

# Periodontal Tissue Engineering and Regeneration: A Summary of Three Consensus Reviews on Periodontal Regeneration

Sixth European Workshop on Periodontology, February 2 – 6, 2008, Charterhouse Ittingen, Thurgau, Switzerland

In February 2008 the European Academy of Periodontology (EAP), a standing committee of the European Federation of Periodontology (EFP), invited seventy-three researchers and clinical experts from Europe and overseas for a 5-day consensus meeting on “Contemporary Periodontics.” Five working sessions covered the topics “Innovations in Periodontal Practice,” “Periodontal Tissue Engineering and Regeneration,” “Critical Issues in Bone Regeneration,” “Peri-implant Infections,” and “Periodontal Disease and Health.” The proceedings, 24 reviews and five consensus reports, were published in the Journal of Clinical Periodontology.

In the workshop on Periodontal Tissue Engineering and Regeneration, enamel matrix proteins (EMPs) and Straumann® Emdogain®, the commercial formulation of enamel matrix derivative (EMD), was a major aspect in discussions. The following articles summarize the reviews pertaining to this particular topic. The full reviews and consensus papers can be found in the Journal of Clinical Periodontology, volume 35, supplement 8.

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**Experts of group B: "Periodontal Tissue Engineering and Regeneration"**

**Back row, left to right:** Kuonen, P., Jepsen, S., Fourmousis, I., Van der Velden, U., Hughes, F., Etienne, D., Sculean, A.,

**Front row, left to right:** Yilmaz, S., Sicilia, A., Palmer, R., De Sanctis, M., Cortellini, P., Trombelli, L., Christgau, M., Bosshardt, D., Cairo, F.

# Positive Influence of Enamel Matrix Proteins on Periodontal Regeneration

## Summary of the paper “Biological mediators in periodontal regeneration: a review of enamel matrix proteins at the cellular and molecular levels”<sup>1</sup>

Dr. D. Bosshardt, University of Berne, Switzerland

### INTRODUCTION

Despite the fact that EMPs (enamel matrix proteins) have been in clinical use for more than 10 years<sup>2</sup> and a large body of clinical and histological data demonstrates the beneficial effect for regenerative periodontal therapy, the underlying mechanisms on the cellular and molecular level are not well understood. The aim of the review, therefore, was to analyze the functions of EMPs at cellular and molecular levels.

### METHODS

An extensive literature search was performed, using a stringent systematic approach with either of the key words:

- Enamel matrix proteins
- Enamel matrix derivative
- Emdogain
- Amelogenin

The search was conducted separately for cementoblasts, epithelial cells, gingival fibroblasts, osteogenic/chondrogenic/bone marrow cells, periodontal ligament cells, wound healing, and bacteria.

Inclusion criteria were:

1. Articles written in English;
2. In vitro and in vivo studies.

Exclusion criteria were:

1. Articles written in languages other than English;
2. Clinical or radiographic studies;
3. Periodontal regeneration studies with descriptive histology, histomorphometry, immunohistochemistry, or in situ hybridization;
4. In vivo and in vitro tooth developmental studies (with ameloblasts).

### RESULTS

Data from a total of 103 papers met the inclusion criteria and were analyzed. The results indicate that EMPs affect a variety of cell types, and influence:

- Cell attachment, spreading and chemotaxis
- Cell proliferation and survival
- Expression of transcription factors, growth factors, cytokines,
- Extracellular matrix constituents and other macromolecules
- Expression of molecules involved in regulating bone remodeling

In detail, in most studies EMPs caused an increase in cell attachment of epithelial cells, gingival fibroblasts and PDL fibroblasts, whereas adhesion of osteogenic cells was promoted depending on the differentiation/maturation state. EMD also had a chemotactic effect on endothelial cells.

The data on cell proliferation show that EMPs favor proliferation of PDL fibroblasts over gingival fibroblasts whereas the effect on epithelial cells appears to be cytostatic (but not cytotoxic).

Osteogenic cell proliferation is most prominent for cells in early maturation/differentiation stages and appears to decrease with increasing cell differentiation/maturation. Enhanced cell migration and proliferation appears to lead to accelerated wound fill rates in vitro using PDL fibroblasts, gingival fibroblasts and osteoblast-like cells.

