

DIFFERENT COMBINATIONS OF GUIDED TISSUE REGENERATION, BONE GRAFTS AND ENAMEL MATRIX DERIVATIVES IN THE TREATMENT OF INTRABONY PERIODONTAL DEFECTS: A SYSTEMATIC REVIEW

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ABSTRACT

Aim of the study Modern periodontal treatment has two main tasks. The first is to eliminate microorganisms and their toxins, thus affecting inflammatory processes. The second task is related to the complete regeneration of the lost periodontal structures. Today, clinicians have increasingly begun to look for innovative surgical approaches to ensure predictable regenerative outcomes. This systematic review aims to examine which combined regenerative methods have been most preferred over the years, in which bone defects they have been applied, and how effective they have been. **Materials and methods.** The electronic databases Web of Science, Scopus and PubMed were searched for publications related to the topic of this study for the period January 2000 to January 2025. The research was executed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. Fifteen studies were included in this systematic review. **Results** The different combined methods used in the treatment of vertical bone defects for the last 25 years were investigated and their results related to the parameters of probing depth, clinical attachment level and bone fill were analysed. **Conclusions** This systematic review can be successfully used as a guide as to which combined methods in the contemporary treatment of vertical bone defects are most preferred and effective.

Key words: Regenerative periodontal therapy, Combined regenerative therapy, Guided tissue regeneration, Enamel matrix derivative

INTRODUCTION

The regeneration of alveolar bone deficiencies has become a subject of increased interest over the years. These defects can be caused by traumatic injuries, infectious processes, tumors, periodontal disease, endodontic lesions, etc. [1-3]. To meet the growing need for bone preservation and augmentation, various novel materials and methods have been introduced to periodontology, implant dentistry, and oral surgery [4-9]. Their biocompatibility, safety, and regenerative potential if first validated by proper radiological examination, histological assessment with appropriate staining methods,

and histomorphometric evaluation [10-12].

In modern periodontal treatment, strict adherence to the treatment sequence first introduced by Ramfjord is fundamental. It includes a constitutive, hygienic, corrective and maintenance phase [13]. Successful periodontal treatment, clinically, is characterized by elimination of symptoms of inflammation (bleeding on probing $\leq 10\%$, absence of purulent discharge) and reduction of probing depth, gain of clinical level of attachment and radiologically detected bone filling [14]. Over the years, it has been confirmed the hypothesis that these clinical and radiological goals can only be achieved

with the implementation of an exact hygienic phase, accompanied by good patient motivation and education to observe better personal oral hygiene [15, 16].

However, there are cases where these measures do not always achieve satisfactory results in all areas. In the presence of periodontal defects at the reassessment stage after the hygiene phase, which are $\geq 4-5$ mm in depth and bleeding on probing is recorded in the area, it is necessary to undertake the next stage of treatment in the corrective phase [15].

Deep vertical bone defects (≥ 3 mm) and Class 2 furcation defects are considered indications for regenerative periodontal therapy [15, 17].

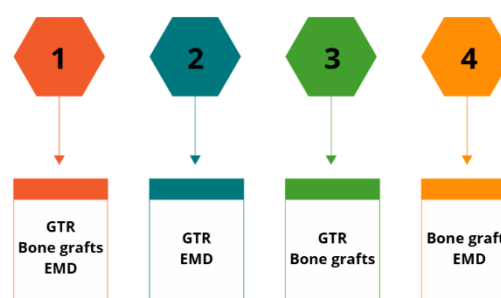
Modern regenerative periodontal therapy combines the application of specific surgical techniques and the use of a diverse range of biomaterials to facilitate the restoration of lost periodontal structures [18, 19].

New biological materials are appearing commercially every day, which aim to overcome the shortcomings of the most common regenerative materials used so far [20-24]. On the other hand, clinicians have increasingly begun to look for innovative surgical approaches to ensure predictable regenerative outcomes [5, 25, 26].

