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# A systematic review: osseous healing after mixing enamel matrix derivatives (EMD) or platelet-derived growth factor with graft material to aid in alveolar ridge preservation (ARP)

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BOSTON UNIVERSITY  
HENRY M. GOLDMAN SCHOOL OF DENTAL MEDICINE

THESIS

**A SYSTEMATIC REVIEW: OSSEOUS HEALING AFTER MIXING ENAMEL  
MATRIX DERIVATIVES (EMD) OR PLATELET-DERIVED GROWTH FACTOR  
WITH GRAFT MATERIAL TO AID IN ALVEOLAR RIDGE PRESERVATION (ARP)**

By

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## **DEDICATION**

To the one who taught me the passion for research and knowledge to feed my desire to learn more about periodontology. To the modest person who taught me that learning is a humble experience and I would begin to fall the moment I think I understood everything. To the one and only who never failed to be generous with his time, support, and priceless advice. To the invaluable Dr. Albert Price, who always had faith in me.

Additionally, I would like to express my sincere gratitude to my supportive and loving spouse, Andrew Rasla, my daughter, who is my inspiration, Ayla Rasla, my parents, Fifi and Georgy, and my parents in law, Aida and Amin for their unwavering support and guidance.

Also, I want to express my gratitude to my siblings (Karim, Christine, Kirollos, Wael, Haidy, Christine, Marina, Michael), My nieces (Karen, Loren, Lily, Rose, Lorena, Celeine and Julene), My nephews (Mathew and Kevin), as well as my dearest friends, Sara Angelos, Monica Yacoub, Fr. Paul and Fr. Shenouda for their unwavering encouragement and support. I am unable to adequately express my gratitude to these individuals for their contributions to my academic career.

## **ACKNOWLEDGMENT**

Dr. Neal Fleisher and Dr. Salib Rasla independently reviewed the titles and abstracts produced from the research as outlined in Materials and Methods. Based on this review, the articles included in the respective studies were identified. Dr. Fleisher's efforts are greatly appreciated.

**A SYSTEMATIC REVIEW: OSSEOUS HEALING AFTER MIXING ENAMEL  
MATRIX DERIVATIVES (EMD) OR PLATELET-DERIVED GROWTH FACTOR  
(PDGF) WITH GRAFT MATERIAL TO AID IN ALVEOLAR RIDGE PRESERVATION  
(ARP)**

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**ABSTRACT**

Alveolar ridge preservation (ARP) is a technique used after tooth extraction to preserve bone volume within the extracted sockets. It involves a minimally traumatic tooth extraction protocol followed by immediate grafting. This is crucial for preventing alveolar ridge resorption and minimizing the early bone loss associated with wound healing after extraction. This systematic review was conducted to assess the effect of adding Enamel matrix derivatives (EMD) or platelet-derived growth factor (PDGF) to graft material used for alveolar ridge preservation (ARP) as measured by assessing their effect on the osseous healing of extraction sockets.

Using a systematic search process guided by PICO and PRISMA, a research question was formulated, and four electronic databases, PubMed, Embase, Web of Science, and Cochrane, were searched for studies to answer the research question. The analysis was conducted by two independent reviewers, who were guided by defined inclusion and exclusion criteria.

The preliminary search, defined by PICO-derived mesh terms, resulted in a list of 292 publications. The titles and abstracts were further evaluated using the PRISMA checklist and defined inclusion and exclusion criteria, resulting in a refined list of 15 articles. A further full

document review resulted in the exclusion of 11 more articles, leaving a final list of 4 articles.

Analysis of these selected articles resulted in the following conclusion.

The lack of consistency in study designs and the individual investigator's criteria for data evaluation made it challenging to reach a definitive conclusion. The use of different bone graft and membrane materials introduced variables that raise the question of whether the additive effect on osseous quality is derived from PDGF, EMD, bone, or the membrane material.

Most available studies aimed to assess the impact of EMD or PDGF on either delayed ridge augmentation or intrabony periodontal defects, which added more variables to the equation, and we excluded them from our analysis. Further investigations and comparative human studies using randomized controlled clinical trial protocols are needed to confirm whether either EMD or PDGF has an additive effect on the socket graft quality of healing when added to a bone graft during Alveolar ridge preservation.

## TABLE OF CONTENTS

DEDICATION	iv
ACKNOWLEDGMENT	v
ABSTRACT	vi
TABLE OF CONTENTS	viii
LIST OF TABLES	ix
LIST OF FIGURES	ix
LIST OF ABBREVIATIONS	x
INTRODUCTION	1
MATERIALS AND METHODS	8
SEARCH RESULTS	10
STUDY RESULTS	18
Analysis of results	23
DISCUSSION	27
CONCLUSION	34
LIST OF JOURNAL TITLE ABBREVIATIONS	36
BIBLIOGRAPHY	37
CURRICULUM VITAE	43

## **LIST OF TABLES**

Table 1: PICO Question

Table 2: Database Search

Table 3: Inclusion and Exclusion Criteria

Table 4: Reason for each article exclusion after full text analysis

Table 5: Included Articles (Author, title, design)

Table 6: Mesh classification of bone density

## **LIST OF FIGURES**

Figure 1: PRISMA Criteria

Figure 2: Role of PDGF in bone regeneration

## List of abbreviations

- ARP .....Alveolar Ridge Preservation
- CBCT .....cone-beam computed tomography
- EMD.....Enamel Matrix Derivatives
- FDBA .....Freeze-Dried Bone Allograft
- MCBS..... Mineral Collagen Bone Substitute
- MESH ..... Medical Subject Headings
- NLM .....National Library of Medicine
- PDGF.....Platelet-Derived Growth Factor
- PICO ..... Population, Intervention, Comparison,  
Outcome
- PRF ..... Platelet Fibrin
- PRISMA..... Preferred Reporting Items for Systematic Reviews and Meta-  
Analyses
- PRP ..... Platelet Protein
- RCM.....Resorbable collagen membrane
- Rh-PDGF.....Recombinant Human Platelet-Derived Growth  
Factor
- TCP..... Tri-Calcium Phosphate

## INTRODUCTION

Alveolar ridge preservation (ARP) following tooth extraction is considered the first line of defense against physiological vertical and horizontal alveolar ridge resorption, thereby reducing the need for ancillary ridge augmentation before or at the time of implant placement (1, 2). Inappropriate handling of dental sockets, such as not grafting after tooth extraction, especially when a bony wall is missing, can lead to bony defects that require more elaborate bone regeneration protocols. (1, 23). Different terminologies refer to the concept of an extraction socket graft, such as socket preservation, socket augmentation, or alveolar ridge preservation. These different terminologies all refer to a technique used after teeth extraction to preserve bone volume by immediately grafting the socket (1).