Furthermore, it could be shown that EMPs stimulate the outgrowth of new blood vessels and increase the number of endothelial cells. EMD and particularly its vehicle, propylene glycol alginate (PGA) also demonstrated antibacterial properties.\*

In addition to these effects on a cellular level, various effects on the expression of transcription and growth factors are reported. EMPs have been shown to increase the expression of transcription factors related to the differentiation of osteoblasts/cementoblasts as well as chondroblasts. In terms of gene expression EMPs down-regulate genes involved in early inflammatory processes, while genes that encode growth and repair promoting molecules (including but not limited to TGF- $\beta$ , BMP-2, BMP-7, PDGF-AB, and VEGF) are up-regulated.

EMPs also stimulate total protein synthesis and the synthesis of specific extracellular matrix molecules. Finally, studies that evaluate the bone remodeling regulation system indicate that EMPs influence this by modulating the OPG and RANKL expression, thus indicating an indirect involvement in the bone remodeling process.

### CONCLUSION

EMPs increase cell proliferation of PDL and gingival fibroblasts and cells of osteoblast and chondrocyte lineage. EMPs have biological effects on cells of the osteoblast lineage including upregulation of markers of bone formation.<sup>3</sup> In conclusion the data analyzed in this review provides evidence that EMPs support wound healing and new periodontal tissue formation.

### PRACTICAL IMPLICATIONS

A large body of information is available provides a biological rationale for the use of EMPs for periodontal regeneration.

\*Olitzy, I (1965) Antimicrobial properties of a propylene glycol based topical therapeutic agent. *Journal of Pharmacological Science* 54, 787-788

# Well Established Clinical Evidence for the use of Emdogain in Intra-bony Defects

## Summary of the paper “Clinical outcomes with bioactive agents alone or in combination with grafting or guided tissue regeneration”<sup>4</sup>

L. Trombelli, R. Farina, University of Ferrara, Italy

### INTRODUCTION

While bone grafting and guided tissue regeneration (GTR) alone or in combination have been thoroughly investigated in the literature, a complete and predictable reconstruction of periodontal tissues is difficult to obtain with these methods. The review therefore aimed at determining the effect of the use of bioactive agents alone or in combination with grafts and/or GTR in intra-osseous and furcation defects. For purposes of this evaluation, these bioactive agents included Emdogain, recombinant human platelet-derived growth factor-BB (PDGF), platelet-rich plasma (PRP), peptide P-15, insulin-like growth factor (IGF), fibroblast growth factor (FGF) and bone morphogenetic proteins (BMPs).

### METHODS

Literature research was conducted using the MEDLINE database and the Cochrane Oral Health Group Specialist Register. Reference lists of review articles and relevant texts have been searched.

Only English articles with bioactive agents that had been tested clinically were included. As randomized controlled trials (RCTs) with bioactive agents are scarce (with the exception of Emdogain), the available published evidence was analyzed for each bioactive agent in different categories:

- Proof of principle (reporting on descriptive studies)
- Clinical effectiveness (only including RCTs and systematic reviews [SRs])
- Combination with grafts and/or GTR (descriptive studies, RCTs and SRs)
  - clinical effect of bioactive agent with graft and/or GTR
  - clinical adjunctive effect of bioactive agent combined with graft and/or GTR, compared to graft and/or GTR alone
  - clinical adjunctive effect of the graft and/or GTR when combined with the bioactive agent compared to the bioactive agent alone.

A total of 149 studies were included in this review.

### RESULTS

The number of available studies that could be included was by far highest for Emdogain (111 studies), followed by PRP (19 studies), P-15 (10 studies) and PDGF (6 studies). With the exception of Emdogain, RCTs evaluating the clinical effectiveness of different biologic agents are scarce and Emdogain was the only biologic agent where SRs, the highest level of evidence, are available [Fig. 1]. Several reports demonstrated substantial clinical attachment level (CAL) gains following application of Emdogain in intra-osseous defects, often accompanied by radiographically assessed defect fill. In furcation defects treated with Emdogain a case series as well as a RCT could be analyzed, confirming CAL and probing depth (PD) improvements over baseline that could be maintained over time. Furthermore Emdogain was evaluated in combination with different types of bone graft materials (autogenous, allogenic, xenogenic and alloplastic) in intra-osseous defects

and data indicate that the combination may improve the clinical performance over Emdogain alone, while the addition of a GTR membrane did not further improve the treatment result.