The main regenerative methods are guided tissue regeneration and regenerative therapy using enamel matrix derivatives (EMD) [14]. Over time, the so-called combined regenerative methods have become necessary. The introduction of these methods is due to the fact that, when two or more regenerative materials are combined, they can overcome their obvious disadvantages when applied alone [7].

The combined methods to be investigated in this study are presented in Fig. 1. These include various combinations using barrier membranes, bone repair materials and enamel matrix proteins.

Figure 1. Investigated combined methods`



The aim of this systematic review is to identify which combined regenerative methods have been most preferred over the years to date, in which bone defects they have been applied and what their effectiveness has been.

MATERIALS AND METHODS

This study is registered in the international prospective register of systematic reviews (PROSPERO, registration ID: 645127).

1. Eligibility Criteria

This systematic review includes only original articles, clinical trials and case reports in English published in the last 25 years (January 2000 to January 2025) and containing the selected keywords.

2. Information Sources

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (12).

A thorough search for articles across multiple electronic databases (Web of Science, Scopus, and PubMed) was conducted on 31 January 2025.

3. Search Strategy

Only full-text articles written in English are included. The electronic search approach included an advanced search in the chosen databases:

- The following formula was used in the Web of Science database, including the main keywords – (((((((((TS=(Regenerative periodontal therapy)) AND TS=(Combined

regenerative therapy)) OR TS=(Guided tissue regeneration)) AND TS=(Enamel matrix derivative)) AND TS=(Bone grafts)) OR TS=(Guided tissue regeneration)) AND TS=(Enamel matrix derivative)) OR TS=(Guided tissue regeneration)) AND TS=(Bone grafts)) OR TS=(Bone grafts)) AND TS=(Enamel matrix derivate)

- In the Scopus database the following formula was used, including the keywords - (ALL (regenerative AND periodontal AND therapy) AND ALL (combined AND regenerative AND therapy) OR ALL (guided AND tissue AND regeneration) AND ALL (enamel AND matrix AND derivative) AND ALL (bone AND grafts) OR ALL (guided AND tissue AND regeneration) AND ALL (enamel AND matrix AND derivative) OR ALL (guided AND tissue AND regeneration) AND ALL (bone AND grafts) OR ALL (bone AND grafts) AND ALL (enamel AND matrix AND derivate))

- In the PubMed database, the following formula including the keywords was applied - (((((((((Regenerative periodontal therapy) AND (Combined regenerative therapy)) OR (Guided tissue regeneration)) AND (Enamel matrix derivative)) AND (Bone grafts)) OR (Guided tissue regeneration)) AND (Enamel matrix derivative)) OR (Guided tissue regeneration)) AND (Bone grafts)) OR (Bone grafts)) AND (Enamel matrix derivate)

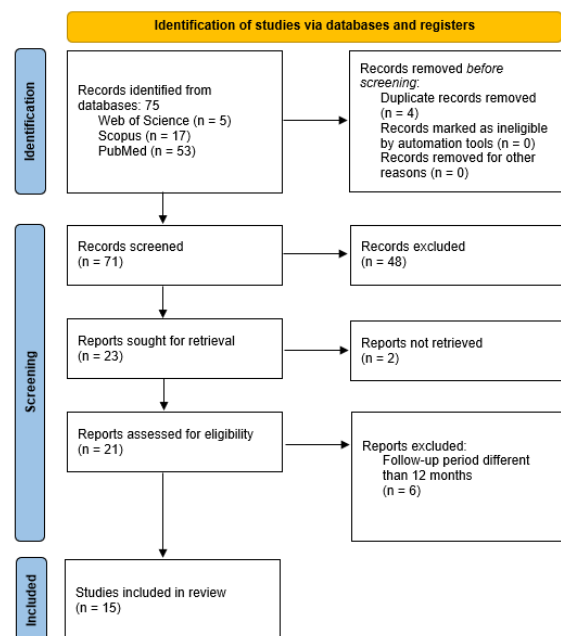
4. Study Selection and Data Collection Process

Titles and abstracts were reviewed and assessed for eligibility by three independent reviewers. The databases used were those of Web of Science, Scopus and PubMed. Article titles, author collective, year of publication and DOI-number were exported to an MS Excel spreadsheet. Duplicate articles were eliminated. Articles not found with full text or not published in English were excluded from

the list. All articles with a follow-up period other than 12 months were removed to perform an accrual analysis of the data. Discrepancies among the reviewers were reconciled through conversation until an agreement was achieved.

