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Enamel matrix derivate induces periodontal regeneration by activating growth factors: A review

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SUMMARY

Objective. The aim of this article is to review the effect of enamel matrix derivate (EMD) on growth factors activation for periodontal regeneration.

Material and methods. Online databases, such as PubMed, Cochrane Library, PMC, Science Direct were searched by using the following keywords in various combinations: emdogain, periodontal regeneration, growth factors, transforming growth factor, bone morphogenetic protein, fibroblast growth factor and vascular endothelial growth factors. All studies fulfilling the selection criteria were carefully reviewed for the focused question: "Does enamel matrix derivate induces the activity of growth factors, important in periodontal regeneration?".

Results. 1378 articles were found in the databases using keywords. After duplicate citations screened, inclusion/exclusion criteria applied, excluded articles after titles, summaries and full-text reading 14 articles were included in the literature review.

Conclusion. Enamel matrix derivate (EMD) was found to have a possitive effect on periodontal tissue regneration. By stimulating secretion and activating functions of growth factors, such as transforming growth factor-β (TGF-β), bone morphogenetic proteins (BMP), vascular endothelial growth factors (VEGF) and fibroblast growth factor-2 (FGF-2), EMD induces production of new alveolar bone, new root cementum and functionl periodontal ligament (PDL) and new blood vessels formation in periodontal area. Due to this production, the probing depth of periodontal pocket is being reduced.

Key words: emdogain; enamel matrix derivate; growth factors; periodontal regeneration.

INTRODUCTION

Successful periodontal treatment can be achieved by: 1. removal of etiological factor; 2. reduction of inflammation; 3. regeneration of lost periodontal tissue. There are several periodontal regenerative therapy methods, including guided tissue regeneration (GTR), bone grafting (BG) and enamel matrix derivate (EMD) application (1, 2). On the other side, periodontal therapy is performed to reduce periodontal pocket and improve clinical attachment (CAL) levels. Moreover, a significant evidence has been observed that EMD induces regeneration of periodontal tissues and improves CAL and probing pocket depth (PD) (3). EMD is extracted from the developing teeth germs of 6-month old piglets and is also known as Emdogain®. EMD adsorbs on decontamined root surfaces and alveolar bony defects and forms an insoluble scaffold complex. This complex promotes recolonization of periodontal cells, inducing periodontal regeneration (1-5, 8-12). Futhermore, many in vitro studies demonstrated that EMD induces molecular mediators. Enamel matrix proteins have an ability to increase transforming growth factor-β (TGF-β), bone morphogenetic proteins (BMP), vascular endothelial growth factors (VEGF), fibroblast growth factor-2 (FGF-2) production and reduce interleukin-4 gene (IL-4) expression in periodontal ligament (PDL) fibroblasts (4).

MATERIALS AND METHODS

Online databases, such as PubMed, Cochrane Library, PMC, Science Direct were searched. For a literature review search keywords were used: emdogain AND periodontal regeneration AND growth

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factors OR emdogain AND transforming growth factor OR emdogain AND bone morphogenetic protein OR emdogain AND fibroblast growth factor OR emdogain AND vascular endothelial growth factors. We found 236 publications in Pubmed, Cochrane Library – 3, PMC – 916, Science Direct – 223.

Results were checked for duplicates, the inclusion/exclusion criteria applied, the titles, abstracts and full texts were reviewed in order to exclude all inadequate articles and finally we included 14 studies in our literature review. The process of articles selection is presented in the diagram (Figure).

Studies were included despite of the type of scientific articles (in vitro studies, review articles). The article selection criteria were determined according to the subject of study and analysis of the results:

- Articles analyzing the periodontal regenerative treatment approaches of chronic periodontitis;
- Research on effectiveness of treatment;
- Articles describing EMD effect on growth factor activity;
- Articles published in English in 2012-2018.

Articles exclusion criteria were:

- in vivo studies;
- Participants have a systemic disease, p. e., diabetes;
- Study object was soft tissue regeneration, including gingiva and dental pulp;
- Regenerative therapy using enamel matrix derivate was combined with membranes or bone substitute;
- Animal studies.