Alveolar bone resorption is a physiologic phenomenon that occurs following tooth extraction (21). Dimensional changes of the alveolar ridge after tooth extraction are more pronounced in the horizontal dimension (especially on the buccal) than in the vertical dimension. Facial bone thickness at the time of extraction seems to be strongly associated with the extent and magnitude of alveolar bone resorption; the thicker the facial bone, the less the ridge resorption (1).

Lindhe et al. (2015) compared the dimensional changes of the alveolar ridge 4 months after tooth extraction with and without adding grafting material. They found that the placement of a graft material in the socket did not completely prevent resorption of the buccal and palatal bone walls. They did find that the cross-sectional area of the control ridge (unassisted healing) was reduced by about 25%, while that of the test ridge (assisted healing using graft material) decreased by only 3%. It was concluded that the placement of a graft material in fresh extraction sockets markedly counteracted the bone reduction in the extraction sites (22).

Avila Ortiz et al. (2020) compared ARP and non-assisted socket healing following tooth extraction. They found that ARP showed superior maintenance of the alveolar bone after tooth extraction, when observed for up to 14 weeks, and reduced the need for bone augmentation before or at the time of implant placement (2).

When residual bony walls and soft tissue of the dental socket remain intact, they provide a blood supply and mechanical support for bone grafts used alone or in conjunction with a membrane, depending on the size of the defect (1,23).

Alveolar ridge preservation (ARP) commonly includes various grafting materials. Autologous bone is regarded as the gold standard due to its potential osteogenic, osteoinductive, and osteoconductive properties, as well as its lack of immune response. However, because ARP usually requires a large volume of grafting material, and autologous bone is limited and surgically invasive to harvest, alternatives such as allografts, xenografts, and alloplasts have often been used instead. The use of membranes (resorbable and non-resorbable) with ARP serves not only to contain bone graft material within the extraction socket but also to block epithelial and connective tissue from invading the site, following the principles of guided tissue regeneration (GTR). In contrast, when significant tissue regeneration is needed or in cases of locally and/or systemically compromised conditions (i.e., restricted blood supply due to systemic disorder or an uncontained defect) after extraction, the application of grafting materials, more extensive barrier membranes, and/or biologic mediators must be used to promote predictable and sufficient quantity and quality of regenerated tissue (24,27,28, 31).

Biologic mediators are substances made from a living organism or its products, used in the prevention, diagnosis, or treatment of a disease. The utilization of such biomaterials is suggested to result in faster healing and improved regenerative outcomes (31, 34)

The term "biologic mediators/agents" encompasses a variety of different growth factors and/or signaling molecules with diverse origins, mechanisms of action, and targeted tissues and/or cells in the periodontium, and were developed as agents for enhancing alveolar bone growth (35). Recently, there has been a trend towards using Growth Factors, such as platelet-rich fibrin (PRF), platelet-rich plasma (PRP), enamel matrix derivatives (EMD), or recombinant human platelet-derived growth factors (rhPDGF-BB), for tissue regeneration, or by mixing them with the grafting materials. Although some of these biological agents have received FDA approval for periodontal regeneration and bone augmentation procedures, adherence to surgical principles, patient selection, and site selection remain crucial for achieving predictable clinical outcomes. (12, 31).

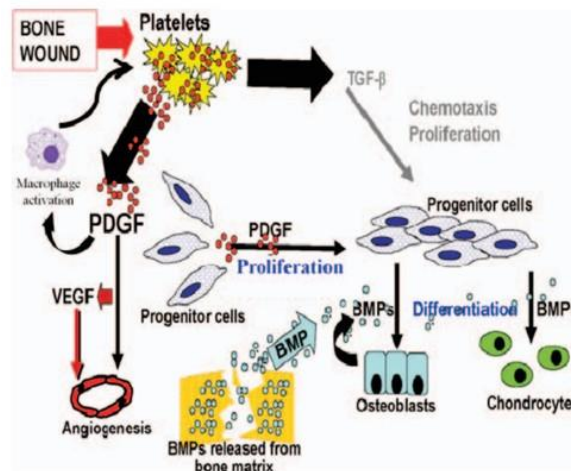
In the 1970s, Russell Ross discovered and characterized platelet-derived growth factor (PDGF) while investigating the cellular and molecular mechanisms underlying the formation of atherosclerotic lesions (35). The family of PDGFs consists of 4 isoforms: PDGF-A, PDGF-B, PDGF-C, and PDGF-D. The four isoforms combine in nature to form 5 biologically active homodimers or heterodimers, PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD. These dimers exert their biological effects through two cell surface tyrosine kinase receptors, PDGF receptor  $\alpha$  or PDGF receptor  $\beta$ , which are dimeric and can present as three homodimer receptors (PDGF  $\alpha\alpha$ , PDGF  $\beta\beta$ ) and the heterodimer (PDGF $\alpha\beta$ ). The PDGF-BB homodimer is the only isoform that can activate all three receptors. The biological events triggered by binding to these receptors include chemotaxis and mitogenesis of cells of mesenchymal origin, such as

progenitor cells, osteoblasts, and chondrocytes, making it the most favored PDGF isoform for bone regeneration (36). In addition to its effect on connective tissue cells, PDGF-BB plays a role in angiogenesis by stimulating VEGF and vA3 integrin expression<sup>46Y50</sup> and is known to work synergistically with BMP-2 in bone formation. A recombinant human version of PDGF-BB (rhPDGF-BB) has been synthesized and approved for clinical applications of periodontal regeneration (31, 33, 36).

The mechanism of action of naturally occurring PDGF in bone regeneration can be summarized as follows:

After hard or soft tissue injury, PDGF is released by blood platelets, binding to specific cell surface receptors. PDGF has been shown to promote fibroblast, cementoblast, and osteoblast, proliferation and migration into the surgical area as well as new blood vessel formation (angiogenesis). These cells in turn provide increased matrix synthesis, resulting in the formation of new alveolar bone, periodontal ligament, and cementum, leading to the enhancement of the wound/socket healing process through (11):

- 1- Chemotaxis (Attracting different cell types to the injury site)
- 2- Mitogenesis (increase in the cell populations of healing cells),
- 3- Angiogenesis (endothelial mitoses into functioning capillaries)
- 4- Macrophage activation (debridement of the wound site and a second-phase source of growth factors for continued repair and bone regeneration) (14).



