Growth and Amelogenin-Like Factors in Periodontal Wound Healing. A Systematic Review

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Background: Regeneration of tooth-supporting structures destroyed by periodontitis is a major goal of periodontal therapy. Periodontal tissue engineering utilizing growth and amelogenin-like factors (GAFs) applies advances in materials science and biology to regenerate alveolar bone, periodontal ligament, and cementum. Amelogenin-like factors (e.g., enamel matrix derivative [EMD]) and growth factors (e.g., platelet-derived growth factor [PDGF] and bone morphogenetic proteins [BMPs, also considered morphogens]) have demonstrated pleotrophic effects on the stimulation of several key events required for tissue regeneration including DNA synthesis, chemotaxis, differentiation, and matrix synthesis.

Rationale: GAFs have been used for the treatment of periodontal disease as shown in preclinical and clinical studies. This systematic review evaluates the evidence to support the utilization of EMD and growth factors (GFs) for periodontal repair and regeneration associated with natural teeth.

Focused Question: In patients with periodontal osseous defects, what is the effect of GAFs compared with controls on clinical, radiographic, histologic, adverse, and patient-centered outcomes?

Search Protocol: Two investigators searched MEDLINE, pre-MEDLINE, and the Cochrane Oral Health Group trials register for clinical and preclinical studies published in English. Hand searches were performed on the *International Journal of Periodontics and Restorative Dentistry, Journal of Clinical Periodontology, Journal of Dental Research, Journal of Periodontology*, and *Journal of Periodontal Research*. Searches were performed for articles published through April 2002. In addition, investigators contacted manufacturers of GAF products for related unpublished data and studies in progress.

Selection Criteria

Inclusion criteria: Randomized controlled clinical trials (RCTs), cohort studies, case-control studies, case reports, and preclinical (animal) randomized controlled investigations that included a cohort population diagnosed with periodontal disease and presenting data on intrabony/interproximal defects and/or furcation defects were screened.

Exclusion criteria: In vitro studies or those that did not include quantifiable data with respect to clinical or bone measures were not included.

Data Collection and Analysis: Meta-analyses were performed for studies that fulfilled the eligibility criteria for the following continuous variables: clinical attachment level (CAL), probing depth (PD), or bone level (radiographic, re-entry, or histologic). Heterogeneity was assessed to determine whether the differences among therapies were due to systematic confounding factors (as noted in study quality assessments).

Main Results

1. Eight studies, representing 7 RCTs and 1 quasi-experimental study, representing a total population of 511 subjects were analyzed with respect to EMD.
2. The majority of the remaining papers had a low evidence rating.
3. Most reports were case studies or case series without controls.
4. There were insufficient data to conduct a meta-analysis on the effect of growth factors used in periodontal repair around teeth.

Reviewers' Conclusions

1. There is evidence supporting the use of EMD for periodontal osseous defects to improve CAL and reduce PD, although long-term benefits have not been established.
2. EMD has demonstrated notable consistency among the studies investigated in terms of superiority to controls (in general compared to open flap debridement [OFD]).

3. EMD appears to be safe for single and multiple administrations in terms of lack of elicitation of antibody responses or other local/systemic inflammatory events.

4. Preclinical and initial clinical data for growth factors appear promising but are insufficient to draw definitive conclusions at this time.

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KEY WORDS

Bone morphogenetic proteins; enamel matrix derivative; growth factors, platelet-derived; periodontal diseases/therapy; review literature; meta-analysis.

BACKGROUND

Growth factors (GFs) are natural biological mediators that regulate crucial cellular events involved in tissue repair, such as DNA synthesis, chemotaxis, differentiation, and matrix synthesis.[1] Examples of GFs used experimentally to treat periodontal disease include platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-ß), basic fibroblast growth factor (FGF-2), insulin-like growth factor-1 (IGF-1), bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF), and parathyroid hormone (PTH).

Enamel matrix proteins or enamel matrix derivative (EMD) have also been suggested to promote periodontal regeneration by way of mimicking the specific events that occur during the development of the periodontium. Developing enamel matrix consists mostly of proteins derived from the amelogenin gene (90%), with the remainder comprised of amelin (shethlin, ameloblastin) (~8%), enamelin (~2%), enzymes, and serum proteins.[2] In contrast, EMD is composed of amelogenins, with metalloendoprotease and serine protease activity, but minimal to no "non-amelogenin"-like proteins.[3] Although it is still necessary to further clarify the role of EMD in epithelial-mesenchymal interactions, these proteins promote periodontal wound healing as shown in multiple investigations (see this review). EMD is currently the only biologic that is commercially available for human use, although other GFs are in various stages of development.