RESULTS AND DISCUSSIONS

The initial number of identified articles related to the present topic for the last 25 years is 75. 4 duplicate studies were removed. Thus, the potentially relevant articles that underwent analysis and evaluation were 71. Finally, 15 studies were assigned to



the current systematic review. Fig. 2 presents a PRISMA flow diagram illustrating the entire process of selecting relevant articles.

Figure 2. PRISMA flow diagram

Table 1 presents all examined characteristics of the studies included in this systematic review. Risk of bias assessment of the included studies was performed, based on the type of study (43, 44) (Fig. 3 and Fig. 4).

| | Study | Study type | Studied combined regenerative method | Bone defects | Number of bone defects | Mean reduced PPD, mm | Mean CAL gain, mm | Bone filling, mm |
|----|------------------------------------|-----------------------------|--------------------------------------|-------------------------------|------------------------|----------------------|-------------------|---------------------------|
| 1 | Moreno Rodríguez et al., 2022 (28) | Randomized Controlled Trial | Bone graft (not specified), EMD | intrabony periodontal defects | 12 | 6.83 | 7.08 | not studied |
| 2 | Cortellini and Tonetti, 2011 (29) | Randomized Controlled Trial | Xenograph (BMD), EMD | intrabony periodontal defects | 15 | 4.00 | 3.70 | present, no data provided |
| 3 | Döri F et al., 2005 (30) | Randomized Controlled Trial | Natural bone mineral (NBM), EMD | intrabony periodontal defects | 12 | 4.70 | 4.30 | 4.10 |
| | | | Alloplast, EMD | | 12 | 4.60 | 4.10 | 4.00 |
| 4 | Cortellini and Tonetti, 2005 (31) | Clinical Trial | GTR, bone graft (not specified) | intrabony periodontal defects | 11 | 6.10 | 6.00 | not studied |
| 5 | Aspriello et al., 2011 (32) | Randomized Controlled Trial | Allograft (DFDBA), EMD | intrabony periodontal defects | 28 | 5.00 | 4.00 | 4.00 |
| 6 | Guida et al., 2007 (33) | Randomized Controlled Trial | Autograft, EMD | intrabony periodontal defects | 14 | 5.10 | 4.90 | 4.30 |
| 7 | Ogihara and Tarnow, 2014 (34) | Randomized Controlled Trial | Allograft (FDBA), EMD | intrabony periodontal defects | 21 | 4.40 | 4.10 | 4.23 |
| | | | Allograft (DFDBA), EMD | | 23 | 3.70 | 3.50 | 4.26 |
| 8 | Ogihara and Tarnow, 2015 (35) | Randomized Controlled Trial | Allograft (FDBA), EMD | intrabony periodontal defects | 25 | 4.30 | 4.30 | present, no data provided |
| | | | Allograft (DFDBA), EMD | | 24 | 4.20 | 3.90 | not studied |
| 9 | Döri et al., 2013 (36) | Randomized Controlled Trial | Natural bone mineral (NBM), EMD | intrabony periodontal defects | 12 | 5.50 | 4.50 | not studied |
| 10 | Yilmaz et al., 2010 (37) | Randomized Controlled Trial | Autograft, EMD | intrabony periodontal defects | 20 | 5.60 | 4.20 | 3.90 |
| 11 | Paolantonio et al., 2020 (38) | Randomized Controlled Trial | Autograft, EMD | intrabony periodontal defects | 22 | 3.96 | 3.29 | 2.68 |
| 12 | Agrali and Kuru, 2015 (39) | Case Report | Xenograph (BMD), EMD | intrabony periodontal defects | 1 | 3.71 | 2.84 | not studied |
| 13 | Döri et al., 2013 (40) | Randomized Controlled Trial | Natural bone mineral (NBM), EMD | intrabony periodontal defects | 11 | 4.50 | 3.60 | not studied |
| | | | Alloplast, EMD | | 11 | 4.80 | 3.70 | not studied |
| 14 | Hoffmann et al., 2016 (41) | Randomized Controlled Trial | Alloplast, EMD | intrabony periodontal defects | 15 | 3.45 | 2.00 | 2.70 |
| 15 | Losada et al., 2017 (42) | Randomized Controlled Trial | Alloplast, EMD | intrabony periodontal defects | 26 | 3.14 | 2.38 | 2.71 |