(Fig. 2) The Role of PDGF in bone regeneration (Shah et al.2014) (11)

### Biologics:

GEM 21S (Lynch biologics) is a common growth factor-enhancement product used in periodontal regeneration. This product combines  $\beta$ -tricalcium phosphate ( $\beta$ -TCP) as a carrier for a highly purified rhPDGF-BB, providing physical structural support and space maintenance for a steady and slow release of rhPDGF-BB. Its use has been extensively investigated in preclinical and clinical studies, including animal and human subjects (31). Although the FDA has approved PDGF for treatment of periodontal related defects (e.g., intrabony defects, furcation, and gingival recessions defect), the effectiveness of this biologic agent for implant related problems such as vertical and horizontal bone augmentation (12,31), sinus augmentation procedures (37), and ridge preservation procedures (8) has also been widely studied.

Another biological mediator that is widely used in periodontal regeneration is Enamel Matrix Derivative (EMD). The first studies on clinical applications of EMD were published in 1997 (40,41). Since then, research groups have studied the mechanism of action of EMD and its clinical potential, as well as working further to evolve its therapeutic potential. In 2004, a

Cochrane review (42) concluded that EMD significantly improves periodontal attachment levels and reduces probing pocket depth compared to open-flap debridement. Many case reports and clinical studies have been published, emphasizing the clinical effect of EMD when used in periodontal regeneration procedures.

Enamel Matrix Derivative (EMD) comprises different enamel-related proteins, with amelogenin being the main component (>90%). It also contains proteins such as enamelin, tufflin, and ameloblastin, among others (38). Embryologically, during root development, enamel matrix proteins are secreted by the Hertwig's epithelial root sheath cells, with cementogenesis being its primary function (39). Although these proteins have shown favorable outcomes in periodontal regeneration, resulting in new bone formation, periodontal ligament (PDL), and cementum (42), the exact mechanism of action remains unclear.

Emdogain (Straumann, Switzerland) is the standard commercially available product containing EMD. This product is extracted from developing porcine tooth buds. Recently, it has been demonstrated to induce the proliferation of gingival mesenchymal stem cells and enhance their osteogenic differentiation in vitro (31,43). Emdogain® is the only product on the market that has potential for triggering clinically significant regenerative responses in periodontal ligament cells. If, as several observations suggest, amelogenin deposition precedes cementum formation, then EMD treatment may mimic odontogenesis and work by restarting dormant developmental programs in cells to regenerate the tooth attachment apparatus. Such responses typically involve sequential cascades of growth factors that act on the multitude of cells needed to reconstitute the lost periodontal tissues. It has been assumed that the most important

mechanism of action of EMD is to initiate periodontal regeneration by recruiting cementoblasts to the root surface and stimulating these to form root-cementum. However, many recent studies report that amelogenins can also interact directly with cell types other than cementoblasts, suggesting that these molecules have a more direct role in the regrowth of mesenchymal tissues (52).

EMD has been studied for use in various fields of periodontology, primarily for treating intrabony and furcation defects, as well as for covering gingival recession. When examining the efficacy of EMD for treating intrabony defects, Tonetti et al. (2002) concluded in a clinical study that EMD provided a beneficial effect in terms of CAL gain and reduction in probing depths compared to open flap debridement alone (45). However, when compared with GTR, results from recent systematic reviews found no difference between the two techniques (46). On the other hand, a systematic review of non-contained intrabony defects suggested a benefit of GTR over EMD alone (47). Similarly, for the treatment of class II furcation defects, EMD has been employed either alone or in combination with various grafting materials and is reported to have achieved different levels of success (48). Regarding the treatment of recession defects with EMD, most studies agree on the superiority of CAF + CTG in combination with EMD compared to CAF alone (49, 50). The utilization of EMD in various areas of the implant field, including sinus augmentation, treatment of peri-implantitis defects, and Alveolar ridge preservation (ARP), is currently being investigated (48, 49, 9, 31). At this time, EMD has been demonstrated to promote periodontal regeneration to a certain degree, although its actual effect remains to be determined. In addition, EMD has been shown to influence different genes expressed during bone remodeling (bone resorption and formation), promoting an anabolic effect. Few studies

have investigated and reported the comparison of EMD and PDGF as additives to bone grafts for alveolar ridge preservation (ARP) (2).

This systematic review was conducted to assess the effect of adding Enamel matrix derivatives (EMD) or platelet-derived growth factor (PDGF) to graft material for alveolar ridge preservation (ARP) as measured by assessing their effect on the osseous healing of extraction sockets.

## **MATERIALS AND METHODS**

The systematic review utilized the PICO format (Population, Intervention, Comparison, Outcome) to generate MESH terms (Medical Subject Headings) for the review of four databases. A specific research question was formulated: “Does using Enamel matrix derivatives (EMD) or Platelet-derived growth factors (PDGF) mixed with bone graft for alveolar ridge preservation (ARP) have an added effect on osseous healing of the extraction socket?”

The next step was to transform this question into individual PICO statements and to develop a research protocol, before formulating inclusion and exclusion criteria to identify which studies would qualify for inclusion in the systematic review. (See Table 1, Pg. 9)

<b>Table 1. PICO Guided Question Formation</b>	
P	patients who have a fresh tooth extraction socket(s)
I	Adding Platelet-Derived Growth Factor (PDGF) or Enamel matrix derivatives (EMD) to tooth extraction sockets mixed with bone graft material for alveolar ridge preservation (ARP).
C	Compare the effect of PDGF versus EMD on Osseous healing in the extraction socket.
O	Using EMD or PDGF mixed with a bone graft has more, less, or no significant clinical outcomes compared with techniques using a bone graft alone.

The PICO framing of the search question was then utilized to develop specific keywords: (“bone regeneration,” “bone graft”, “socket graft”, “alveolar ridge preservation ARP”, “growth factors,” “enamel matrix derivatives EMD,” and “Platelet-derived growth factor PDGF”), for the search of electronic databases.

These keywords and terms were used to identify Medical Subject Headings (referred to as “MESH” terms), which is a controlled and hierarchically organized vocabulary produced by the National Library of Medicine. It is used for indexing, cataloging, and searching of biomedical and health-related information. MESH includes the subject headings appearing in MEDLINE/PubMed, the NLM Catalog, and other NLM databases. (NLM)

Using these MESH terms, an electronic search was conducted, with the help of the academic librarian, across four databases (PubMed, Embase, Web of Science, and Cochrane) to identify relevant studies. (See Table 2, Pg. 10)

