Periodontal Regeneration – Intrabony Defects: A Systematic Review From the AAP Regeneration Workshop

Richard T. Kao,*† Salvador Nares,‡ and Mark A. Reynolds§

Background: Previous systematic reviews of periodontal regeneration with bone replacement grafts and guided tissue regeneration (GTR) were defined as state of the art for clinical periodontal regeneration as of 2002.

Methods: The purpose of this systematic review is to update those consensus reports by reviewing periodontal regeneration approaches developed for the correction of intrabony defects with the focus on patient-, tooth-, and site-centered factors, surgical approaches, surgical determinants, and biologics. This review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews.

A computerized search of the PubMed and Cochrane databases was performed to evaluate the clinically available regenerative approaches for intrabony defects. The search included screening of original reports, review articles, and reference lists of retrieved articles and hand searches of selected journals.

All searches were focused on clinically available regenerative approaches with histologic evidence of periodontal regeneration in humans published in English. For topics in which the literature is lacking, non-randomized observational and experimental animal model studies were used.

Therapeutic endpoints examined included changes in clinical attachment level, changes in bone level/fill, and probing depth. For purposes of analysis, change in bone fill was used as the primary outcome measure, except in cases in which this information was not available. The SORT (Strength of Recommendation Taxonomy) grading scale was used in evaluating the body of knowledge.

Results: 1) Fifty-eight studies provided data on patient, tooth, and surgical-site considerations in the treatment of intrabony defects. 2) Forty-five controlled studies provided outcome analysis on the use of biologics for the treatment of intrabony defects.

Conclusions: 1) Biologics (enamel matrix derivative and recombinant human platelet-derived growth factor-BB plus β-tricalcium phosphate) are generally comparable with demineralized freeze-dried bone allograft and GTR and superior to open flap debridement procedures in improving clinical parameters in the treatment of intrabony defects. 2) Histologic evidence of regeneration has been demonstrated with laser therapy; however, data are limited on clinical predictability and effectiveness. 3) Clinical outcomes appear most appreciably influenced by patient behaviors and surgical approach rather than by tooth and defect characteristics. 4) Long-term studies indicate that improvements in clinical parameters are maintainable up to 10 years, even in severely compromised teeth, consistent with a favorable/good long-term prognosis. *J Periodontol 2015;86(Suppl.):S77-S104.*

KEY WORDS

Controlled clinical trial; patient outcome assessment; periodontal diseases; tissue engineering; reviews.

* Private practice, Cupertino, CA.
† Division of Periodontology, School of Dentistry, University of California at San Francisco, San Francisco, CA.
‡ Department of Periodontics, College of Dentistry, University of Illinois at Chicago, Chicago, IL.
§ Department of Periodontics, School of Dentistry, University of Maryland, Baltimore, MD.

See related practical applications paper in Clinical Advances in Periodontics *(February 2015, Vol. 5, No. 1) at www.clinicalperio.org.*

doi: 10.1902/jop.2015.130685

Periodontitis is commonly characterized by the formation of intrabony defects. Multiple surgical approaches for treating intrabony defects have shown effectiveness in improving clinical and radiographic parameters, such as clinical attachment level (CAL) and defect depth. Moreover, histologic evidence demonstrates the potential to achieve regeneration of the periodontal attachment apparatus—including new bone, cementum, and periodontal ligament (PDL)—using different therapeutic approaches.[1-14] However, limitations in the predictability and effectiveness of regenerative therapy, including bone replacement grafts and guided tissue regeneration (GTR), are well documented in the literature.[15-24] A combination of factors related to the patient, defect morphology, and surgical procedure appear to influence the overall predictability and effectiveness of periodontal regenerative approaches.[25] Although some of these factors, such as defect morphology, provide insight into the selection and treatment strategy for optimizing regenerative outcome, a clinical need remains for more accurate predictive models and more robust reconstructive and regenerative strategies.

This systematic review examines available published evidence to address focused questions related to the predictability and effectiveness of regenerative therapies in the treatment of intrabony defects. Case-based scenarios are used to develop evidence-based recommendations for the use of regenerative therapy in the management of periodontal intrabony defects in daily clinical practice. This review is a continuing effort to develop treatment options for optimizing periodontal regenerative strategies.