RATIONALE

GAFs have been used for the treatment of periodontal disease as shown in preclinical and clinical studies. This systematic review evaluates the evidence to support the utilization of EMD and growth factors (GFs) for periodontal repair and regeneration associated with natural teeth.

FOCUSED QUESTION

In patients with periodontal osseous defects, what is the effect of GAFs compared with controls on clinical, radiographic, histologic, adverse, and patient-centered outcomes?

SEARCH PROTOCOL

The two authors (WG and MS) searched for preclinical and clinical studies in the English language utilizing MEDLINE, Pre-MEDLINE and the Cochrane Oral Health Group trials register (CCTR) as the on-line databases. Publications up to April 2002 were selected based on the following search terms: "Attachment factors," "basic fibroblast growth factors" (bFGF or FGF-2), "bone morphogenetic proteins" (BMPs), "differentiation factors," "enamel matrix proteins," "epidermal growth factors" (EGF), "growth factors," "insulin-like growth factors" (IGF-1, -2, or IGF), "parathyroid hormone" (PTH), "platelet-derived growth factor" (PDGF), "osteoinductive factors," "periodontal wound healing," "periodontal regeneration," "tissue engineering," "transforming growth factor-beta" (TGF-beta), and "vascular endothelial growth factor" (VEGF). All of the search terms were meshed with "periodontal."

A hand search was performed to include the *International Journal of Periodontics and Restorative Dentistry, Journal of Clinical Periodontology, Journal of Dental Research, Journal of Periodontal Research*, and *Journal of Periodontology* as well as discussions with representatives of companies developing GAFs for periodontal use. Following this, abstracts of articles derived from this broad search were screened and pertinent publications were further reviewed on a full-text format. Final selection was based on predetermined inclusion and exclusion criteria.

Inclusion criteria: Initially, randomized controlled clinical trials (RCTs), cohort studies, case-control studies, case reports and preclinical (animal) randomized control investigations were screened. Reviewed publications included a cohort population diagnosed with periodontal disease as well as presenting with periodontal osseous defects. For the animal data, only RCTs were pre-selected. Accordingly, the following therapeutic interventions were integrated in the analysis: utilization of GAFs versus open flap debridement (OFD), carrier or vehicle controls; GAFs in conjunction with guided tissue regeneration (GTR) versus OFD, carrier or vehicle controls; GAFs in conjunction with bone replacement grafts (BRGs) versus OFD, carrier or vehicle controls; GAFs in conjunction with root conditioning versus OFD, carrier or vehicle controls; and studies with no treatment controls or scaling and root planing alone.

Exclusion criteria: In vitro studies or those that did not include quantifiable data with respect to clinical or bone measures were not included.

Outcomes

The criteria of efficacy of GAFs compared to controls were based on defined clinical outcome measures. These outcomes were weighted on clinical relevance

and they were selected prior to initialization of the search. Hence, primary outcomes considered were changes in clinical attachment levels (CAL), changes in radiographic bone density or linear bone height, changes based on direct measurement of bone levels obtained at surgical re-entry, and histological measures of periodontal regeneration (i.e., new bone density, new bone height, length of new cementum, and length of new attachment). Secondary outcomes were considered probing depth changes (PD), gingival recession changes (REC), changes in tooth mobility, and changes in oral hygiene efficacy and compliance. In addition, patient-centered outcomes were considered including surgical complications, ease of maintenance based on residual PD, disease control (incidence of relapsing or recurrent disease), and ability to support prostheses. Finally, adverse outcomes considered were pain, tooth hypersensitivity, swelling, soft tissue dehiscences, secondary infection, antibody formation to recombinant molecules, clinical foreign body reactions, and ankylosis.

Data Collection and Analysis

During the search, reviewed studies received a predetermined scoring proposed by the investigators. They were based on the quality of the study methodology as follows: randomized controlled clinical trials: Level 1; quasi-experimental studies (e.g., no randomization): Level 2; controlled observational studies (i.e., case-control and cohort studies): Level 3; observational studies (without control groups): Level 4; and randomized preclinical controlled trials (animal) studies (PCRCTs): Level 5.

The quality assessment of each study was measured using guidelines from Consolidated Standards of Reporting Trials (CONSORT) and the Quality of Reporting of Meta-analyses (QUOROM). Meta-analyses were performed for studies that fulfilled the eligibility criteria and the following continuous variables: CAL, PD, or bone level (radiographic, re-entry, or histologic). Heterogeneity was assessed to determine whether the differences among therapies were due to systematic confounding factors (as noted in study quality assessments). Cohen's d (unadjusted) and Hedges g (adjusted) were used to test for heterogeneity.[4,5]