<b>Table 2</b>	<b>Database search (Terms used in each search)</b>
Database	Search
PubMed	("bone regeneration"[mesh] OR "bone regen*" OR "bone growth") AND ("bone graft" OR "Bone Transplantation"[Mesh]) AND ("Alveolar Ridge preservation" OR "ARP"[Mesh] AND ("Platelet-Derived Growth Factor"[Mesh] OR pdgf OR "platelet derived growth factor" OR emdogain OR "Gem 21" OR "enamel matrix derivatives" OR EMD[tiab])
Embase	('bone graft'/exp OR 'autograft, bone' OR 'autograft, spongy bone' OR 'autologous bone graft' OR 'bone autograft' OR 'bone graft' OR 'bone grafts' OR 'compact bone autograft' OR 'free bone graft' OR 'graft, bone' OR 'osseous graft' OR 'osseous grafts' OR 'osteoarticular graft' OR 'spongy bone autograft' OR OR 'viable bone graft') AND ('emdogain'/exp OR emdogain OR 'platelet derived growth factor'/exp OR 'alveolar ridge preservation' OR 'ARP' OR 'pdgf' OR 'growth factor, platelet derived' OR 'growth factor, thrombocyte' OR 'platelet derived growth factor' OR 'platelet growth factor' OR 'platelet-derived growth factor' OR 'thrombocyte derived growth factor' OR 'thrombocyte growth factor' OR Gem21 OR 'enamel matrix derivatives') AND ('bone regeneration'/exp OR 'bone regeneration' OR 'regeneration, bone')

Web of science	<p>((TS=("bone regeneration" OR "bone growth" OR "ARP" OR "alveolar ridge preservation"))) AND TS=("bone graft" OR "Bone Transplantation")) AND TS=( pdgf OR "platelet derived growth factor" OR emdogain OR EMD OR "enamel matrix derivatives" OR "Gem 21")</p>																		
Cochrane	<table border="0"> <thead> <tr> <th data-bbox="440 569 519 609">ID</th> <th data-bbox="519 569 1432 609">Search Hits</th> </tr> </thead> <tbody> <tr> <td data-bbox="440 646 519 686">#1</td> <td data-bbox="519 646 1432 686">"bone regen*" OR "bone growth" 358</td> </tr> <tr> <td data-bbox="440 724 519 764">#2</td> <td data-bbox="519 724 1432 764">MeSH descriptor: [Bone Regeneration] explode all trees 894</td> </tr> <tr> <td data-bbox="440 802 519 842">#3</td> <td data-bbox="519 802 1432 842">#1 OR #2 1234</td> </tr> <tr> <td data-bbox="440 879 519 919">#4</td> <td data-bbox="519 879 1432 919">MeSH descriptor: [Bone Transplantation] explode all trees 1055</td> </tr> <tr> <td data-bbox="440 957 519 997">#5</td> <td data-bbox="519 957 1432 997">#4 OR "bone graft" 2526</td> </tr> <tr> <td data-bbox="440 1035 519 1125">#6</td> <td data-bbox="519 1035 1432 1125">MeSH descriptor: [Platelet-Derived Growth Factor] explode all trees 153</td> </tr> <tr> <td data-bbox="440 1163 519 1266">#7</td> <td data-bbox="519 1163 1432 1266">#6 OR pdgf OR emdogain OR EMD OR "enamel matrix derivatives" OR "Gem 21" 1461</td> </tr> <tr> <td data-bbox="440 1304 519 1344">#8</td> <td data-bbox="519 1304 1432 1344">#3 AND #5 AND #7 13</td> </tr> </tbody> </table>	ID	Search Hits	#1	"bone regen*" OR "bone growth" 358	#2	MeSH descriptor: [Bone Regeneration] explode all trees 894	#3	#1 OR #2 1234	#4	MeSH descriptor: [Bone Transplantation] explode all trees 1055	#5	#4 OR "bone graft" 2526	#6	MeSH descriptor: [Platelet-Derived Growth Factor] explode all trees 153	#7	#6 OR pdgf OR emdogain OR EMD OR "enamel matrix derivatives" OR "Gem 21" 1461	#8	#3 AND #5 AND #7 13
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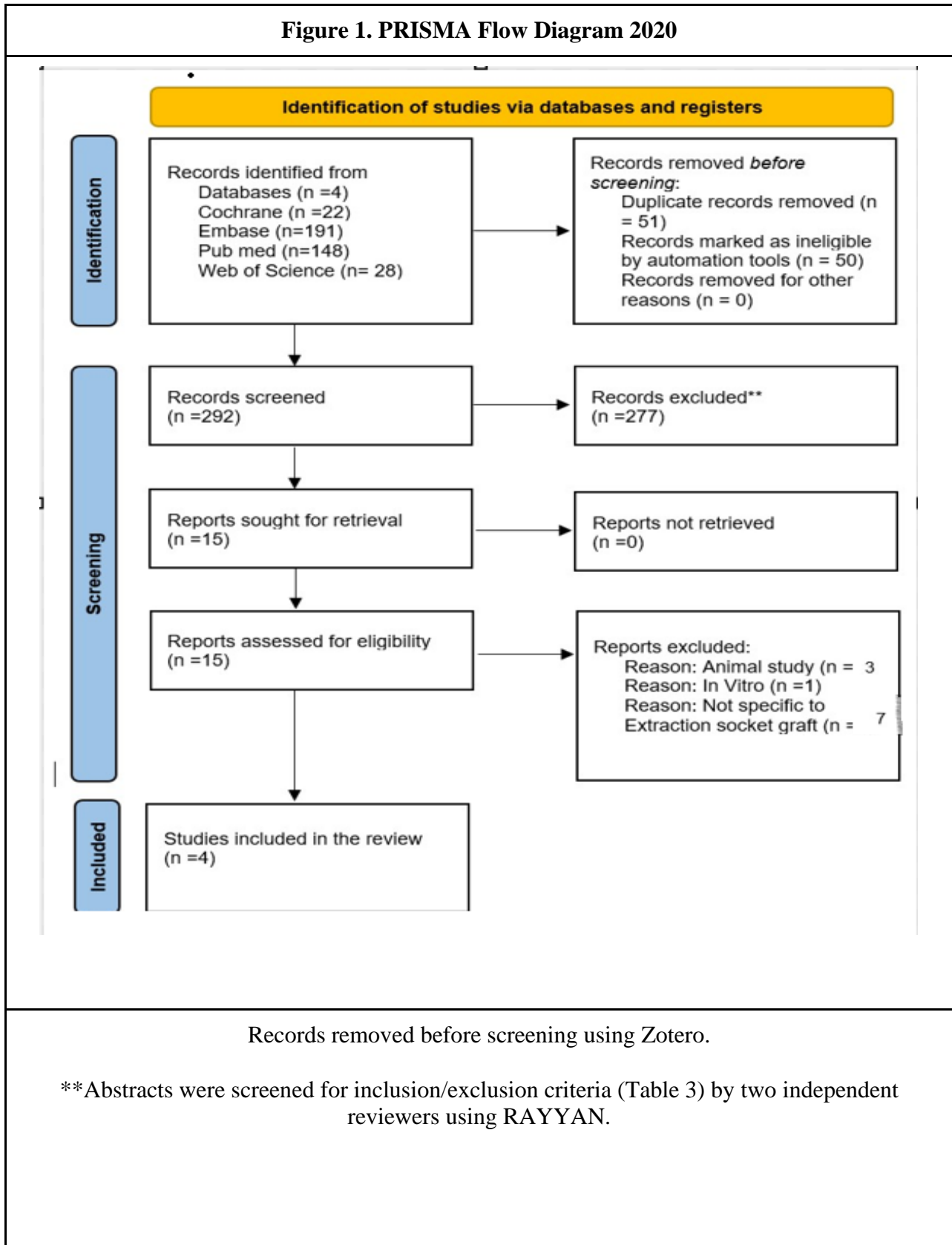
This systematic review followed the guidelines established by the PRISMA checklist (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). PRISMA consists of 27 item checks and 4 phase flow diagrams, which help analyze the quality of the review and allow replication of the review methods (50). Inclusion and exclusion criteria were predefined before conducting the database search. Inclusion criteria were randomized controlled trials published before September 2022, in humans with alveolar ridge preservation (socket grafting) using EMD or PDGF. Exclusion criteria were animal, pilot, orthopedic studies, literature, and other systematic reviews, other periodontal regeneration or ridge augmentation procedures using EMD or PDGF, articles not retrieved, and articles written in a foreign language (See Table 3, Pg. 13).