SEARCH PROTOCOL

PRISMA Compliance

This review adheres to the 2009 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews.[26]

Focused Questions

Focused questions included the following. 1) What is the evidence for periodontal regeneration in intrabony defects related to the following: a) patient-centered behavioral and systemic considerations; b) what is achievable and maintainable; c) the influence of tooth mobility; d) surgical considerations (flap design); e) surgical considerations (defect morphology, including width, depth, and containment); and f) surgical complications, factors to increase stability, and stability relapse management? 2) What is the evidence for the following regenerative procedures: a) updated classic regenerative approach (demineralized freeze-dried bone allograft [DFDBA]; GTR, and GTR combined with graft materials); b) laser-assisted regeneration (LAR)‖; c) enamel matrix derivative¶ (EMD) (EMD alone, EMD versus GTR, and EMD combination); and d) recombinant human platelet-derived growth factor BB# (rhPDGF-BB)? 3) What is the optimal timing of regenerative treatment of intrabony defects in relation to orthodontic and endodontic therapy?

Data Sources and Search Strategies

The screening process is outlined in Figure 1, and search strategies, search words, time frame of the search, and total number of references identified from PubMed and Cochrane databases are described in Table 1. The search strategy attempted to directly identify the following: 1) new reports of bone graft and GTR in clinical periodontal regeneration since October 2002; 2) the role of biologics and laser; 3) patient, tooth, and surgical considerations for improved regeneration outcome; 4) the relationship of regenerative therapy outcomes with endodontic and orthodontic therapy; and 5) short- and long-term (>5 years) regenerative outcomes. For purposes of analysis, change in bone fill was used as the primary outcome measure, except in cases in which this information was not available.

These searches were supplemented by screening review articles and reference lists of retrieved articles and preprint online publications of *Journal of Periodontology*, *Journal of Clinical Periodontology*, and *Journal of Periodontal Research*. In situations in which the same findings were reported in two separate journals, only the most detailed reports were included, and the secondary report was rejected. All abstracts were read by two authors (RTK and SN), and disagreements were resolved by consensus after discussion with the third author (MAR).

Inclusion criteria. All searches were limited to regenerative approaches with histologic "proof of principle" that the periodontal apparatus can be regenerated in human studies. Evidence from early studies and approaches have been summarized in several systematic reviews.[15,16] New regenerative approaches discussed in this review have provided similar histologic proof of principle[4,27-32] The search parameters were limited to studies published in English using autogenous bone, DFDBA, GTR, EMD, rhPDGF-BB, and LAR with the neodymium: yttrium-aluminum-garnet (Nd:YAG) laser. Studies included randomized clinical trials (RCTs), cohort studies, and selected case controlled studies. For topics in which the literature is lacking, non-randomized

‖ Laser-Assisted New Attachment Procedure (LANAP), Millennium Dental Technologies, Cerritos, CA.
¶ Emdogain, Institute Straumann, Andover, MA.
# GEM 21S, Osteohealth, Shirley, NY.

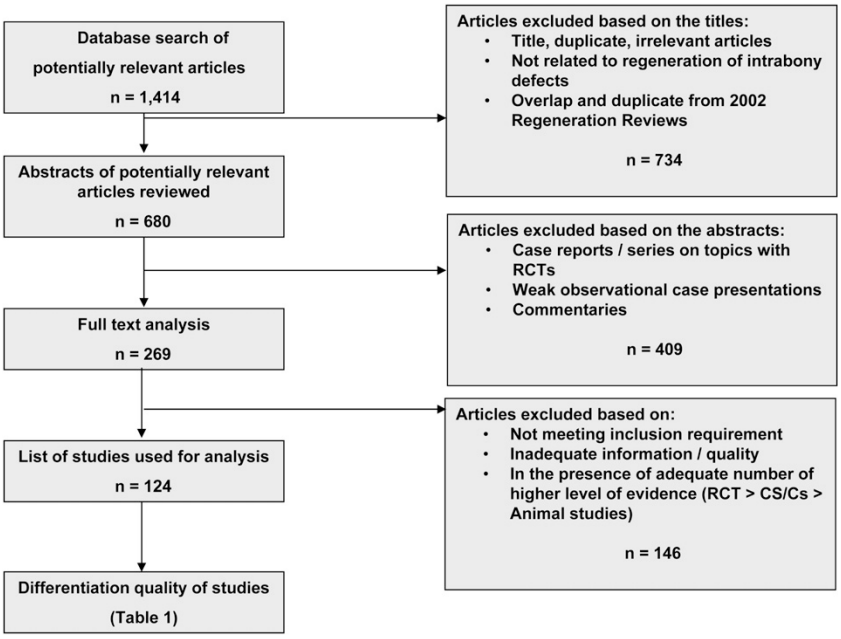

Figure 1.
Procedural flowchart of the screening process. CS = case series; C = case report.

observational and experimental animal model studies were used.

