

# THE USE OF AN ENAMEL MATRIX PROTEIN DERIVATIVE (EMDOGAIN®) IN REGENERATIVE PERIODONTAL THERAPY. WHICH APPLICATIONS ARE EVIDENCE-BASED? PART III. RESULTS FROM HUMAN HISTOLOGICAL STUDIES

**Stefan-Ioan Stratul<sup>1</sup>, Darian Rusu<sup>1</sup>, Anton Sculean<sup>2</sup>**

## REZUMAT

Scopul terapiei parodontale regenerative este reconstituirea structurilor parodontale pierdute (de exemplu neformarea de cement radicular, ligament parodontal și os alveolar). Rezultatele cercetării fundamentale au arătat rolul important al derivaților proteinelor matricii smalțului (EMD) în vindecarea plăgii parodontale. Rezultatele histologice ale studiilor pe subiecți animal și umani au arătat că tratamentul cu EMD promovează regenerarea parodontală. Mai mult, studiile clinice au indicat faptul că tratamentul cu EMD influențează pozitiv vindecarea plăgii parodontale la om. Scopul trecerii în revistă de față este de a prezenta, bazat pe dovezile existente, indicațiile clinice pentru terapia regenerativă cu EMD.

**Cuvinte cheie:** regenerare parodontală, derivați ai matricii smalțului, studii de histologie umană

## ABSTRACT

The goal of regenerative periodontal therapy is the reconstitution of the lost periodontal structures (i.e. the new formation of root cementum, periodontal ligament and alveolar bone). Results from basic research have pointed to the important role of the enamel matrix protein derivative (EMD) in the 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 the current overview is to present, based on the existing evidence, the clinical indications for regenerative therapy with EMD.

**Key Words:** periodontal regeneration, enamel matrix derivative, human histology studies

Results of the first human-histological biopsy were published by Heijl in 1997.<sup>1</sup> A recession defect on a lower incisor was surgically created and treated with EMD. After a healing period of four months, the tooth as well as the surrounding soft and hard tissue was extracted and histologically evaluated. The histological investigation showed that a new layer of acellular root cementum covered 73% of the original defect depth. New alveolar bone has regenerated on 65% of the initial bone height.

In another study, Yukna and Mellonig treated with EMD 10 intrabony periodontal defects in eight patients.<sup>2</sup> The histological analysis six months after the treatment has shown in three biopsies a complete periodontal regeneration (i.e. new formation of root cementum, periodontal ligament and alveolar bone), while in three further biopsies, the healing was characterized by a new connective tissue attachment (i.e. new cementum with inserting collagen fibers). Four biopsies healed by a long junctional epithelium and without any signs of periodontal regeneration.

In a comparative clinical and histological investigation, the healing of intrabony periodontal defects was evaluated following treatment with EMD or Guided Tissue Regeneration (GTR) with a bioabsorbable barrier.<sup>3</sup> Six months after therapy, the clinical attachment level (CAL) showed a mean gain of  $3.2 \pm 1.2$  mm in the EMD group and of  $3.6 \pm 1.7$  mm in the GTR group. The histological analysis showed that in both groups the healing was mainly characterized by periodontal regeneration.<sup>3</sup> The mean value of new

<sup>1</sup> Department of Periodontology, Victor Babes University of Medicine, Timisoara, <sup>2</sup> Department of Periodontology, Radboud University Medical Center, Nijmegen, The Netherlands

Correspondence to:  
Anton Sculean, Department of Periodontology, Radboud University Medical Center, P.O. Box 9101, Philips van Leydenlaan 25, 6500 Nijmegen, the Netherlands, Tel: + 31 24 361 63 71, Fax: + 31 24 361 46 57  
Email: a.sculean@dent.umcn.nl

Received for publication: Feb. 22, 2008. Revised: May 19, 2008.

cementum and periodontal ligament amounted to  $2.6 \pm 1.0$  mm in the EMD group and to  $2.1 \pm 1.0$  mm in the GTR group. The mean value of new alveolar bone was  $0.9 \pm 1.0$  mm in the EMD group and  $2.1 \pm 1.0$  mm in the GTR group. A reparative healing by a long junctional epithelium occurred only in one biopsy from the EMD group. The results of the study have provided evidence that treatment with EMD promotes periodontal regeneration in humans and may lead to comparable clinical and histological results than the GTR therapy. These results were confirmed in subsequent reports by other authors, not only in intrabony but also in recession-type defects.<sup>4-9,10,11</sup>

EMD has been used as an adjuvant for laterally-positioned flap in the treatment of gingival recession. In an electronmicroscopic appraisal, a study from 2007 sought to illustrate the ultrastructural changes associated with a human gingival wound at 10 days after the application of EMD as an adjunct to a laterally-positioned flap in a patient with gingival recession.<sup>12</sup> The study suggested that EMD may enhance certain features of gingival wound healing, which may be attributable to its anti-apoptotic, anti-bacterial or anti-inflammatory properties.