| Study | D1 | D2 | D3 | D4 | D5 | D6 | Overall |
|-------------------------------|----|----|----|----|----|----|---------------|
| Moreno Rodríguez et al., 2022 | Y | Y | N | PY | N | N | Some concerns |
| Cortellini and Tonetti, 2011 | Y | Y | N | PY | N | N | Some concerns |
| Döri F et al., 2005 | Y | Y | N | Y | N | N | Low |
| Cortellini and Tonetti, 2005 | N | Y | N | Y | N | N | Some concerns |
| Aspriello et al., 2011 | Y | PY | N | Y | N | N | Some concerns |
| Guida et al., 2007 | PY | PY | N | Y | N | N | Some concerns |
| Ogihara and Tarnow, 2014 | Y | Y | N | Y | N | N | Low |
| Ogihara and Tarnow, 2015 | Y | Y | N | Y | N | N | Low |
| Döri et al., 2013 | Y | PY | N | Y | N | N | Some concerns |
| Yilmaz et al., 2010 | PY | Y | N | PY | N | N | Some concerns |
| Paolantonio et al., 2020 | PY | Y | N | PY | N | N | Some concerns |
| Döri et al., 2013 | PY | Y | N | PY | N | N | Some concerns |
| Hoffmann et al., 2016 | Y | Y | N | Y | N | N | Low |
| Losada et al., 2017 | PY | Y | N | PY | N | N | Some concerns |

- D1: Was the allocation sequence random?
- D2: Was the allocation sequence concealed until participants were enrolled and assigned to interventions?
- D3: Did baseline differences between intervention groups suggest a problem with the randomization process?
- D4: Was an appropriate analysis used to estimate the effect of assignment to intervention?
- D5: Were there failures in implementing the intervention that could have affected the outcome?
- D6: Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?

Figure 3. Risk of bias assessment of clinical trials

| Study | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | Overall |
|-----------------------|----|----|----|----|----|----|----|----|---------|
| Agrali and Kuru, 2015 | Y | Y | Y | Y | Y | Y | Y | Y | Low |

- D1: Were patient's demographic characteristics clearly described?
- D2: Was the patient's history clearly described and presented as a timeline?
- D3: Was the current clinical condition of the patient clearly described?
- D4: Were diagnostic tests or assessment methods and the results clearly described?
- D5: Was the intervention(s) or treatment procedure(s) clearly described?
- D6: Was the post-intervention clinical condition clearly described?
- D7: Were adverse events (harms) or unanticipated events identified and described?
- D8: Does the case report provide takeaway lessons?

Figure 4. Risk of bias assessment of case reports

The years in which the 15 studies meeting the eligibility criteria were published and the type of articles studied are presented in Fig. 5 and Fig. 6.