RESULTS

A total of 559 articles were identified initially among those published up to April 2002. In vitro studies or those that did not possess quantifiable data with respect to clinical measures or bone measures of regeneration were eliminated. There remained 60 studies that fulfilled the criteria set forth by the search protocol. Three studies were based on bFGF,[6-8] 11 on BMPs,[9-19] 37 on enamel matrix derivative (EMD),[20-56] 5 on PDGF or PDGF/IGF-1,[57-61] and 4 others with combined GFs.[9,62-64] On the preliminary inspection of these potential studies, it was noticed that significant variability existed regarding their methodology, including objectives, methods of investigation (i.e., lack of randomization or masking), and data collection. In addition, it is important to note that most of the growth factors available for investigation are currently not approved for human utilization. For this reason, with the exception of EMD studies, the vast majority of the initially screened articles were based on animal data, where clinical efficacy has not been validated. Only 2 out of the 23 studies utilizing GAFs other than EMD have published results based on human investigations.[19,61] Review of animal trials revealed a vast heterogeneous methodology. Consequently, after statistical analysis, it was concluded that animal data were insufficient for a meta-analysis. This was due mainly to the differing study designs, outcome variables, and inconsistent dose levels tested.

With respect to human trials, a total of 32 studies were initially identified. When these studies were stratified by GAF type, 30 out of 32 involved the utilization of EMD. One involved a Phase I/II clinical trial utilizing a combination of PDGF-BB and IGF-1 for treatment of periodontal osseous defects[61] and the other a study of a human-derived, partially-purified BMP (osteogenin) for regeneration of submerged and nonsubmerged periodontal lesions.[19] After careful review of each study, it was demonstrated that the majority of human trials in the literature were based on non-controlled methodologies. The heterogeneity of the reports precluded any meaningful pooling of the data from these reports, or any attempt at a meta-analysis of the data. Consequently, the structure of this review, originally intended to be a systematic review, was modified to summarize the pertinent literature relating to EMD. Only 8 studies out of the 32 demonstrated sufficient data to be considered in a meta-analysis.[22,25,30,34,46,52,65,66] The data obtained from these 8 trials were based on RCTs (Level 1) or quasi-experimental (Level 2) and are summarized in Table 1. There were sufficient data to display changes in PD and CAL in all of the mentioned studies.

Of the 8 studies that were eventually considered in the analyses, 7 were RCTs and one was a quasi-experimental study (Table 1). These studies allowed meta-analysis for CAL gain and PD reduction and for forest plot analysis shown in Figures 1 and 2. In general, the studies report highly consistent and statistically significant results demonstrating marked improvements in CAL gain, PD reduction, and osseous defect fill as measured radiographically.

Figure 1 demonstrates results for probing depth for the 8 studies. By 2 different methods Cohen's d and Hedges g heterogeneity was statistically significant. Normally a statistically significant result for heterogeneity would suggest that the studies should not be put together for a meta-analysis. However, in this case all of the studies were positive (favoring EMD) and 6 out of the 8 favored were statistically significant. If the 2 most positive studies[22,52] are removed from the

Table 1.

Studies Evaluating the Effect of Enamel Matrix Derivative on Repair of Periodontal Osseous Defects

Reference	Study Design	Study Population	Agent	Study Outcomes	Funding/Location	Study Ranking
Heijl et al.[25] 1997	RCT Split-mouth 2 treatment groups 8 to 36 months duration	34 subjects 27 completed Mean age 48	Control: MWF Test: EMD	ΔPD, ΔCAL, ΔREC, Δradiographic bone density	Company	1
Zetterström et al.[55] 1997	Quasi-design Split-mouth 2 treatment groups 8 to 36 months duration	140 subjects 69 female Mean age 48	Control: MWF Test: EMD	ΔPD, ΔCAL, ΔREC, Δradiographic bone density, safety assessments	Company	2
Silvestri et al.[52] 2000	RCT Parallel Group 3 treatment groups 12 months duration	30 subjects 19 females Mean age 46	Control: MWF Test: EMD	ΔPD, ΔCAL, ΔREC	University and company	1
Froum et al.[22] 2001	RCT Split-mouth 2 treatment groups 12 months duration	23 subjects Mean age 45.5	Control: Flap Test: EMD	ΔPD, ΔCAL, ΔREC, GI, PI, bone height, bone fill (%), defect resolution	Company	2
Sculean et al.[46] 2001	RCT Parallel group 4 treatment groups 12 months duration	56 subjects 32 females Mean age 36	Control: Flap Test: EMD	ΔPD, Δplaque, ΔGI, ΔCAL, ΔREC	Not given	1
Tonetti et al.[65] 2002	RCT Parallel group 2 treatment groups 12 months duration	172 subjects 12 test centers 166 completed Mean age 48	Control: Papilla preservation surgery Test: EMD	ΔPD, ΔCAL, ΔREC	University and company	1
Okuda et al.[30] 2000	RCT Split-mouth 2 treatment groups 12 months duration	16 subjects 8 females Mean age 56	Control: Flap Test: EMD	ΔPD, ΔCAL, ΔREC, ΔGI, ΔBOP, Δmobility, Δradiographic bone density	Not given	1
Pontoriero et al.[34] 1999	RCT Split-mouth 5 treatment groups 12 months duration	40 subjects 25 females Age 32 to 61	Control: Flap Test: EMD	ΔPD, ΔCAL, ΔREC	University and company	1

