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# Enamel Matrix Derivative: An effective regenerative modality (A Literature Review).

Medical Science

**KEYWORDS :** Enamel matrix derivative, Emdogain, Periodontal regeneration

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## ABSTRACT

*The role of regenerative periodontal therapy is the reconstitution of lost periodontal structures i.e. formation of new root cementum, periodontal ligament, and alveolar bone. The outcome of basic research has pointed to the important role of enamel matrix protein derivative (EMD) in periodontal wound healing. Histological results from animal and human studies have shown that treatment with EMD promotes periodontal regeneration. Moreover, clinical studies have indicated that treatment with EMD positively influences periodontal wound healing in humans. The goal of this paper is to review the existing literature on EMD.*

**Introduction**

One goal of periodontal therapy is to provide a dentition that functions in health and comfort for the life of the patient.1 Studies reporting tooth loss among patients receiving periodontal treatment show that, this goal is a reality.2,3 The validity of this statement is enhanced in view of the contrary results observed among those who were untreated.4 Therapeutic approaches to the treatment of periodontitis may be non surgical and surgical.5 Surgical procedures involving root conditioning, autografts, allografts, xenografts, and/or barrier membranes for guided tissue regeneration have been shown to contribute to a successful regenerative outcome.6

In 1997, an alternative approach for periodontal regeneration was introduced that was based on embryonic tooth formation.7,8 This approach uses an extract of embryonic enamel matrix, termed 'enamel matrix derivative' (EMD), thought to induce mesenchymal cells to mimic the processes that take place during the development of the nascent root and periodontal tissues.

**Composition of enamel matrix proteins**

The major fraction of the enamel matrix proteins is composed of amelogenins. The second largest component is the enamelins.9 Enamelins have been found to contain serum proteins,10,11 and the more general term "non-amelogenin" is now commonly used to describe this high molecular weight fraction, which includes proline-rich enamelin, tuftelin, and tuft proteins.12-14 Three matrix proteins, corresponding to amelogenin, enamelin, and sheathelin, and two enzymes, corresponding to MMP-20 and EMSP115, have been purified and the cDNA cloned from developing porcine teeth. EMD and amelogenins stimulate growth of multiple mesenchymal cell types including fibroblasts, cementoblasts, osteoblasts, and stem cells.16,17 They also enhance expression of tissue-specific maturation markers, such as alkaline phosphatase, collagen, and osteocalcin, within osseous tissues.18

The commercially available EMD (Emdogain®, Biora AB, Malmo, Sweden) is used for the treatment of periodontal defects. It acts as a tissue-healing modulator mimicking the events that occur during root development and helps to stimulate periodontal regeneration.19,20

**Mode of action**

Effect of EMD on periodontal ligament (PDL) cells in culture has been investigated.21 EMD enhanced proliferation of PDL cells, but not epithelial cells. It increased total protein production by PDL cells and promoted mineralized nodule formation of PDL cells.22 Scanning electron microscopy showed that EMD appeared to increase attachment of periodontal ligament fibroblasts to diseased root surfaces. In addition, amelogenin was shown to have a cell-adhesive activity, which may partially explain the therapeutic effect of EMD in periodontal regeneration.23

Not all cells involved in periodontal regeneration respond to EMD in a comparable manner. Attachment rate, growth factor production, proliferation, and metabolism of human PDL cells in culture were all significantly increased in the presence of EMD (24). In contrast, EMD increased cAMP and PDGF-AB secretion in epithelial cell cultures. Results from this and earlier studies suggest that EMD favors mesenchymal cell growth over growth of epithelial cells. Furthermore, it had been shown earlier that EMD also seems to exhibit a cytostatic effect upon cultured epithelial cells.25 This may explain EMD's biological 'guided tissue regeneration' effect observed in vivo, analogous to the mechanical prevention of barrier membranes. The effect of EMD on matrix synthesis was investigated with the use of cultured periodontal fibroblasts. EMD was found to regulate cementoblast and osteoblast activities.26 In addition, EMD can regulate dental follicle cell activity by increasing matrix protein production and the follicle cell differentiation into cementoblasts and osteoblasts.