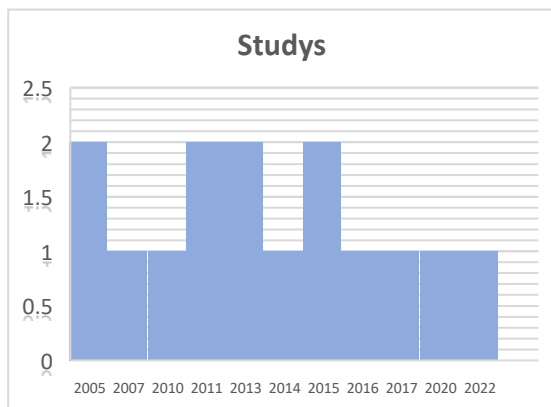


Figure 5. Studies' published years

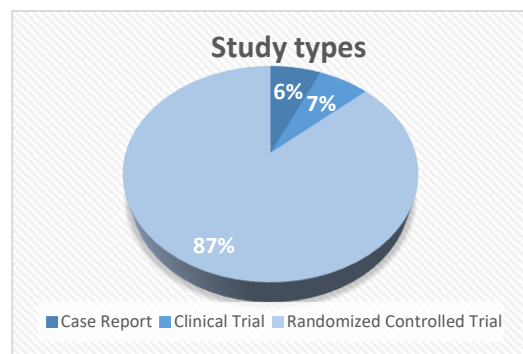


Figure 6. Types of articles studied

It appears that for the past 25 years, the most preferred combination method in the regenerative treatment of vertical bone defects is one that uses bone-repair materials together

with EMD (#4). One article out of the 15 studied, presents a combined regenerative method #3 (Guided tissue regeneration (GTR), bone grafts). No studies were found investigating the combined methods #1 (GTR, bone grafts, EMD) and #2 (GTR, EMD) (Fig. 7).

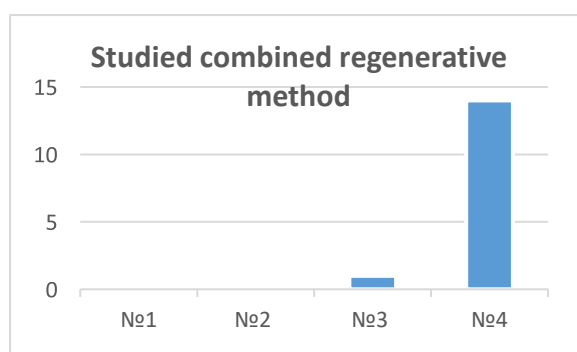


Figure 7. Combined regenerative methods studied

Fourteen of the articles in this systematic review, examined a total of 18 types of combined regenerative methods that investigated the synergistic effectiveness of bone regenerative materials and EMD, but the differences in their results stem from the fact that different types of bone regenerative materials were used (Fig. 8).

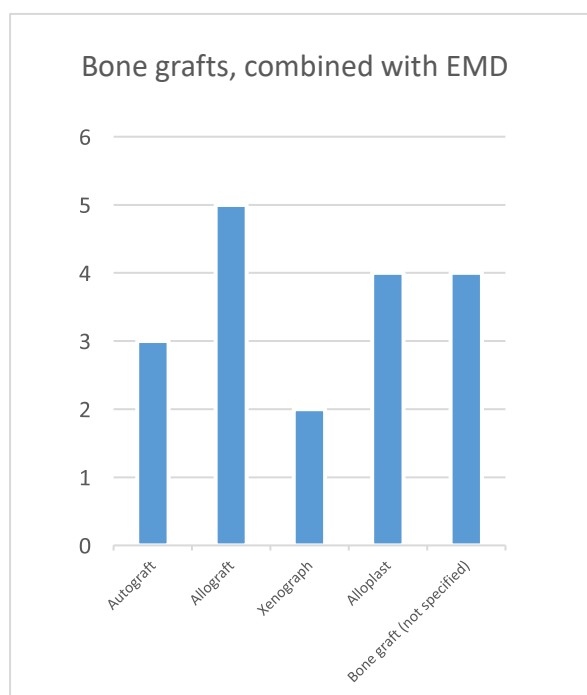


Figure 8. Types of Bone grafts

The averaged results of the combined methods of group 4 (Bone grafts, EMD) depending on the type of bone repair material are presented in Table 2.

| | Studied method | Mean reduced PPD, mm | Mean CAL gain, mm | Bone filling, mm |
|----|--------------------------------|----------------------|-------------------|------------------|
| 1. | Autograft, EMD | 4.89 | 4.13 | 3.63 |
| 2. | Allograft, EMD | 4.32 | 3.96 | 4.16 |
| 3. | Xenograft, EMD | 3.86 | 3.27 | present, no data |
| 4. | Alloplast, EMD | 4.00 | 3.05 | 3.14 |
| 5. | Bone graft (not specified),EMD | 5.38 | 4.87 | 4.10 |