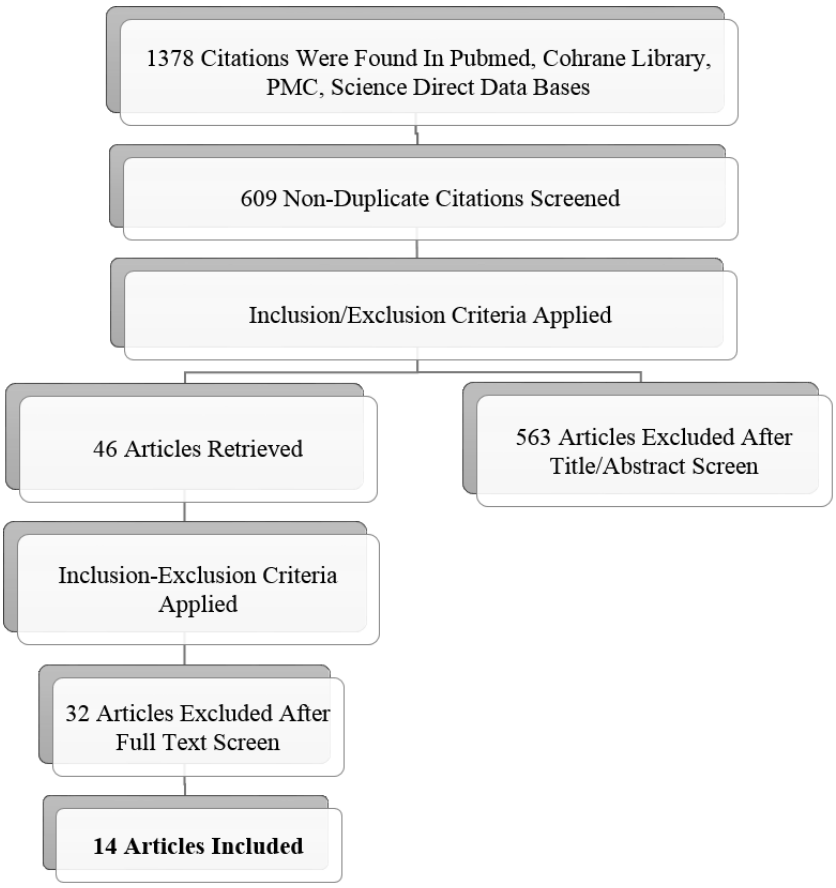

Fig. The PRISMA Flow Diagram

RESULTS

1378 articles were found in the databases using keywords: emdogain, periodontal regeneration, growth factors, transforming growth factor, bone morphogenetic protein, fibroblast growth factor and vascular endothelial growth factors. The studies over 6 years were not included in this review, except 4 articles. After duplicate citations screened, inclusion/exclusion criteria applied, excluded articles after titles and summaries screen – 46 articles were retrieved. The articles which conformed the requirements were downloaded and read. After full-text reading 14 articles were involved in the literature review. 32 articles were not included because study subjects and analysis of the results were not suitable for this review.

TGF-β growth factor was described in 6 articles. 5 articles discussed the studies on BMP, VEGF and PDGF growth factors, while FGF-2 growth factor was represented in 4 articles.

12 of the included articles presented in vitro studies of EMD affect on growth factors and 2 articles were original researches, one of them was about all involved growth factors (including TGF-β, BMP, VEGF, PDGF and FGF-2) and the other one overviewed EMD effect only on BMP growth factor. (Table).

DISCUSSION

According to analyzed literature, primary human osteoblasts and periodontal ligament (PDL) cells were isolated from non-impacted premolars. Those cells were exposed to EMDs carriers and examined for its ability to induce cell proliferation and differentiation in vitro. Results were obtained, stained and examined with light microscopy (2, 3, 7, 8, 11, 13).

It has been suggested that EMD stimulates pre-osteoblasts proliferation and osteoblasts - like cells differentiation and proliferation. Based on this effect, it is obviously that EMD induces pre-osteoblasts and osteoblasts - like cells differentiation to osteoblasts that play an important role in formation of new alveolar bone, root cementum and functional periodontal ligament (1, 4, 7).

First, specific cells must be attached to the substrate before migrating and proliferating to the healing area where those cells provide the cellular and molecular mechanisms needed to clean the inflammatory area and initiate the new tissue growth via effects on growth factors (1).

Growth factors are involved in numerous important cellular events that play an important role in many physiological and pathological processes by binding to specific cell surface receptors. It has been established that a number of polypeptide growth regulate cell proliferation, chemotaxis or differentiation. Specific growth and differentiation factors, such as insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor-β (TGF-β) and bone morphogenetic protein (BMP) 2, have an effect on stimulating cellular activities associated with periodontal regeneration (4).

To begin with, TGF-β belongs to TGF-β superfamily, which consists of 5 isoforms of TGF-β (2-7). This growth factor is important in regulating many cellular processes. It has been established that TGF-β plays a significant role in cellular growth, apoptosis, homeostasis, differentiation, migration, wound healing, fibrosis, angiogenesis and carcinogenesis (2, 4, 6). TGF-β has been specified to take an important part in development of periodontium, growth and differentition of fibroblasts and tissue formation, including collagen synthesis, formation of extracellular peri-