analysis, the resulting analysis is highly significant for the effect of EMD and the heterogeneity is non-significant. Thus, the heterogeneity does not bring into question whether EMD is effective, since virtually all of the studies are positive, but only brings into question the estimate of the size of effect. There was a similar result for attachment level (Fig. 2). In this case, the removal of only one of the studies[52] resulted in an analysis that is highly significant for the effect of EMD and the heterogeneity is non-significant. For both outcome variables the meta-analysis suggests that there is a consistent and highly significant beneficial effect for EMD.

Heijl et al.[25] published the earliest results demonstrating the effects of EMD in a multi-center RCT. This investigation studied 33 subjects with paired 1- or 2-wall osseous defects in a split-mouth design (EMD + modified Widman flap [MWF] or MWF alone). The treated defects were evaluated at 8, 16, and 36 months post-treatment and assessments were made for changes in PD, CAL, REC, and radiographic bone density. Mean values for CAL gain in EMD and control sites at 8 months were 2.1 and

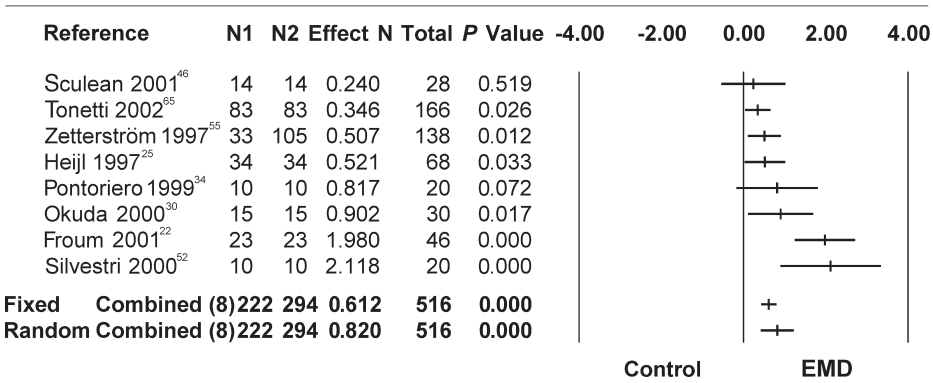

Figure 1.
Meta-analysis depicting the effectiveness of EMD combined with surgery on probing depth reduction as compared to control flap surgery alone. The use of EMD showed a significant improvement in PD reduction. Heterogeneity was significant with P <0.0001.

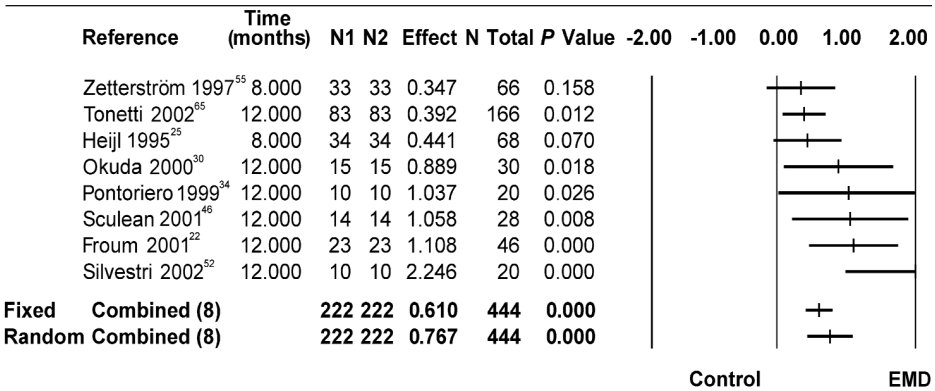

Figure 2.
Meta-analysis depicting the effectiveness of EMD combined with surgery on clinical attachment level gain as compared to control flap surgery alone. The use of EMD showed a significant improvement in CAL gain. Heterogeneity Cohen's D, P = 0.04, Hedge's g P = 0.16.

1.5 mm, respectively; at 16 months, 2.3 and 1.7 mm, respectively; and at 36 months, 2.2 mm and 1.7 mm, respectively, with statistically significant differences at all time points. The radiographic bone density changes increased over the 36 months (66% fill) at the EMD sites while the bone level remained essentially unchanged in the MWF-treated sites.