Exclusion criteria. Exclusion criteria included nonrandomized (e.g., case series and case reports) and experimental animal model studies in situations in which there is an inadequate number of RCTs. In certain new areas of regeneration, case series were used to supplement and support findings from RCTs.

Although there are extensive studies on various bone replacement grafts and platelet-rich plasma (PRP) preparations, such healing occurs by the formation of long junctional epithelium. Furthermore, although clinical stability was observed with grafting strategies, it was not in the scope of this review because of the lack of human histologic evidence of periodontal regeneration as reported in a previous systematic review.[15]

Translation for evidence-based recommendations. The grading system and recommendations were made based on the SORT (Strength of Recommendation Taxonomy) grading system. The quality and consistency of evidence were used to define the strength of recommendation. The quality rating score system is a three-tier grade that deemphasizes observational studies, with RCTs receiving highest score: A) consistent good-quality patient-oriented evidence; B) inconsistent or limited-quality patient-oriented evidence; and C) consensus, disease-oriented evidence, usual practice, expert opinion, or case series.[33]

VARIABLES INFLUENCING PERIODONTAL REGENERATION

Patient-Centered Considerations

Patient-centered variables are modifiable factors that have the potential to significantly influence regenerative outcomes even under the most ideal surgical conditions. Control of these variables should be achieved before initiating regenerative procedures.

Diabetes mellitus. Studies examining the physiologic effect of diabetes mellitus on regenerative outcomes are lacking, given the ethical considerations of conducting prospective clinical trials when comparing regenerative outcomes in uncontrolled patients with diabetes with individuals with well-controlled or no diabetes. Even with the lack of direct evidence in humans, recent animal studies confirm the detrimental effects on periodontal tissues and the poor regenerative capacity of animals with diabetes compared with animals without it.[34-36] Moreover, the use of biomimetic agents, such as EMD, did not improve the compromised healing response of animals with diabetes[35] (SORT level C).

Smoking. Smoking is a modifiable factor that is clearly associated with compromised regenerative outcomes.[10-12,37] The detrimental effects on oral tissues appear multifactorial in nature, affecting numerous aspects of the inflammatory and immune responses.[13] Recent studies comparing regenerative outcomes and complication rates in smokers with non-smokers continue to confirm that smokers have less reduction in probing depth (PD),[11,12] smaller gains in CAL,[11,12,14,38,39] increases in recession (REC),[40] significantly less bone fill/bone gain,[10,41] and a higher incidence of membrane exposure[10] and are less likely to achieve ≥65% defect resolution[42] compared with non-smokers (SORT level A).

Biofilm control. Elements of plaque biofilm have the capacity to trigger an exuberant proinflammatory response that counteracts the wound-healing processes necessary for periodontal regeneration. Clinical studies demonstrate that poor plaque control and residual periodontal infection are associated with compromised outcomes after regenerative surgery.[14,43-49] A

Table 1.