Table . Analyzed researches'results

No.	Authors	Year	Study	Described growth factor in the study				
				TGF-β*	BMP**	VEGF***	PDGF****	FGF-2*****
1	Marzina Wyganowska - Swiatkowska, et al.	2015	*Review*	+	+	+	+	+
2	Sakoda K., et al.	2012	*in vitro*			+		+
3	Masahiro Kitamura, et al.	2016	*in vitro*					+
4	Oscar Villa, et al.	2016	*in vitro*			+	+	+
5	Richard J Miron, et al	2015	*in vitro*	+	+			
6	Karim M. Fawzy El-Sayed, et al.	2013	*in vitro*		+			
7	Fernando Suarez-Lopez del Amo, et al.	2015	*Review*		+			
8	Nora H.M. Heng, et al.	2015	*in vitro*	+				
9	Kristina Bertl et al.	2009	*in vitro*	+		+	+	
10	Alexandra Sta¨ hli et al.	2014	*in vitro*	+				
11	Bradshaw M. Stout et al.	2013	*in vitro*			+		
12	Chol H. Chong et al.	2009	*in vitro*				+	
13	Nokhbehsaim M. Et al.	2011	*in vitro*	+				
14	Philippe Kémoun et al.	2011	*in vitro*		+			

*TGF-β - transforming growth factor-β
**BMP - bone morphogenetic proteins
***VEGF - vascular endothelial growth factors
****PDGF - platelet–derived growth factors
*****FGF-2 - fibroblast growth factor–2

odontal matrix formation (2, 4). Some studies have postulated that TGF-β also regulates proliferation of oral epithelial cells and human gingival fibroblasts. It can be concluded that EMD induces DNA synthesis and cell proliferation in human PDL fibroblasts by stimulating of TGF-β releasing (2, 5, 7).

The other biological agent - BMP is a member of TGF-β superfamily of growth factors (1, 4, 5, 8, 9). BMP takes part in morphogenesis and development of various tissue, cell proliferation, apoptosis and extracellular matrix synthesis. This growth factor is also involved in stimulation of cartilage and bone formation (1, 4, 8). In periodontics, BMP induces PDL cell differentiation into osteoblasts and increases tissue mineralization. Moreover, several studies have suggested that BMP downregulates mineralization of cementoblasts. Additionally, this growth factor modulates bone formation, contour and density through endochondral formation and autoinductive bone formation (1). The other important BMP function is synthesis of extracellular matrix proteins that are involved in stimulation of glycosaminoglycan and collagen type II production. This function depends on the balance of metalloproteinase-2 (MMP-2) and its inhibitor. Moreover, this inhibitor can cooperate with FGF and VEGF via structurally similar proteins that are the main signal transducers for receptors of the FGF-β superfamily, which are critically important for regulating cell development and growth (SMAD) (4, 8).

As for VEGF, this growth factor stimulates endothelial proliferation, migration and specialization of new blood vessels during embryogenesis, later development and healing (4, 6, 10, 11). Studies in vitro has shown EMD induced chemotactic effect on endothelial cells. It has also been proved that EMD stimulates the secretion of VEGF in PDL cells and fibroblasts (4, 6). Moreover, EMD stimulates numerous molecular and cellular processes, involved in angiogenesis (10, 12). Formation of new blood vessels plays an important role in reduction of inflammation and stimulation of healing (4, 6, 10).

In fact, PDGF activates proliferation, migration and stimulates matrix sythesis in gingival and PDL fibroblasts, cementoblasts, pre-osteoblasts and osteoblasts (1, 4, 6, 11, 13). Several studies have proved the cooperation of PDGF with other growth factors, such as TGF-β, VEGF. PDGF has VEGF-like effects on new blood vessels formation (4, 13).

The last discussed growth factor FGF-2 has an angiogenetic and mitogenetic effects on mezenchymal cells during organogenesis (4, 10, 11, 14). This growth factor plays an important role in the recruitment of hemopoietic elements in bone marrow stroma (4). FGF-2 also cooperates with VEGF. When present together may result in a synergistic effect on angiogenesis (10). Because of this mechanisms, EMD has been observed to stimulate healing of connective tissue. Very similar FGF-2 and VEGF cooperation in a synergistic way has been established in many studies of those growth factors effect on PDL cells (4, 10). Based on this synergistic mechanism, it can be concluded that FGF-2 is a key in periodontal regeneration (10). The other important FGF-2 function is interpreted by its effect on osteoblasts. EMD has an ability to increase TGF-β and FGF-2 in osteoblasts. FGF-2 stimulates proliferation of osteoblasts but reduces their differentiation (4). Moreover, histological studies revelead that recombinant human fibroblast growth factor-2 (rhFGF-2) enhances the amount of Sharpey‘s fibers in new root cementum, new functionally oriented PDL fibers nd new alveolar bone (14).

CONCLUSION

The regenerative EMD impact on periodontal tissue can be assocciated with its effect on growth factors, such as transforming growth factor – β, bone morphognetic proteins, fibroblast growth factor, vascular endothelial growth factor and platelet-derived growth factor. These biological agents are involved in new alveolar bone, root cementum and functional periodontal ligament formation. With reference to new periodontal tissue formation, the depth of probing periodontal pocket can be reduced. It can be concluded, that the main goal of periodontal therapy, which is the seeking of regeneration, can been achieved via this pathway.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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