Zetterström et al.,[55] reported findings from a safety study that also included efficacy for the repeated application of EMD to periodontal defects in a quasi-experimental design. A total of 140 subjects possessing ≥4 mm deep osseous defects were recruited for study. Thirty-three individuals served as controls and the other 107 had 2 surgical sites treated 2 to 6 weeks apart to determine the immunological responses to the repeated EMD application. Serum samples were taken for assessment of total and specific antibody levels. None of the harvested serum samples at various time points revealed indications of an antibody response that was different from the baseline values. Furthermore, statistically significant results were found between EMD and control treatments for PD, CAL, and radiographic bone density for up to 3 years (a total of 65 individuals were evaluated at the 3-year time point). The investigators stated that the 2.5 to 3 mm increase in CAL and radiographic bone level was similar to other studies reported for EMD.

The study by Silvestri et al.[52] reported the results from an RCT that included a total of 30 patients comparing 3 surgical modalities: GTR plus flap, MWF alone, and EMD plus flap. Following surgical therapy the outcome measures evaluated were CAL gain, PD reduction, and REC. Comparing 12-month results, it was noted that EMD resulted in 4.8 and 4.5 mm improvements in PD and CAL changes, respectively, while MWF surgery alone resulted in 1.4 and 1.2 mm improvements in PD and CAL, respectively. Furthermore, the results between the positive control GTR and EMD were found to be similar, with no statistically significant differences between the groups.

A study by Froum et al.[22] compared OFD with and without EMD in the treatment of intrabony periodontal lesions. Twenty-three subjects with a minimum of 2 intrabony defects were entered into this split-mouth design RCT. Closed measures (PD, CAL, gingival index [GI], plaque index [PI]) and open bone measures (surgical re-entry at 1 year) were performed in a total of 53 osseous defects. For all categories, with the exception of PI and GI, EMD was statistically superior to OFD. EMD resulted in 2.7 mm and 1.5 mm improvements in PD and CAL, respectively as compared to OFD. On average, osseous defect fill was ~3 times greater for EMD as compared to OFD (74% fill for EMD versus 23% fill for OFD). In terms of defect resolution (considering crestal resorption), the mean resolution for EMD treated defects at 12 months was 83.2%, while OFD sites revealed 48.1%. These differences were statistically significant.

A comparative study by Sculean and co-workers[46] evaluated the treatment effect of EMD, GTR, combination of GTR + EMD, and OFD alone on the repair of intrabony periodontal defects. This 12-month RCT enrolled 56 subjects each possessing one intrabony

defect measuring ≥6 mm in depth. Several parameters were assessed (Table 1). The results of the study found that all therapies led to PD reduction, but without statistically significant differences between the groups. However, for CAL, EMD, and EMD + GTR were superior to OFD, while no additive effect was noted when EMD was combined with GTR.

Tonetti et al.[65] reported results of the largest RCT performed to date comparing EMD to papilla preservation surgery in patients with severe periodontitis. This multicenter (12 sites in 7 countries) investigation evaluated a total of 172 subjects, with 166 individuals completing the study at 12 months. Patients required the presence of at least one intrabony defect of ≥3 mm. The clinical parameters included PD, CAL, and REC. EMD enhanced 3.1 mm of CAL gain, while flap only resulted in 2.5 mm of CAL gain. EMD promoted 3.9 mm decrease in PD, while flap only resulted in 3.3 mm PD reduction. Differences between EMD and control were statistically significant for both PD and CAL. Both groups displayed 0.8 mm of REC post-treatment. Multivariate analysis demonstrated treatment effects based on treatment center, baseline PD, and the presence of defect corticalization (all at $P<0.01$).

Okuda et al.[30] reported the results of a split-mouth design RCT on a Japanese patient population. A total of 16 individuals, each of whom possessed a minimum of one pair of contralateral bony defects were recruited to compare EMD plus flap surgery to flap surgery alone. At baseline and the 12-month visits several parameters were assessed including changes in PD, CAL, GI, bleeding on probing (BOP), mobility, and radiographic bone density. Statistically significant improvements in PD, CAL, BOP, and radiographic bone density were noted between OFD and EMD plus OFD at 12 months. EMD treatment resulted in 20.2% gain in bone density, while flap alone resulted in a 3.9% loss ($P<0.05$).

Pontoriero et al.[34] provided results from a RCT comparing EMD to 3 different GTR barriers or flap surgery (controls) in a split-mouth design. The entry criteria for the osseous lesions included contralateral angular bony defects, PD ≥6 mm, CAL ≥7 mm, and an intrabony defect measuring ≥3 mm. Twelve months following surgery the treatment sites were remeasured. No differences were noted between the EMD and control groups for recession (both 1.7 mm increase from baseline). EMD treatment resulted in 4.4 and 3.0 mm changes for PD and CAL, respectively, while control surgery gave 3.5 mm and 1.8 mm changes for PD and CAL, respectively. The differences were statistically significant between EMD and control. EMD showed no evidence of a difference in results as compared to the 3 other GTR treatment modalities.