<b>Table 3. Inclusion and Exclusion Criteria</b>	
Inclusion Criteria	<ul style="list-style-type: none"> <li>• RCT</li> <li>• Human studies</li> <li>• Alveolar ridge preservation using EMD or PDGF</li> <li>• Published before September 2022</li> </ul>
Exclusion Criteria	<ul style="list-style-type: none"> <li>• Animal studies</li> <li>• Pilot study</li> <li>• Literature review and systematic reviews</li> <li>• Periodontal regeneration</li> <li>• Articles not in English</li> <li>• Not retrieved articles</li> <li>• Weak publication</li> <li>• Orthopedic studies</li> <li>• Ridge Augmentation using EMD or PDGF</li> <li>• In-Vitro studies</li> </ul>

After searching the databases on September 27, 2022, the research yielded the following number of articles per database: PubMed, 148 articles; Embase, 191 articles; Web of Science, 28 articles; and Cochrane, 22 articles, totaling 389 articles. The search results were then downloaded from the databases and uploaded to Zotero (A reference management software to manage bibliographic data and related research materials) by the librarian to identify and exclude duplicate articles. A total of 51 duplicate articles were removed, leading to an updated number of 292 articles in total. The updated list of articles was then uploaded to RAYYAN (A web-based tool designed to assist researchers in conducting systematic reviews by screening and selecting articles based on specified inclusion and exclusion criteria) for screening.

Using mesh terms derived from PICO, the electronic database search resulted in a list of 292 articles for review. Two reviewers independently reviewed titles and abstracts of 292 potential studies for primary screening, which resulted in the exclusion of 277 articles based on the predefined inclusion and exclusion criteria. A total of 15 articles were then identified for full-text evaluation or secondary screening using the PRISMA guidelines. This screening resulted in the exclusion of 11 articles that did not meet the predefined inclusion and exclusion criteria (See Fig. 1). Reasons for the exclusion of each of the 11 articles are listed (see Table 4).

Figure 1. PRISMA Flow Diagram 2020



**Table 4. Reason for exclusion of 11 articles after full-text analysis**

Beker, et al (1992)	Animal studies
Prata, et al (2007)	
Simon, et al (2009)	
Nevins, et al (2005)	Periodontal intra-bony defect
Sculean, et al (2008)	
Crea, et al (2009)	
Hoffmann, et al (2011)	
Urban, et al (2013)	Case report, Horizontal GBR, not extraction socket graft
Funato, et al (2013)	Vertical GBR, not socket graft
Simon, et al (2007)	Case report, Vertical GBR, not extraction socket graft
Jiang, et al (1999)	In Vitro study

The completed screening resulted in the inclusion of a total of 4 articles in the systematic review. It was determined that a Meta-Analysis could not be conducted since this requires homogeneous quantitative data to develop a conclusion with greater statistical power, which was not achieved with the available data from the included studies (50). The information collected from the included studies was systematically listed and analyzed in tables (5, 5a,5b, 5c, 5d). The

data were categorized into the following categories: Author, title, study design, Population, intervention, comparison, and outcome.

## STUDY RESULTS

<b>Table 5. Included Articles (Author, title, design)</b>			
<b>Article</b>	<b>Author</b>	<b>Title</b>	<b>Study Design</b>
1	Nevins, et al (2011)	Human Buccal Plate Extraction Socket Regeneration with Recombinant Human Platelet-Derived Growth Factor BB or Enamel Matrix Derivative	Randomized Controlled Clinical Trial.
2a	Geurs, et al (2014)	Using Growth Factors in Human Extraction Sockets: A Histologic and Histomorphometric Evaluation of Short-Term Healing	Randomized Controlled Clinical Trial.
2b	Ntounis, et al (2015)	Clinical Assessment of Bone Quality of Human Extraction Sockets After Conversion with Growth Factors	Randomized Controlled Clinical Trial.
3	Hong Lee, et al (2020)	Effect of enamel matrix derivative on alveolar ridge preservation in the posterior maxilla: A randomized controlled clinical trial	Randomized Controlled Clinical Trial

Table 5a. Information collected from the included studies					
Article	Author	(1)Population/ Type of defect	(2) Intervention (Bone graft material)	(2) intervention (Membrane)	(2) Interventio n (Location)
1	Nevins, et al (2011)	-n=15 patients with 16 extraction sockets -Age: 18-70 y/o -Divided into 4 groups - <b>Type of defect:</b> <u>Extraction socket with Buccal wall defect</u>	<b>gp. A:</b> MCBS* <b>gp. B:</b> MCBS+ rhBDGF <b>gp. C:</b> MCBS+ EMD <b>gp. D:</b> Bone ceramic (alloplast) + EMD  *MCBS= Mineral Collagen Bone Substitute	NO membrane	No mention of the extraction socket location
2a	Geurs, et al (2014)	-n= 41 patients -Age= >19 - Divided into 4 groups - <b>Type of defect:</b> Extraction socket (no mention of extra defects)	Mineralized freeze-dried bone allograft (FDBA)/ Tri-Calcium Phosphate (TCP) 8:2 ratio	No membrane (used Collagen Plug)	Anterior or premolar teeth
2b	Ntounis, et al (2015)	-n=41 patients -Age= >19 -Divided into 4 groups - <b>Type of defect:</b> Extraction socket (no mention of extra defects)	Mineralized freeze-dried bone allograft (FDBA)/ Tri-Calcium Phosphate (TCP) 8:2 ratio	No membrane (used Collagen Plug)	Anterior or premolar teeth
3	Hong Lee, et al (2020)	-n=28 patients -Age= >19 y/o - Divided into 3 groups - <b>Type of defect:</b> Extraction socket (no mention of extra defects)	Bovine bone mineral (Bio-Oss Collagen)	Yes (used resorbable collagen membrane (RCM))	Posterior maxilla