Periodontal intrabony defects, referred to as "vertical" defects, are anatomical consequences of the development of periodontal disease, characterized by a base located apically to the inter-dental alveolar crest and surrounded by one, two, or three bony walls (45). In many situations, non-surgical periodontal therapy, with good motivation and education on the part of the patient, would resolve cases (46). In vertical bone defects, however, there are complications in the prognosis and treatment of the affected teeth, and very often the self-applied non-surgical periodontal therapy is extremely insufficient in them (47).

A pioneering study from the 1970s found that intrabony defects hold the potential to fully recover through the use of a barrier membrane (48).

Over the years, a variety of surgical approaches have been investigated with the goal of providing more successful and predictable outcomes in regenerative periodontal therapy (5, 49, 50, 51). The present study included 15 articles investigating combined regenerative approaches in the treatment of vertical bone defects.

As it has become clear, combined regenerative methods are characterized by the simultaneous application of various alternative approaches to periodontal reconstruction to overcome their shortcomings present in their single application (52). For example, bone-restoring materials can orthographize and maintain the periodontal defect space without problems, but this task is impossible for EMDs unless the defect is of minimalist dimensions (7, 8). On the other hand, there are countless biological and clinical studies in the literature that demonstrate the impressive effectiveness of EMD when used alone in regenerative periodontal therapy (5, 53, 54). Its biological effects are associated with its influence on cell adhesion, proliferation, proliferation and survival of many cell types (55).

In modern clinical dental practice, the use of bone-restoring materials is a routine procedure. These materials are classified as autogenous, allogeneic, xenogeneic, and alloplastic grafts (8). Their application in periodontology aims, from a clinical point of view, to reduce the probing depth and result in a gain of clinical attachment level, while from a radiological point of view the aim is for complete bone filling to occur (56).

Although systematic review articles comparing different regenerative methods can be found in the literature (19, 57), it should be clarified that to date we are not aware of any similar work published that aims to evaluate, analyze, and compare specific groups of combined regenerative methods in the treatment of vertical bone defects.

In this systematic review, the clinical and radiological results after applying pre-marked, different combined regenerative methods to a total of 315 intrabony periodontal defects are included. Particular attention is paid to the indicators of probing depth, clinical attachment level, and bone filling of the defect. In the combined methods of group #4 (Bone grafts, EMD), the average probing depth

decreased (PPD) by 4.29mm and the gain per clinical level of attachment was 3.71mm. The mean atheromatous bone fill in the defects was 3.69mm, but it should be emphasized that in two of the groups of combined methods studied - the authors confirm that bone fill is observed, but do not specify with exact values, while in the other six groups this indicator has not been studied.

The averaged values of the parameters probing depth, clinical attachment level and bone filling in the different variants of the combined methods of group 4 (Bone grafts, EMD) are presented in Table 2. The most pronounced reduction in probing depth and the greatest gain in clinical attachment level were observed with the combination of bone graft (not specified) and EMD (5.38 mm and 4.87 mm, respectively). In terms of bone fill rate, the combination of allograft and EMD demonstrated the best results (4.16 mm).

The only study that examined the results of the combined methodology #3 (GTR, bone grafts) is not discussed.

CONCLUSIONS

1. The growing need for better and effective regenerative approaches has led to the development of so-called combination methods.

2. These are characterized by the simultaneous application of different alternative approaches to periodontal reconstruction to overcome their shortcomings present when applied alone.

3. The most common combined method for the last twenty-five years is regenerative therapy with Bone grafts and EMD.

4. In the future, it is necessary to look at other combined methods, including GTR, bone grafts and EMD, in order to monitor their results and compare them with those of regenerative therapy with Bone grafts and EMD.

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Disclosure

The author reports no conflicts of interest in this work.

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