Of the remaining studies directed at determining the effects of EMD on periodontal repair, the majority were either case series or case reports. In general, these studies found that the application of EMD greatly enhanced CAL and bone gain as well as promoted probing depth reduction. In addition, histological evidence of periodontal regeneration to varying degrees was reported in several case reports.[26,29,43,54,66] Thus, in total, the effects of EMD appear to be very consistent in terms of promotion of clinical attachment level gain and probing depth reduction in humans above that of controls (flap surgery alone).

DISCUSSION

A goal of a systematic review is to take into consideration existing hierarchical evidence to determine the utility of treatment approaches for delivery of patient care. GAFs for periodontal repair represent one of the most rapidly developing technologies in periodontology. Much progress has been made in this area over the past decade; however, many of these therapies are still in their nascent stages. As described in the results section, the only member of GAFs available for systematic review was EMD. Nevertheless, brief highlights for the most well studied GFs for periodontal tissue engineering are presented below: FGF-2, PDGF or PDGF/IGF-1, and the BMPs. This section will conclude with a discussion related to the EMD studies presented above and their impact toward achieving the ultimate goal of predictable periodontal regeneration in humans.

BONE MORPHOGENETIC PROTEINS

Bone morphogenetic proteins (BMPs) belong to the large superfamily of transforming growth factor β (TGFβ) proteins.[67] BMPs are powerful regulators of cartilage and bone formation during embryonic development and regeneration in post-natal life. A striking and discriminatory feature of some of these proteins is their ability to induce *de novo* endochondral osteogenesis in ectopic sites (e.g., skin or muscle).[68]

Preclinical animal models have shown a potent effect of BMP-2 on bone apposition to implant surfaces.[69,70] The clinical use of BMP-2 in humans has been recently reviewed.[72] Recombinant human BMP-2 has been safely applied for implant site development[73] and for sinus floor elevation in human trials[74] (also see systematic review for alveolar ridge augmentation[75]). Margolin et al. found increases in bone mineral density, using BMP-7 (or osteogenic protein-1 [OP-1]) that was similar to the carrier alone.[76] Van den Bergh et al. also reported initial data on 3 human subjects treated with BMP-7 for sinus floor augmentation.[77] The authors concluded that the OP-1 device has the potential for initiating bone formation in the human maxillary sinus within 6 months after a sinus floor elevation operation. However, the various findings in the patients studied indicate that the behavior of the material is at this moment insufficiently predictable.[77]

BMPs have shown potent effects in stimulating periodontal tissue repair in several experimental animal model

systems.[11-13,78,79] In most of these studies of large critical size alveolar bone defects, bone and cementum were predictably regenerated. Bowers et al. demonstrated significant periodontal regeneration in humans using DFDBA plus a partially-purified extract of BMP (osteogenin, also called BMP3). "Pin point" ankylosis was noted on submerged roots treated with DFDBA plus osteogenin.[19] Human trials using recombinant molecules have been completed to examine the efficacy of BMP-2 or BMP-7 for regeneration of chronic periodontitis lesions (from Genetics Institute, Cambridge, Massachusetts and Stryker Biotech, Hopkinton, Massachusetts, respectively). The results however have not been released at this time. To date, no local or systemic safety concerns have been noted in humans after local application of BMP-2 or BMP-7 in periodontal osseous defects (unpublished data).

FIBROBLAST GROWTH FACTOR (FGF-2)

Basic fibroblast growth factor (bFGF or FGF-2) is a member of a heparin-binding family that possesses potent angiogenic properties. FGF-2 is mitogenic and chemotactic for endothelial cells, fibroblasts[80] and periodontally-derived cells.[81] Among other origins, bFGFs are synthesized by inflammatory cells and are stored in the extracellular matrix by binding to heparan sulfate proteoglycans. FGF-2 has been extensively studied for its role in dermal wound healing both in preclinical and in human clinical trials.[82] More recently, periodontal models reveal a potential benefit of FGF-2 for closure of class 3 furcations or for regeneration of intrabony defects.[6-8] To date, no human trials are ongoing using FGF-2 for periodontal repair to the knowledge of the reviewers.