**Table 5b. Information collected from included studies, continued...**

<b>Article</b>	<b>Author</b>	<b>(2) Intervention (Used EMD)</b>	<b>(2) Intervention (Used rh-PDGF)</b>	<b>(3) Comparison groups</b>
<b>1</b>	<b>Nevins, et al (2011)</b>	Yes	Yes	<b>gp. A:</b> Mineral collagen bone substitute (MCBS/Bio-Oss Collagen) <b>gp. B:</b> MCBS+ rhPDGF <b>gp. C:</b> MCBS+ EMD <b>gp. D:</b> EMD+ bone ceramic (alloplast)
<b>2a</b>	<b>Geurs, et al (2014)</b>	No	Yes	<b>gp.1:</b> Collagen plug <b>gp.2:</b> Collagen plug+ FDBA+TCP <b>gp.3:</b> Collagen Plug+ FDBA+TCP+PRP <b>gp.4:</b> Collagen Plug+ FDBA+TCP+rhPDGF
<b>2b</b>	<b>Ntounis, et al (2015)</b>	No	Yes	<b>gp. 1:</b> Collagen plug <b>gp. 2:</b> Collagen plug+FDBA+TCP <b>gp. 3:</b> Collagen Plug+ FDBA+TCP+PRP <b>gp.4:</b> Collagen Plug+ FDBA+TCP+rhPDGF
<b>3</b>	<b>Hong Lee, et al (2020)</b>	Yes	No	<b>gp. 1:</b> Bio-Oss collagen + EMD+RCM <b>gp. 2:</b> Bio-Oss collagen +RCM <b>gp. 3:</b> No intervention (control)

**Table 5c. Information collected from the included studies continued...**

<b>Article</b>	<b>Author</b>	<b>(4) post-op (Follow-Up)</b>	<b>(5) Outcome evaluation (Histology)</b>
<b>1</b>	<b>Nevins, et al (2011)</b>	5 months after socket graft	Yes (Biopsy at time of implant placement)
<b>2a</b>	<b>Geurs, et al (2014)</b>	8 Weeks after socket graft	Yes (Biopsy at time of implant placement)
<b>2b</b>	<b>Ntounis, et al (2015)</b>	8 Weeks after socket graft	Yes (compared bone quality measured by three clinicians with Misch clinical classification (See Table 6, pg. 24) at the time of implant placement, to the histology from the same sites.
<b>3</b>	<b>Hong Lee, et al (2020)</b>	5 months after socket graft	No Histology Used CBCT linear measures.

**Table 5d. Information collected from included studies continued...**

<b>Article</b>	<b>Author</b>	<b>(5) Outcome evaluation (Bone Quality/ Percentage of new bone)</b>	<b>(5) Outcome evaluation (Horizontal and vertical height changes)</b>	<b>(6) Results Evaluation of the outcome (PDGF/EMD Effectiveness Criteria )</b>
1	Nevins, et al (2011)	Yes	No	Increased bone quality Increased %New bone formation.
2	Geurs, et al (2014)	Yes	No	Increased bone quantity Increased %New bone formation
3	Ntounis, et al (2015)	Yes	No	Increased bone quality Using feedback from drilling as their measurement after using 2mm trephine to collect 2x6mm specimen.
4	Hong Lee, et al (2020)	No	Yes	Increased HZ &VT bone height Using CBCT linear measure.

## **ANALYSIS OF TABLES 5a-d**

### **Study design**

All the included studies were prospective, randomized controlled clinical trials. They were all single-center, meaning that each study was conducted at a single clinical or research facility. Hong Lee et al. were single-blinded, while the rest were not blinded. Geurs et al. (2014) and Ntounis et al. (2015) published two papers based on the same study and compared clinical measurements with histological findings. Both used the same subjects but with different evaluation methods (Histology and clinical).

### **Population/ Defect**

Nevins et al. (2011) used a total of 15 patients, aged 18 to 70 years, with 16 extraction socket with buccal wall defects. They were then divided into 4 test groups. Geurs and Ntounis et al. used 41 subjects, 19 y/o or older with extraction sockets, and divided them into four test groups. On the other hand, Hong Lee et al. used 28 subjects, aged 19 years or older with an extraction socket, and divided them into three test groups.

### **Intervention and Comparison**

Nevins et al divided the subjects into four groups. He used the MCBS, which is an alloplast, in groups A, B MCBS + rhPDGF, and C MCBS + EMD. For group D, he used bone ceramic along with EMD. There was no mention of the commercial name of the bone ceramic or its characteristics (ex., Particle size). Nevins et al. mentioned that he used sterile water to hydrate the MCBS in group A, while he used rhPDGF in a solution form (0.3 mg/mL) and EMD in a gel form to hydrate the alloplast in the remaining groups. No membrane was used since the test

objective was to avoid the use of a membrane over the buccal defect, and there was no mention of the tooth location of the intervention site.

Geurs and Ntounis et al. divided the subjects into four test groups and used only a Collagen plug for group 1 (control). In comparison, the other three groups used a collagen plug along with FDBA/Beta-TCP (group 2), FDBA/TCP/PRP (group 3), or FDBA/TCP/rhPDGF (group 4). Although they mentioned the location of the extraction socket (anterior or premolar teeth), they did not define the arch (maxillary or mandibular).

Hong Lee et al. mentioned the location of the extraction sockets (Posterior maxilla) and divided the subjects into three test groups. They used bovine bone mineral (Bio-Oss Collagen) along with Collagen membrane (RCM) for group 1 and group 2, with the addition of EMD to group 1. They used group 3 as a control, representing healing without the addition of any materials. For group 2, they mentioned using a double layer of RCM membrane that was soaked in EMD for two minutes, and the bone graft itself was hydrated using EMD.

### **Postoperative follow-up**

All articles included in this study had a minimum of 8 weeks of follow-up; however, there was no mention of the frequency of follow-ups after extraction and socket augmentation. Two articles used the same source study: Geurs et al (2014) and Ntounis et al included results after 8 weeks of extraction and ARP. They intentionally chose the 8 weeks as they wanted to evaluate the early stage of osseous healing. The other two studies, Nevins et al. (2011) and Hong Lee et al. (2020), provided results after 5 months.