Search Strategies

Topic of Interest (on intrabony periodontal regeneration)	Search Words (English)	Search Time Frame (month/year)	Total Results	Citations Used	Quality of Evidence Used* (n citations)
Diabetes	Periodontal regeneration + diabetes mellitus + human	10/02 to 3/14	28	3	Level 3 (3)
Tooth mobility	Periodontal regeneration + tooth mobility + human	Up to 3/14	63	3	Level 1 (2) Level 2 (1)
Splinting	Periodontal regeneration + splinting + human	Up to 3/14	10	3	Level 1 (2) Level 2 (1)
Non-surgical therapy	Periodontal regeneration + non-surgical therapy + human	10/02 to 3/14	40	2	Level 1 (1) Level 2 (1)
Smoking	Periodontal regeneration + smoking + human	10/02 to 3/14	103	8	Level 1 (1) Level 2 (6) Level 3 (1)
Defect morphology: number of walls, width, and depth	Periodontal regeneration + defect morphology + human (152) Periodontal regeneration + bony walls + human (7) Periodontal regeneration defect width + human (43) Periodontal regeneration defect depth + human (229)	10/02 to 3/14	431	6	Level 1 (4) Level 2 (1) Level 3 (1)
Access flap surgery	Periodontal flap surgery + periodontal regeneration + human patients	10/02 to 3/14	429	16	Level 1 (9) Level 2 (5) Level 3 (2)
Conservative and minimally invasive surgery	Periodontal regeneration + minimally invasive surgery + human	10/02 to 3/14	38	17	Level 1 (6) Level 2 (5) Level 3 (6)
EMDs/enamel matrix proteins	Enamel matrix derivatives/enamel matrix proteins + periodontal regeneration + human patients	Up to 3/14	110	43	Level 1 (40) Level 2 (3)
PDGF	Platelet-derived growth factor + periodontal regeneration + human patients	Up to 3/14	35	8	Level 1 (3) Level 2 (5)
Laser periodontal therapy	Laser periodontal therapy + periodontal regeneration + human patients	Up to 3/14	37	2	Level 2 (2)
Orthodontic treatment	Orthodontic treatment + periodontal regeneration + intrabony/infrabony/intraosseous defects + human patients	Up to 3/14	69	10	Level 1 (1) Level 2 (9)
Endodontic treatment	Endodontic treatment + periodontal regeneration + intrabony/infrabony/intraosseous defects + human patients	Up 3/14	21	3	Level 2 (3)

* Level 1 = good-quality patient-oriented evidence (meta-analysis and randomized clinical trials); Level 2 = limited-quality patient-oriented evidence (lower-quality clinical trial with inconsistent findings, cohort study, and case-control study); and Level 3 = other evidence (consensus guidelines, extrapolations from bench research, usual practice, and case series).

full-mouth plaque score and/or full-mouth bleeding score of ≤15%,[50-52] ≤20%,[53,54] and ≤25%[55-58] have been reported as measures of acceptable preoperative oral hygiene (SORT level C).

Tooth-Related Considerations: Mobility

The effect of tooth mobility on regenerative therapy remains controversial. In a retrospective study comparing results between degrees of mobility, Trejo and Weltman[59] concluded that favorable periodontal regenerative outcomes were achieved on teeth with presurgical Miller Class 1 or 2 mobility.[60] After 1 year, no difference in PD and CAL was found between non-mobile teeth (Class 0) and mobile teeth (Class 1 or 2). Participants maintained low plaque and gingival index scores and were enrolled in a 2- to 3-month maintenance program to limit inflammation.[59] The therapeutic potential of splinting was revisited by Schulz et al.[61] Presplinting of mobile teeth treated using a bone replacement graft resulted in significantly reduced PD compared with non-splinted, grafted teeth at 1 year. The authors conclude that the observed differences may be attributable to loss of bone grafting material caused by tooth mobility and that tooth stability is beneficial to the wound-healing process when using a bone replacement graft.[61] Cortellini et al.[57] performed GTR therapy on severely mobile (Class 3), "hopeless" teeth. Twenty-two of the 25 teeth were splinted preoperatively, and patients had a high degree of compliance with home and professional care. After 5 years, 92% (23 of 25) of teeth were in function with an average gain in CAL of 7.7 mm at 1 year, which was maintained over 5 years. Siciliano et al.[62] reported on regenerative outcomes on teeth with primarily 1-wall defects and Class 1 or 2 mobility. Mobile teeth were splinted before surgery, and, although no comparison between splinted and non-splinted teeth was made, statistically significant improvements were reported compared with baseline measurements[62] (SORT level B).

Therapeutic Approaches and Surgical Considerations

Surgical regenerative strategies diverge primarily with respect to flap design and use of barrier membranes and materials. Conventional flap access designs primarily focus on buccal and lingual/oral flap reflection beyond the limits of the intrabony defect, whereas minimally invasive surgical approaches primarily focus on conservative flap reflection to the bony limits of the defect or to single-flap designs. Both flap approaches have been reported incorporating the use of membranes, bone replacement grafts, and/or biomimetic agents (EMD and rhPDGF-BB).