PLATELET-DERIVED GROWTH FACTORS

Granules of platelets are a source of PDGF but may be produced by many cell types. There are 4 isoforms of PDGF (-A, -B, -C, and -D), although all periodontal studies have investigated -A and -B chains.[83] PDGFs exert multiple biological responses, including mitogenesis and chemotaxis of periodontal ligament fibroblasts,[84] cementoblasts,[85] and osteoblasts.[86]

There is evidence that PDGF has potential for enhancing periodontal wound healing. A single bolus delivery of PDGF alone or combined with insulin-like growth factor-1 (IGF-1) for a transient period appears to be sufficient to enhance the regenerative process. It has been suggested that this is due to the fact that many critical events involved in wound repair occur within the first few days.[57] PDGF has also shown positive stimulatory effects on periodontal regeneration in preclinical non-human primate models[58,60,62,87] and in a multi-center human trial.[61] PDGF-BB promotes periodontal regeneration at the histologic level as published in two recent human case reports.[88,89] In addition, a multi-center human trial of 13 centers is ongoing with results due for evaluation in late 2003 (from BioMimetic Pharmaceuticals, Franklin, Tennessee).

ENAMEL MATRIX DERIVATIVE

One strategy for promoting periodontal regeneration is to mimic the specific events that occur on the development of supporting tissues during tooth organogenesis. It has been shown that inner cells from the Hertwig's epithelial root sheath (apical extension of the dental organ) have a secretory stage prior to cementum formation, suggesting that epithelial-mesenchymal interactions are essential for formation of the periodontium.[92,93] In recent years, several clinical studies have been conducted using EMD for multiple periodontal indications such as treatment of intrabony defects,[22,25,52,55,65] in conjunction with GTR,[34,42,45,46,52,56] in combination with bone grafts,[92] together with gingival curettage,[93] and for root coverage procedures.[94,95] Clinical trials comparing GTR with EMD have generally found no evidence of a difference in clinical parameters in the treatment of intrabony defects.[34,39,45] In addition, GTR plus EMD has shown no additional effect in clinical parameters when compared to each component alone.[45] Although this systematic review focused on the parameters with the most plentiful data (i.e., CAL and PD changes), it has been noted that EMD appears to be safe with single and multiple administration in terms of lack of elicitation of antibody responses or other local/systemic inflammatory events.[23,55] EMD stimulates bone regeneration as measured at surgical re-entry, radiographically, and histologically.[22,25,26,29,43,55] Furthermore, EMD has demonstrated notable consistency among the studies investigated in terms of superiority to controls (in general, OFD) and either equivalence or no significant differences between GTR. Thus, the evidence as determined by this systematic review supports the utilization of EMD for periodontal osseous defects to promote CAL gain and PD reduction. Nevertheless, long-term benefits of EMD have not been demonstrated, including those relevant to tooth survival. Future clinical protocols that provide detailed descriptions of defects that include patient-specific characteristics should assist in defining clinical indications for EMD use as a part of periodontal regenerative therapy.

REVIEWERS' CONCLUSIONS

1. There is evidence supporting the use of EMD for periodontal osseous defects to improve CAL and reduce PD, although long-term benefits have not been established.
2. EMD has demonstrated notable consistency among the studies investigated in terms of superiority to controls (in general compared to OFD).
3. EMD appears to be safe for single and multiple administrations in terms of lack of elicitation of antibody responses or other local/systemic inflammatory events.

4. Preclinical and initial clinical data for growth factors appear promising but are insufficient to draw definitive conclusions at this time.

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APPENDIX A
CONSENSUS REPORT

Members of the Section read and studied the review titled "Growth and Amelogenin-like Factors in Periodontal Wound Healing. A Systematic Review" by William V. Giannobile and Martha J. Somerman. The focused PICO question addressed by this evidence-based systematic review is: "In patients with periodontal osseous defects, what is the effect of growth and amelogenin-like factors (GAFs) compared with controls on clinical, radiographic, histologic, adverse, and patient-centered outcomes?"

INTRODUCTION

Two authors searched for preclinical and clinical studies in the English language utilizing MEDLINE, pre-MEDLINE, and the Cochrane Oral Health Group Trials Register (CCTR) as the on-line databases. Publications up to April 2002 were selected based on qualifier terminology. A manual search was performed to include the *International Journal of Periodontics and Restorative Dentistry, Journal of Clinical Periodontology, Journal of Dental Research, Journal of Periodontal Research*, and *Journal of Periodontology*. Following this, abstracts of articles derived from this broad search were screened and pertinent publications were further reviewed on full-text format. Final selection was based on predetermined inclusion and exclusion criteria. Section members evaluated the manuscript that summarized this information and in open forum evaluated the evidence and conclusions brought forth from this review.

1. Does the section agree that the evidence-based systematic review is complete and accurate?

The Section was in agreement that the systematic review was accurate and complete. The focused question was viewed as appropriate to address the content of the available evidence.