## Evaluation of the outcome/ Results

All the articles measured the effectiveness of a biological material (PDGF, EMD, or PRP) based on either quantitative or qualitative analysis of the bone at the time of implant placement following the socket graft procedure. Two out of three studies included in this review provided data on bone histology after the procedure: Nevins et al. (2011), Geurs et al. (2014), and Ntounis et al. (2015) compared clinical qualitative assessments to the histology of Geurs. One study provided CBCT linear scan measurements (Hong Lee et al., 2020). Each study described the protocol used for measuring bone gain after 2-5 months from the extraction socket graft approach.

Geurs et al. (2014) and Ntounis et al. (2015) utilized the same study to assess the bone histology at the time of implant placement, but with different purposes. The first paper aimed to evaluate the healing of grafted and non-grafted sockets, as well as the effect of PDGF on early remodeling, focusing on assessing bone quantity and quality by performing quantitative and qualitative analyses of mineralized versus non-mineralized tissue using Nikon Elements Software. On the other hand, Ntounis assessed the bone quality clinically using Misch's clinical classification, which is based on the clinician's subjective feedback from the drilling experience during the time of implant placement, and compared it to the histologic findings in the Geurs paper (8).

**Geurs et al (2014)** found that more new bone and amorphous organic matrix were noted in the histologic findings of the control group (where only a collagen plug was used). In sites where

bone graft was combined with growth factors (PRP or PDGF), the number of residual particles was less than in sites where bone graft alone was used.

**Ntounis et al (2015)** found that using the bone graft shifted the bone quality (See Table 6) from D4 to D3, while the inclusion of PRP or PDGF in bone grafting gave the same effect of eliminating the incidence of D4 bone, establishing D3 and D2 quality bone, and reducing residual bone graft particles.

<b>Table 6 Misch Classification</b>			
<b>Category</b>			
D1	Dense compact bone	Anterior mandible	Resembles oak wood
D2	Dense to thick porous compact and coarse trabecular bone	Anterior and posterior mandible	Resembles pine wood
D3	Porous compact and fine trabecular bone	Posterior and anterior maxilla	Resembles balsa wood
D4	Fine trabecular bone	Resorbed posterior maxilla	Resembles Styrofoam

Misch CE. Density of bone: Effect on treatment plans, surgical approach, healing, and progressive bone loading. *Int J Oral Implantol* 1990

**Hong Lee et al (2020)** conducted a randomized controlled clinical trial to evaluate the dimensional bony changes along with soft tissue wound healing after extraction socket graft with and without EMD. He compared the CBCT images taken before and after 5 months of the socket graft procedure to evaluate the dimensional changes in bone quantity. The study revealed no significant differences in bone dimension changes between test groups 1 and 2; however, the control group exhibited significantly greater changes at the alveolar ridge crest. Early

postoperative discomfort and soft tissue wound healing outcomes were not significantly different (9).

As for **Nevins et al. (2011)**, they assessed the quality of osseous healing in the extraction socket with a buccal defect after grafting with MCBS mixed with EMD, PDGF, MCBS alone, or bone ceramic + EMD. Fifteen patients with sixteen teeth requiring extraction were treated, with four teeth randomized to each of the four groups. The study resulted in uneventful healing for all subjects, along with adequate bone for the placement of standard-size implants and trephine core biopsies. The light microscopy and B-SEM images were evaluated for the percentage of newly formed bone and the rate of the test material. Histomorphometry analysis showed no significant differences in bone percentage between the treatment groups.

## **Discussion**

### **Summary of the main findings**

This systematic review aimed to assess the effects of incorporating platelet-derived growth factor (PDGF) or enamel matrix derivatives (EMD) into graft material for alveolar ridge preservation by assessing the osseous healing of the extraction socket.

The data collected from this review indicate that EMD did not provide additional clinical or radiographic benefits when used with standard ARP materials in the posterior maxilla. ARP with MSCB and membrane alone was effective in preserving ridge dimensions and facilitating implant placement (Hong et al. 2020) (9).

On the other hand, using rhPDGF for ARP along with bone graft material resulted in fewer residual bone graft particles compared to using bone graft alone, which indicates more rapid turnover of the bone graft when rhPDGF is added (Geurs et al. 2014) (7). Additionally, the inclusion of rhPDGF to the bone graft material enhanced the subjective bone quality after 8 weeks of ARP, indicating that rhPDGF may enhance the extraction socket healing and decrease the healing time before dental implant placement (Ntounis et al. 2015) (8).

Upon comparing the effect of rhPDGF and EMD on osseous healing histologically and clinically at the time of implant placement, it was noted that the use of PDGF resulted in a higher percentage of new bone formation,  $39.6\% \pm 11.3\%$ , versus the use of EMD, which resulted in  $23.9\% \pm 9.3\%$ . Although this percentage difference was not statistically significant, a clinical observation in the same study reported that the rhPDGF-treated sites demonstrated a convex ridge form that was optimal for implant placement when compared to the EMD and control groups that demonstrated incomplete ridge regeneration (concave) and compromised implant placement (Nevins et al. 2011) (6).

#### **Study limitations:**

##### **Nevins et al (2011):**

- **Small Sample Size:** Only 16 sites (4 per group) were analyzed, limiting statistical power and generalizability.
- **Biopsy Location Bias:** Core samples were often taken from palatal areas (due to inadequate ridge preservation in some groups), which may have included native bone and skewed histomorphometry results. There was no mention of the extraction socket location within the arch (anterior, posterior, maxillary, or mandibular)

- **Statistical Non-Significance:** Despite observed trends, no statistically significant differences were found among groups ( $P = .18$ ).
- **Inability to Distinguish New vs. Native Bone:** Histomorphometry measured total bone percentage but couldn't reliably differentiate between newly formed and existing bone.
- **Short Follow-up:** Evaluation was limited to 5 months, not assessing long-term bone stability or implant success.

**Geurs et al (2014) & Ntounis et al (2015):**

- Although the study mentioned that it was done in a bicuspid area, it didn't determine the location of each bicuspid (maxillary, mandibular, right, or left)
- The specimen collected was superficial, and according to the study, its dimensions were 2x6 mm. However, they mentioned using a 2mm trephine drill, which does not correlate with the size of the collected sample.
- **Short follow-up period (8 weeks):** Does not reflect long-term healing or implant success.
- **Small sample size (41 patients):** Reduces statistical power and generalizability.
- **Homogeneous population:** Mostly Caucasian women around 52 years old, limiting applicability to other demographics.
- **No use of barrier membranes:** Atypical for standard guided bone regeneration protocols.
- **No volumetric or radiographic data:** Only histologic assessment was used to evaluate healing.
- **Single socket per patient:** Limits analysis of inter-site variability within individuals.
- There was no mention of the implant type, size, or length.