Subsequent immunohistological studies have shown that following surgery, EMD remains up to 4 weeks on the root surface and the wound healing and/or remodeling process can be followed for a period of up to 6 months after treatment with EMD therapy.<sup>13-15</sup> A very recent human histology study has attempted to characterize the tissues developing on the root surface at 2 to 6 weeks following treatment of intrabony defects with EMD.<sup>16,17</sup> The results have shown that the newly formed tissues on the root surfaces were thick, collagenous, devoid of extrinsic fibers, and had an irregular surface contour. The presence of electron-dense, organic material in the collagenous matrix indicated at least partial mineralization. Embedded cells were numerous and the cells on the matrix surface were very large in size. It was concluded that following treatment with EMD, a bone-like tissue resembling cellular intrinsic fiber cementum may develop on the root surfaces, instead of acellular extrinsic fiber cementum. Furthermore, EMD may both induce *de novo* formation of a mineralized connective tissue on scaled root surfaces and stimulate matrix deposition on old native cementum. External root resorption was observed in two cases at six and 24 months following treatment with EMD, while no periodontal regeneration was observed, when EMD was applied in a non-surgical way into intrabony periodontal defects.<sup>18,19</sup>

Alternatively, EMD as a pulpotomy agent in primary teeth have been also evaluated histologically. In a study on ten carious primary canines among teeth deemed for serial extraction, Emdogain gel was used as pulp dressing material on the amputated pulp stumps.<sup>20</sup> 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. Based on the experiment, Emdogain showed promising results as a valuable material for use in pulpotomy procedures, especially in the primary dentition.

Based on the available evidence from human histological studies it may be concluded that the application of EMD in conjunction with periodontal surgery may promote formation of new cementum, periodontal ligament and bone in intrabony and recession defects. Moreover, when applied during periodontal surgery, EMD can be detected on the root surfaces for a period of at least four weeks. Based on current knowledge, there are no histologic data from human material evaluating the regenerative potential of EMD in furcation defects. There are also histological evidences that EMD may enhance the gingival wound healing in recession-type defects, while showing promising histological results in pulpotomy procedures on primary teeth.

## REFERENCES

1. Heijl L. Periodontal regeneration with enamel matrix derivative in one human experimental defect. A case report. *J Clin Periodontol* 1997;24:693-6.
2. Yukna RA, Mellonig J. Histologic evaluation of periodontal healing in humans following regenerative therapy with enamel matrix derivative. A 10-case series. *J Periodontol* 2000;71:752-9.
3. Sculean A, Donos N, Windisch P, et al. Healing of human intrabony defects following treatment with enamel matrix proteins or guided tissue regeneration. *J Periodont Res* 1999;34:310-22.
4. Mellonig JT. Enamel matrix derivative for periodontal reconstructive surgery: technique and clinical and histologic case report. *Int J Periodontics Restorative Dent* 1999;19:9-19.
5. Sculean A, Chiantella GC, Windisch P, Donos N. Clinical and histologic evaluation of treatment of intrabony defects with an enamel matrix protein derivative (Emdogain). *Int J Periodont Rest Dent* 2000;20:375-81.
6. Mazjoub Z, Bobbo M, Atiyeh F, Cordioli G. Two patterns of histologic healing in an intrabony defect following treatment with an enamel matrix derivative: a human case report. *Int J Periodontics Restorative Dent* 2005;25:283-94.
7. Rasperini G, Silvestri M, Schenk RK, Nevins ML. Clinical and histological evaluation of human gingival recession treated with a subepithelial connective tissue graft and enamel matrix derivative (Emdogain): a case report. *Int J Periodontics Restorative Dent* 2000;20:269-75.
8. Carnio J, Camargo PM, Kenney EB, Schenk RK. Histological evaluation of 4 cases of root coverage following a connective tissue graft combined with an enamel matrix derivative preparation. *J Periodontol* 2002;73:1534-43.

9. McGuire MK, Cochran DL. Evaluation of human recession defects treated with coronally advanced flaps and either enamel matrix derivative or connective tissue. Part 2: Histological evaluation. *J Periodontol* 2003;74:1126-35.
10. Sculean A, Windisch P, Dori F, et al. Emdogain in regenerative periodontal therapy. A review of the literature. *Fogorv Sz* 2007;100(5):220-32, 211-9.
11. Sculean A, Rathe F, Junker R, et al. The use of Emdogain in periodontal and osseous regeneration. *Schweiz Monatsschr Zahnmed* 2007;117(6):598-606.
12. Lafzi A, Farahani RM, Tubbs RS, et al. Enamel matrix derivative Emdogain as an adjuvant for laterally-positioned flap in the treatment of gingival recession: an electron microscopic appraisal. *Folia Morphol (Warsz.)* 2007;66(2):100-3.
13. Sculean A, Windisch P, Keglevich T, et al. Presence of an enamel matrix protein derivative on human teeth following periodontal surgery. *Clin Oral Invest* 2002;6:183-7.
14. Sculean A, Junker R, Donos N, et al. Immunohistochemical evaluation of matrix molecules associated with wound healing following treatment with an enamel matrix protein derivative in humans. *Clin Oral Invest* 2003;7:167-74.
15. Sculean A, Berakdar M, Windisch P, et al. Immunohistochemical investigation on the pattern of vimentin expression in regenerated and intact monkey and human periodontal ligament. *Arch Oral Biol* 2003;2003;48:77-86.
16. Bosshardt DD, Sculean A, Windisch P, et al. Effects of enamel matrix proteins on tissue formation along the roots of human teeth. *J Periodont Res* 2005;40:158-67.
17. Bosshardt DD, Sculean A, Donos N, Lang NP. Pattern of mineralization after periodontal tissue engineering with enamel matrix proteins. *Eur J Oral Sci* 2006;114 (Suppl. 1):225-31.
18. St. George G, Darbar U, Thomas G. Inflammatory external root resorption following surgical treatment for intra-bony defects: a report of two cases involving Emdogain® and a review of the literature. *J Clin Periodontol* 2006;33:449-54.
19. Sculean A, Windisch P, Keglevich T, et al. Histologic evaluation of human intrabony defects following non-surgical periodontal therapy with and without application of an enamel matrix protein derivative. *J Periodontol* 2003;74:153-60.
20. Sabbarini J, Mounir M, Dean J. Histological evaluation of enamel matrix derivative as a pulpotomy agent in primary teeth. *Pediatr Dent* 2007;29(6):475-9.