2. Has any new information been generated or discovered since the evidence-based search cut-off date?

A systematic review evaluating grafting biomaterials/biological agents with open flap debridement (OFD) was reported by Trombelli et al., who used a meta-analysis to demonstrate the effectiveness of an enamel-matrix derivative (EMD) combined with OFD in treatment of deep intraosseous defects. The results of the analysis showed EMD promoted a significant improvement in clinical attachment level (CAL) above controls.[1]

Three additional citations have been identified that support the conclusions of the current systematic review and provide new information on the potential mechanism of amelogenin-like factors: A randomized controlled clinical trial (RCT) by Yilmaz et al.;[2] A human histological study by Sculean et al.;[3] and a preclinical investigation provided information on the potential mechanism of amelogenin in regulating behavior of cells within the periodontium.[4]

3. Does the section agree with the interpretations and conclusions of the reviewers?

The Section agreed with the interpretations and conclusions of the review.

1. There is evidence supporting the use of EMD for periodontal osseous defects to improve CAL and reduce PD, although long-term benefits have not been established.
2. EMD has demonstrated notable consistency among the studies investigated in terms of superiority to controls (in general compared to OFD).
3. EMD appears to be safe for single and multiple administrations in terms of lack of elicitation of antibody responses or other local/systemic inflammatory events.
4. Preclinical and initial clinical data for growth factors appear promising but are insufficient to draw definitive conclusions at this time.

4. What further research needs to be done relative to the focused questions of the evidence-based review?

It was the consensus of the Section that the following research needs should be addressed:

1. Broadened sources (e.g., foundational, industrial, National Institiutes of Health) of support for randomized controlled clinical trials to expand the knowledge base on these emerging technologies.
2. Emphasis on defining the composition of the material being used and in understanding its mechanism of action. This information will aid in providing a sound rationale for its use and improving treatment outcomes.
3. Conduct trials that compare emerging technologies with current therapies (e.g., nonsurgical, resective, and regenerative). Increased emphasis should be placed on the magnitude of the outcome, treatment predictability, and adverse events (e.g., root resorption, root sensitivity, ankylosis) to establish risk/benefit ratios.
4. Perform prospective long-term (i.e., 3 years or longer) studies on treatment outcomes (e.g., CAL gains and PD reductions and bone level improvements) to determine their stability.
5. Evaluate the effects of the treatment on patient-centered outcomes (e.g., comfort, esthetics, ease of maintenance, function, tooth retention, and systemic status) to enhance patient acceptance.

6. Investigate defect morphologic factors that influence treatment outcomes to provide guidelines that enhance predictability.

7. Identify the role of systemic risk factors, acquired or environmental (e.g., smoking, diabetes) in influencing treatment outcomes.

8. Assess factors that affect clinical predictability (e.g., pre- and postsurgical patient management, intramarrow penetration, flap design, root preparation, operator experience).

9. Research on effective carriers/scaffolds for the delivery of bioactive factors and cells to promote periodontal tissue engineering.

10. Controlled trials are needed to better understand the role of autologous platelet gel (i.e., platelet-rich plasma) for periodontal wound healing.

11. Conduct multi-center, randomized controlled clinical trials using novel tissue engineering devices with bioactive factors.

5. How can the information from the evidence-based review be applied to patient management?

A. The evidence supports the use of EMD for periodontal osseous defects in patients to promote CAL gain and PD reduction.

Level of Evidence:[5] Strong.

Rationale: Assignment of a "strong" level of evidence is based on 7 RCTs and a non-randomized controlled trial.

B. The evidence supports the use of EMD for bone regeneration in patients as assessed by the following outcomes

i. Surgical re-entry:

Level of Evidence: Moderate.

Rationale: Assignment of this level of evidence is based on re-entry data shown in 1 RCT.

ii. Radiographic:

Level of Evidence: Moderate.

Rationale: Assignment of this level of evidence is based on one multi-center RCT.

iii. Histologic:

Level of Evidence: Limited.

Rationale: Assignment of this level of evidence is based on 4 independent human histology case reports.

C. The results of the systematic review suggest no evidence of a difference between EMD and barrier membranes relative to CAL gain and PD reduction.

Level of Evidence: Limited.

Rationale: Assignment of this level of evidence is based on 3 RCTs demonstrating nonsignificant differences between groups.

D. Initial available evidence supports the use of growth factors (i.e., bone morphogenetic proteins [BMPs] and platelet-derived growth factor [PDGF-BB]) to improve patient outcomes.

Level of Evidence: Limited.

Rationale: Assignment of this level of evidence is based on the following: 1 RCT with human histology studying BMPs (i.e., osteogenin); 1 RCT for PDGF-BB combined with insulin-like growth factor-1 (IGF-1), and 2 case reports (with human histology for PDGF-BB).

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