All three SRs indicated significant improvements in post operative CAL, PD and radiographic marginal bone levels when Emdogain was compared to open flap debridement alone.

The use of PDGF showed CAL gain or PD reduction in case reports on the treatment of class II furcation defects when combined with an allograft. However, no additional benefit was found in respect of CAL gain after 6 months of healing when comparing PDGF with the approved carrier graft to the carrier graft alone.

No clinical studies are available for the use of P-15 alone in the treatment of intra-osseous or furcation defects but adjunctive benefits have been observed when combined with a graft as carrier material.

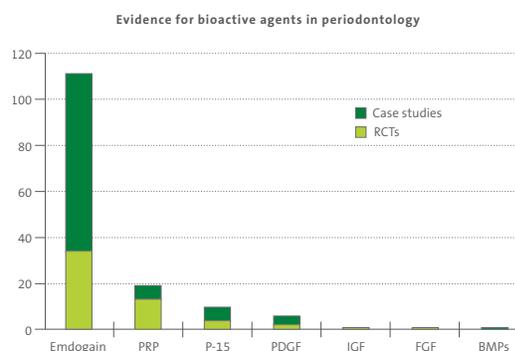
Contrasting results have been reported for the use of PRP in combination with a graft and no RCTs of intra-osseous and furcation defects with PRP alone are available.

### CONCLUSION

**The review concluded that Emdogain alone or in combination with grafts can be effectively used to treat intra-osseous defects and that the clinical results appear to be stable long-term.** With regards to practical implications, currently among the published data reviewed on the bioactive agents such as PDGF, PRP, and P-15, only Emdogain has substantial evidence for its use in intra-bony defects either alone or in combination with bone grafts. In addition, Emdogain is the only agent with evidence for treatment of mandibular class II furcation defects.

### CLINICAL IMPLICATIONS

Comprehensive evidence indicates the clinical use of Emdogain for periodontal regeneration in infrabony defects<sup>3</sup>



**Fig. 1** Number of clinical studies reviewed. Only Straumann® Emdogain has substantial evidence for periodontal regeneration

# Improving Esthetics in Recession Defects with Straumann Emdogain

## Summary of the paper “Treatment of gingival recession with coronally advanced flap procedures: a systematic review”

F. Cairo, U. Pagliaro, M. Nieri, University of Florence, Italy

### INTRODUCTION

Esthetic concerns or root sensitivity frequently require the treatment of buccal gingival recessions, whereby complete root coverage with good tissue appearance and minimal probing depth are the treatment goals. The coronally advanced flap procedure (CAF) is a very common approach to obtain root coverage. This systematic review evaluated this procedure for the treatment of Miller class I and II gingival recession defects<sup>5</sup> and the clinical benefit of adding adjuncts such as connective tissue graft (CTG), barrier membranes or Emdogain.

### METHODS

For this systematic review a literature search was conducted using the MEDLINE database, the Cochrane Oral Health Group Trials Register and previous systematic reviews. Only RCTs of Miller class I and II gingival recession defect treatment were evaluated. Included were studies of at least 6 months' duration using CAF alone or in combination with a connective tissue graft (CTG), a barrier membrane (BM), Emdogain, acellular dermal matrix (ADM), PRP or a living tissue engineered human fibroblast derived dermal substitute (HF-DDS).

The primary outcome measure was complete root coverage (CRC). RCTs comparing CAF with multiple combinations of the above methods were excluded.

No language restriction was applied.

### RESULTS

25 RCTs, reporting on 530 patients and 794 Miller Class I & II single gingival recession defects, fulfilled the requirements and were included in the review.

The findings showed that CAF is a safe and predictive procedure for recession reduction and root coverage, however, the meta-analysis shows that the addition of Emdogain to the procedure increases the probability of obtaining complete root coverage ( $p=0.003$ ) and leads to a greater recession reduction, CAL gain and increase in keratinized tissue (KT) width compared to the CAF alone [Fig. 2].