Access flap surgery/GTR. Systematic reviews provide evidence that clinical outcome measures for GTR are superior to open flap debridement (OFD).[16,63-65] Studies also reported superior outcomes (PD, CAL, and REC) for GTR compared with OFD[66-70] (Table 2).[38,51,71-85] Furthermore, a long-term study (>10 years) and two systematic reviews concluded that regenerative outcomes were comparable between resorbable and non-resorbable membranes.[16,39,64] Regarding membrane exposure, a meta-analysis performed by Machtei[68] found statistically significant differences in mean gain in vertical CAL between exposed and non-exposed membrane groups; however, a mean difference of 0.47 mm in defect fill was found between groups (SORT level A).

Conservative and minimally invasive flap access. Several conservative and minimally invasive flap approaches, including minimally invasive surgery (MIS),[86] a modification called MIS technique (MIST),[53] modified MIST (M-MIST),[54] and the single-flap approach (SFA),[87] have been described (Table 3).[88-98] These techniques minimize the degree of wounding and flap reflection and emphasize wound stability, primary closure, and space maintenance.[99] The use of microsurgical instrumentation and magnification has been advocated when performing these procedures.[99] Currently, studies comparing minimally invasive approaches to OFD are lacking. Harrel and Rees[86] described the MIS technique, which introduced conservative surgical approaches to periodontal regeneration. One- and 6-year results demonstrate favorable clinical outcomes in combination with EMD.[89,91] The MIST and M-MIST[54] techniques capitalize on papilla preservation incision designs. Studies report significant reductions in PD, gains in CAL, and minimal REC at 1 year compared with baseline (Table 3).[52-56,58,88,94-96,99,100] The SFA introduced by Trombelli et al.[75] involves limited reflection of a buccal or lingual envelope flap and placement of a barrier membrane. Improvements in PD and CAL were reported at 6 and 12 months compared with baseline (Table 3).[75,87,92] In a systematic review and meta-analysis, Graziani et al.[101] concluded that, although clinical performance may vary according to the type of surgical flap used, a high rate of tooth retention and improvements in periodontal clinical parameters is possible when conservative surgery is used in the treatment of intrabony defects (SORT level A).

Non-surgical therapy. Ribeiro et al.[94] compared minimally invasive non-surgical technique (MINST) with MIST in the treatment of intrabony defects. Using mini-curets and very thin ultrasonic tips, they reported that the MINST was comparable with MIST in terms of PD reduction, CAL gain, and REC. In a separate study, clinical and radiographic findings were collected retrospectively from patients after non-surgical therapy of intrabony defects.[98] Significant reductions were found in radiographic defect depth and

widening of the radiographic intrabony defect angle, with complete fill in some cases (SORT level C).

Defect morphology: number of walls, width, and depth. Regenerative techniques and the understanding of the factors influencing success or failure have evolved over time. Defects with a depth >3 mm and a radiographic defect angle ≤25 degrees were reported to be most amenable to regenerative procedures using conventional GTR-based approaches.[41,48,49,102-104] Using logistic regression analysis, Cosyn et al.[88] identified non-supportive anatomy—defined as predominantly a 1-wall defect—as a risk factor for failure (odds ratio [OR] ≥10.4). In the same study, non-supportive defect anatomy (1-wall versus 2-wall, OR = 58.8) and a thin-scalloped gingival biotype (OR = 76.9) were identified as risk factors for increased REC at the midfacial aspect.[88] Conversely, other studies[37,38,48,72] and systematic reviews[16,63,99,105] have concluded that periodontal regenerative approaches are effective in the treatment of intrabony defects with a wide range of depths, widths, and bony walls (SORT level B).

Space availability/maintenance and wound/clot stability are key factors in determining success of regenerative therapy.[99] The wound-stabilizing and space-making properties of membranes are generally considered key factors underlying the effectiveness of GTR.[106,107] Tonetti et al.[49] reported that the amount of space available under the membrane, rather than total depth of the intrabony defect, was the most significant predictor of regenerative outcome. Consistent with the latter findings, Trombelli et al.[37] found no correlation between defect morphology and gain in probing bone level.

PERIODONTAL REGENERATIVE MATERIALS AND APPROACH

Bone Replacement Grafts and GTR in Regeneration

Previous reviews summarized the many clinical studies that demonstrated bone replacement grafts and GTR are successful treatment modalities for periodontal regeneration.[15,16] Since these reviews, no RCTs and systematic reviews on bone replacement grafts were identified. Two systematic reviews on GTR have been published to update the field.[17,108] Clinical studies have focused on new membranes and the use of the GTR approach in combination with various bone replacement and EMD.[40,66,71,78,80,109-132] With the exception of studies that examined the use of GTR in conjunction with EMD, the number of studies was limited, and the overall conclusions were consistent with earlier evidence-based reviews.[15,16] The discussion of combination therapy using GTR and EMD is discussed below.

