, faces obstacles through the limitations observed within the included studies. The use of unclear blinding methods together with insufficient long-term follow-up periods and unstandardized EMD application protocols, along with the variety of control treatments used, led to moderate levels of study bias.

Additionally, limitations in the review process, such as restricting the search to English-language publications, not registering the protocol, and the absence of automation tools in screening and data extraction may have contributed to potential selection or reporting biases.

Researchers need to conduct larger standardized multi-center trials as future investigations to resolve the existing concerns. Further research should focus on optimizing EMP formulations and delivery systems to enhance clinical translation and long-term regenerative outcomes.

CONCLUSION

It can be seen that this systematic review and meta-analysis have measured the effectiveness of enamel matrix derivative (EMD) in its adjunctive use with the periodontal regenerative treatments. In the studies that were included as a randomized controlled trial, gains in clinical attachment level (CAL) and reductions in probing pocket depth (PPD) were all shown with slight but not statistically significant improvements in the EMD+ group versus controls.

Although the statistical significance was not demonstrated, the uniform effect direction with repeated trials indicates that EMD use possibly may provide some added clinical advantages. Heterogeneity of regenerative effects stimulates the necessity of standardized protocols and prolonged follow-ups to decide whether these small tendencies can result in significant long-term outcomes. Future research ought to be on standardized outcome measures and the possible synergistic effect of combination with other regenerative-based treatments.

LIST OF ABBREVIATIONS

EMD: Enamel Matrix Derivative

CAL: Clinical Attachment Level

PPD: Probing Pocket Depth

GCF: Gingival Crevicular Fluid

FMPS: Full Mouth Plaque Score

FMBS: Full Mouth Bleeding Score

MBL: Marginal Bone Loss

BOP:Bleeding on Probing

PI: Plaque Index

GI: Gingival Index

PD: Pocket Depth

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CONFLICT OF INTEREST

None

AUTHORS' CONTRIBUTION

All authors contributed equally as per ICMJE.

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