The addition of CTG to CAF similarly leads to better outcomes than CAF alone, whereas the addition of barrier membranes did not improve the results and a high incidence of complications was related to their use. Other adjuncts such as PRP, ADM or HF-DDS could not show an advantage over CAF alone. [Fig. 3]

Therefore only two treatments, CAF + Emdogain and CAF + CTG, could improve outcomes over CAF alone. CAF + CTG was associated with a higher KT gain, but Emdogain + CAF appeared to be an easier procedure and does not require a donor area for the CTG harvest. A split mouth study conducted by McGuire and Nunn (2003) compared CAF + Emdogain with CAF + CTG.<sup>6</sup> This study reported 95.1% mean root coverage in the Emdogain group and 93.8% in the CTG group; however, the difference was not statistically significant.

### CONCLUSION

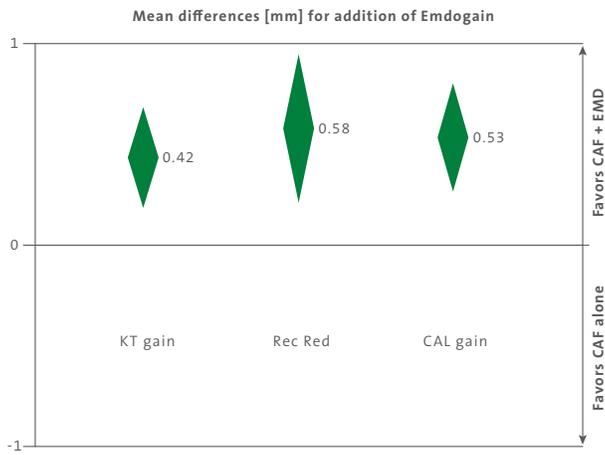
The review concludes that application of Emdogain or CTG in conjunction with CAF increases the probability in achieving complete root coverage in Miller Class I and II recessions. In terms of practical implications, these methods should be considered in conjunction with CAF to improve the probability of complete root coverage.<sup>5</sup>

### CLINICAL IMPLICATIONS

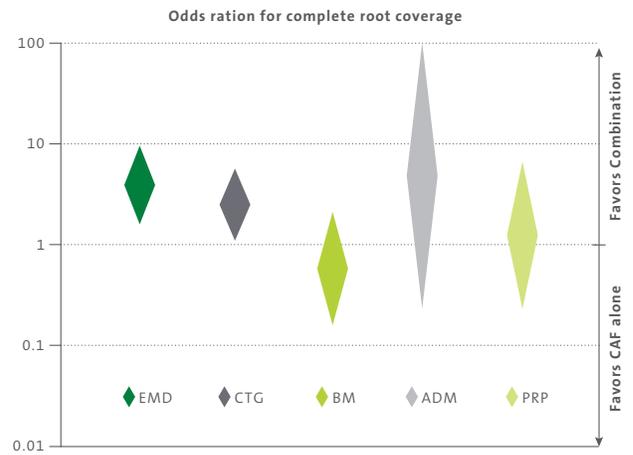
Use of Emdogain may improve the rate of complete root coverage achieved with CAF<sup>3</sup>

**Emdogain in combination with a coronally advanced flap (CAF) leads to a higher percentage of complete root coverage (CRC) than CAF alone**

**Improved clinical parameter through Emdogain**



**Fig. 2** Calculated mean differences for keratinized tissue (KT) gain, recession reduction (Rec Red), and clinical attachment (CAL) gain for additional use of Emdogain with CAF compared to CAF alone (confidence level 95%)



**Fig. 3** Odds ratios to obtain CRC for combinations of the CAF technique with additional materials. Only Emdogain or a connective tissue graft lead to a statistical significant (\*) higher rate of CRC (confidence level 95%).

- ◆ EMD: Emdogain
- ◆ CTG: Connective Tissue Graft
- ◆ BM: Barrier Membrane
- ◆ ADM: Acellular Dermal Matrix
- ◆ PRP: Platelet Rich Plasma

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