Laser. The role of lasers in the treatment of periodontitis remains controversial. At the center of this polemic debate is the LAR protocol. Using the Nd:YAG laser with this procedure, periodontal regeneration is achievable on a previously diseased root surface. Two recent publications, based on human histology, suggest that this protocol may have merit in periodontal therapy.[30,133] In the initial histologic report on the protocol, Yukna et al.[133] reported that the six teeth treated with LAR** demonstrated evidence of new attachment, with new cementum and inserting PDL, after 3 months. Recently, Nevins et al.[30] reported that, of the 10 specimens evaluated after LAR treatment, five teeth had evidence of periodontal regeneration, one tooth had new attachment with new cementum and inserting collagen fibers, and the other four teeth healed with a long junctional epithelium. Unlike the previous study by Yukna et al.,[133] healing was observed after 9 months, which is more consistent with the normally observed 6 to 24 months for optimal regeneration.[16,31,102,105,134-136] This report provides proof of principle that LAR therapy can induce periodontal regeneration (SORT level C).

Despite the evidence for new attachment and periodontal regeneration, information about clinical predictability of this procedure has yet to be demonstrated. There are no well-documented clinical reports or randomized controlled studies that define the frequency and extent of regeneration that can be achieved. However, this technique is intriguing in that it is another approach to minimally invasive surgical therapies as reviewed by Cortellini.[99] A minimally invasive surgical approach may offer advantages in regeneration of defects in the esthetic zone in which minimal soft tissue change is required. Additionally, because of the minimally invasive nature and expendable surgical materials required, this approach may be appropriate for multiple defects as a first line of management.

EMD. EMD has been available as a biologic periodontal regenerative material for ≈15 years.[28,137] The biologic properties of EMD have been summarized recently.[138,139] Several studies have provided human histologic evidences of intrabony regeneration associated with EMD therapy.[3,4,28,29,32] EMD is present on root surfaces for ≥4 weeks after application, and early signs of periodontal wound regeneration can be observed after 2 to 6 weeks.[140,141] Signs of clinical improvement are present as early as 6 months after treatment.[111,112,114,116,120,130]

EMD versus OFD. The first RCT to compare the effectiveness of EMD versus OFD was published by Heijl et al.[137] Clinical reductions in PD, increases in CAL, and increases in linear bone growth with EMD were statistically superior to improvements observed

** LANAP, Millenium Dental Technologies.

Table 2.