EMD has the ability to regulate cells in the osteoblastic lineage.27 EMD induced differentiation of mature well-established osteoblasts that indicates it is an osteoconductive agent.28 However, recent in vitro studies suggest that EMD may have the ability to induce osteochondral progenitor cells to differentiate. In a multipotent mesenchymal cell line (C2C12), it was shown that EMD converts the differentiation pathway of the mesenchymal cells into osteoblasts and/or chondroblasts.29 At high concentrations, EMD inhibits terminal differentiation of cementoblasts with respect to mineralized module formation.30 This supports the idea that EMD is important for increasing the pool of cells required for periodontal regeneration and for stimulating the early differentiation process, but other factors in the environment for certain cell types may be required to continue the regenerative process.

**EMD and GTR**

GTR is a well-established successful therapeutic method for achieving clinical periodontal regeneration in humans, since both non-resorbable31,32 and resorbable barrier membranes33 achieve good clinical results based on histological

assessments. A potent factor which adversely affect the outcome of every regenerative procedure is bacterial load. Several studies have shown that bacteria may heavily colonize exposed membranes, and that there is a negative relationship between attachment gain and bacterial colonization of the barrier material.34-37 EMD has a marked inhibitory effect on the growth of the Gram negative periodontal pathogens, without a similar effect on the Gram-positive bacteria.38 Thus a combination of both techniques can prove very beneficial for regeneration.

EMD in combination with bone grafts

It is well-known that the outcome of any type of regenerative procedure is strongly dependent upon the available space under the mucoperiosteal flap,39, and that the stability of the wound under the flap during healing is a crucial factor for periodontal regeneration. Combining bone grafts or bone substitutes with GTR in the treatment of intrabony defects resolves this problem by providing space maintenance. One of the limitations inherent in the use of early commercially available EMD was related to its physical handling properties.40 The EMD formulation was semi-fluid in consistency and lacked the space-maintenance ability of solid graft materials. Because space maintenance is a desirable physical characteristic of a regenerative material, particularly if bone formation is one of the treatment objectives, it was suggested that a combination of demineralized freeze-dried bone allograft (DFDBA) and EMD be used to overcome problems related to EMD fluidity.41

**EMD and xenograft or alloplast materials**

Bovine-derived bone xenograft (BDX) appears to have the ability to augment the effect of EMD in reducing probing depth, improving clinical attachment level, and promoting defect fill when compared with EMD alone or OFD in the treatment of intrabony periodontal defects.42 Similar results were obtained when EMD or autologous fibrinogen/fibronectin system (AFFS) was used in combination with BDX.43 Moreover, adding a membrane to the combined treatment of BDX and EMD may even enhance these results. Studies have reported conflicting results when EMD and BDX were used in combination compared with BDX alone. No statistically significant differences were found in any of the examined clinical parameters between the 2 treatment groups.44

**Effect of EMD on early wound healing**

A quantitative study by Lafzi et al45 sought to illustrate the ultrastructural changes associated with a human gingival wound 10 days after application of EMD as an adjunct to a laterally positioned flap in a patient with gingival recession. Ten days after the operation, a gingival biopsy specimen was obtained from the dentogingival region and examined using a transmission electron microscope. A considerable difference was found in both the cellular and extracellular phases of the EMD and non-EMD sites. Fibroblasts at the EMD site were rounded with plump cytoplasm and euchromatic nuclei. Well-developed rough endoplasmic reticulum and numerous mitochondria could be detected. In contrast, the fibroblasts at the non-EMD site were of flattened spindle-like morphology. It seems that EMD may enhance certain features of gingival wound healing, which may be attributable to its anti-apoptotic, antibacterial, or anti-inflammatory properties.

**EMD and Pulpotomy**

EMD as a pulpotomy agent in primary teeth has been also evaluated histologically. In a study of 10 carious primary canines among teeth deemed for serial extraction, Emdogain gel was used as a pulp dressing material on the amputated pulp stumps. Most of the teeth showed coalescing islands of dentin-like tissue trying to bridge the full width of the coronal pulp at the interface between the wounded and unharmed pulp tissue below the amputation site. 46

**CONCLUSION**

Application of enamel matrix proteins in the form of Emdogain has set a modern standard for periodontal regeneration therapy. Surgical periodontal treatment of deep intrabony defects with EMD promotes periodontal regeneration. Surgical periodontal treatment of deep intrabony defects using EMD may lead to significantly greater improvements in clinical parameters. A number of experiments are in progress to evaluate the role of EMD and its potential use in endodontics, bone regeneration, implantology, traumatology, and wound care.

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