- **Subjective Bone Quality Assessment:** Bone quality was evaluated based on the surgeon's feel during drilling (Misch classification), which is inherently subjective, even with their use of preoperative calibration.
- **Short-Term Observation:** Healing and bone quality were assessed only 8 weeks post-extraction, which may not fully reflect long-term outcomes.
- **Lack of Objective Bone Density Measures:** No use of CBCT or densitometry to quantify bone quality; reliance on tactile feedback limits scientific rigor.
- **Small Sample Size per Group:** Each group had 9–12 patients, which limits statistical power and generalizability.
- **Histological Data Referenced from Prior Study:** Some results (e.g., histomorphometry) were pulled from a previous publication by the same authors, not newly presented.
- **Potential Bias from Graft Visibility:** Although surgeons were blinded to graft type, residual graft material might have subtly revealed group allocation during surgery, which would be the same case in the Nevins et al (2011) study.
- **The studies lacked specification as they compared the histology collected from the first half of osteotomy (using the trephine) to the subjective feedback from the drilling experience from the second half of osteotomy.**

**Hong Lee et al (2020):**

- **Small Sample Size:** The final analysis included only 28 participants, with only 8 in the control group, which reduced the statistical power, especially for comparisons involving implant placement modalities.

- **Use of Mean Imputation for Missing Data:** To compensate for participant dropouts, the authors used unconditional mean imputation to fill in missing data in the control group. This method may underestimate variability and introduce bias in the results.
- **Subjective Patient-Reported Outcomes:** Measures of postoperative discomfort (e.g., pain, swelling) were based on self-reported questionnaires, which can be influenced by perceptual bias and individual pain thresholds.
- **Lack of Histological Evaluation:** The study did not include histomorphometry or tissue-level analyses, limiting the ability to assess the quality of bone regeneration and the biological effects of EMD at a microscopic level.
- **Limited to posterior maxilla:** The study was confined to the posterior maxilla, so findings may not apply to anterior sites or the mandible, where anatomical and healing dynamics differ.

#### **Agreement and disagreement with other excluded studies using EMD and PDGF**

Jiang et al (1999) conducted an in vitro study to assess the dynamics of the adsorption of PDGF-BB to anorganic bovine bone matrix and to determine if bone cell growth is enhanced by the addition of PDGF-BB to the mineral matrix as compared to the bone matrix alone. Jiang concluded that PDGF-BB can be adsorbed to the anorganic bovine bone mineral matrix and that this growth factor subsequently enhances the osteogenic properties of this bone graft material, suggesting that PDGF-BB has the potential to be combined with bovine bone graft for clinical application (13).

Shah et al. (2014) considered PDGF as one of the facilitating factors in bone regeneration. They mentioned that the most important specific activities of PDGF that assist in bone regeneration and wound healing are: Mitogenesis (increase in the cell populations of healing cells), Angiogenesis (endothelial mitoses into functioning capillaries), and Macrophage activation (debridement of the wound site and a second-phase source of growth factors for continued repair and bone regeneration). And summarized its mechanism of action in the following diagram. Shah concluded that PDGF plays a pivotal role in bone regeneration (11).

In addition, Mendoza-Azpur et al. (2022) concluded in their pilot study on the use of rhPDGF in ridge preservation that PDGF is an efficient biomaterial for avoiding post-extraction resorption of the alveolar ridge. The addition of rhPDGF-BB appears to improve the biologic features of the newly formed bone and decrease bone resorption (14).

Atieh et al. (2023) concluded in their randomized controlled study evaluating EMD in alveolar ridge preservation that there were no significant differences in radiographic mean measurements of alveolar ridge height and width following alveolar ridge preservation with DBBM and EMD, or DBBM alone (14).

These findings align with the conclusions drawn from the results of Hong Lee's (2020) and Nevins' (2011) studies (9) (6).

The findings from this systematic review regarding the effect of PDGF and (EMD) on alveolar socket preservation align with the American Academy of Periodontology's evidence consensus statement on the use of biologics in clinical practice. The consensus concludes that the use of

biologics, including rhPDGF-BB and EMD, is generally safe in the context of periodontal practice. However, due to the limited evidence available for certain indications, such as alveolar ridge preservation and reconstruction, further clinical studies are recommended to confirm the therapeutic effect of biologics.

## Conclusion

This systematic literature review aimed to assess the effect of adding Enamel Matrix Derivatives (EMD) versus Platelet-Derived Growth Factor (PDGF) to bone grafts used for alveolar ridge preservation by evaluating the osseous healing of extraction sockets. The findings shows that:

- Few studies met the inclusion criteria. Screening 292 publications resulted in only four studies (1.3%) that fit the study design criteria.
- The evaluation methods varied among the studies, using histology, clinical scores, histomorphometry, or cone-beam computed tomography (CBCT) evaluation.
- The inconsistency and lack of uniformity in the studies made it difficult to conduct a meta-analysis.
- All the studies included agreed that more human clinical trials need to be done to confirm their findings

Considering the previously discussed issues and within the limited number of studies, we can conclude that:

- 1- rhPDGF-BB may have the potential to positively affect osseous healing when added to the graft material during alveolar ridge preservation, by accelerating the early turnover of the bone graft.
- 2- EMD may have no additive effect on providing additional benefits in the alveolar ridge preservation.
- 3- Upon comparing the effect of rhPDGF and EMD, it seems that rhPDGF results in better clinical outcomes (convex contour on clinical re-entry) when compared to EMD, which resulted in a concave ridge contour upon clinical re-entry. On the other hand, there was

no significant difference in the new bone formation between the rhPDGF and EMD groups.

- 4- Further investigations and comparative human studies using controlled clinical trial protocols are needed to confirm whether either EMD or PDGF has an additive effect on the osseous healing when added to a bone graft during Alveolar ridge preservation.

## LIST OF JOURNAL TITLE ABBREVIATIONS

Biomed Res Int.....	BioMed Research International
Clin Implant Dent Related Res.....	Clinical Implant Dentistry and Related Research
Clin Oral Impl Res.....	Clinical Oral Implants Research
Eur J Oral Implantol.....	International Journal of Oral Implantology
Implant Dent.....	Implant Dentistry
Int J Oral Implantol.....	International Journal of Oral Implantology
Int J Oral Maxillofac Implant..	The International Journal of Oral and Maxillofacial Implants
J Clin Periodontol.....	Journal of Clinical Periodontology
J Periodontol.....	Journal of Periodontology
J Prosthet Dent.....	The Journal of Prosthetic Dentistry
JADA.....	Journal of the American Dental Association
Med Oral Patol Oral Cir Buccal.....	Medecina Oral, Patologia Oral y Cirugia Bucal
Periodontol 2000.....	Periodontology 2000

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## CURRICULUM VITAE