Controlled Clinical Studies Using Access Flap and GTR Approaches

Study	Study Design	Time (months)	Treatment (n defects)	Mean PD Change (mm)	*P*	Mean CAL Change (mm)	*P*	Mean Linear Bone Fill	*P*	Mean REC Change (mm)*	*P*
Aimetti et al., 2005[72]	Paired	12	GTR-R (18) OFD (18) GTR-R vs OFD	3.44 2.39 1.05	<0.001 <0.001 <0.001	2.89 1.50 1.39	<0.001 <0.001 <0.001	2.13 mm 1.05 mm 1.08 mm	<0.001 <0.001 NS	0.56 0.89 –0.330	0.002 <0.001 NS
Cortellini and Tonetti, 2005[51]	Parallel	12	GTR-NR (12) GTR-R (7) GTR-R + BG (11) EMD (10)	6.6 5.9 6.3 5.8	<0.001 <0.001 <0.001 <0.001	1.68 2.59 3.54 4.59	<0.001 <0.001 <0.001 <0.001	94.7% 88.9% 88.2% 95.4%	ND ND ND ND	0.2 0.1 –0.3 0.2	NS NS NS NS
Tonetti et al., 2004[74]	Parallel	12	GTR + BG (61) PPF (59)	3.7 3.2	0.004	3.3 2.5	0.02	ND ND	ND ND	0.3 0.7	0.04
Bianchi and Bassetti, 2009[73]	Case series	12	GTR + BG (14)	5.14	NS	4.57	<0.001	ND	ND	0.57	0.46
Eickholz et al., 2004[38]	Case series	6 24	GTR (50)	4.22 4.38	<0.001 <0.001	3.35 3.38	<0.001 <0.001	0.70 mm 1.21 mm	NS 0.005	ND	ND
Stavropoulos et al., 2004[11]	Case series	12	GTR-nonS (17) GTR-S (15)	5.5 4.5	<0.01	4.3 3.2	0.03	ND ND	ND ND	1.2 1.3	NS
Stravropoulos and Karring, 2005[76]	Case series	12 60	GTR + BG (15)	5.0 4.6	<0.01 <0.01	3.8 4.1	<0.01 <0.01	4.7 mm 4.9 mm	<0.01 0.01	1.2 0.5	<0.01 NS
Stravropoulos and Karring, 2004[77]	Case series	12 60 to 72	GTR (25)	4.9 4.0	<0.01 <0.001	3.8 3.6	<0.01 <0.01	ND ND	ND ND	1.1 0.4	<0.01 NS
Klein et al., 2001[41]	Case series	6 24	GTR (39)	4.2 4.3	<0.001 <0.001	3.15 3.31	<0.001 <0.001	1.30 mm 1.54 mm	<0.01 <0.005	ND ND	ND ND
Cortellini et al., 2011[57]	Parallel	12 12 60 60	GTR (25) Ext/implant/FPD GTR (25) Ext/implant/FPD	8.8 ND 8.9 ND	<0.001 ND NS ND	7.7 ND 7.7 ND	<0.001 ND NS ND	8.5 mm ND 8.6 mm ND	<0.001 ND NS ND	1.1 ND 1.2 ND	0.006 ND NS ND

Table 2. (continued)

Controlled Clinical Studies Using Access Flap and GTR Approaches

Study	Study Design	Time (months)	Treatment (n defects)	Mean PD Change (mm)	*P*	Mean CAL Change (mm)	*P*	Mean Linear Bone Fill	*P*	Mean REC Change (mm)*	*P*
Siciliano et al., 2011[62]	Parallel	12	GTR (20)	5.5	<0.001	4.1	<0.001	ND	ND	0.5	NS
			EMD (20)	2.9	<0.001	2.4	<0.001	ND	ND	0.7	NS
Döri et al., 2005[78]	Parallel	12	EMD + BG + PRP (12)	5.5	<0.001	4.5	<0.001	ND	ND	1.0	<0.01
		12	EMD + BG (12)	5.5	<0.001	4.5	<0.001	ND	ND	1.0	<0.01
		60	EMD + BG + PRP (12)	4.9	<0.001	4.3	<0.001	ND	ND	0.6	<0.01
		60	EMD + BG (12)	5.0	<0.001	4.3	<0.001	ND	ND	0.7	<0.01
Kim et al., 2002[79]	Case series, paired	6	GTR-NR (12)	4.2	ND	2.6	0.012	ND	ND	ND	ND
		6	GTR-R (12)	4.1	ND	3.0	0.012	ND	ND	ND	ND
		60	GTR-NR (12)	2.6	ND	1.6	0.03	1.5 mm	NS	ND	ND
		60	GTR-R (12)	3.6	ND	3.0	0.01	2.1 mm	0.02	ND	ND
Sculean et al., 2004[80]	Parallel	12	EMD (11)	4.6	<0.001	3.4	<0.001	ND	ND	1.3	<0.001
			GTR (11)	4.4	<0.001	3.2	<0.001	ND	ND	1.2	<0.001
			EMD + GTR (10)	4.4	<0.001	3.0	<0.001	ND	ND	1.5	<0.001
			OFD (10)	3.3	<0.001	1.6	<0.001	ND	ND	1.7	<0.001
		60	EMD (11)	4.3	<0.001	2.9	<0.001	ND	ND	1.3	<0.001
			GTR (11)	3.9	<0.001	2.7	<0.001	ND	ND	1.2	<0.001
			EMD + GTR (10)	4.0	<0.001	2.6	<0.001	ND	ND	1.5	<0.001
			OFD (10)	2.7	<0.001	1.3	<0.001	ND	ND	1.7	<0.001
Slotte et al., 2007[81]	Case series	12	GTR + BG (24)	5.2	ND	4.2	ND	6.0 mm	ND	1.0	ND
		36		5.6	ND	4.1	ND	4.8 mm	ND	1.6	ND
		60		5.3	ND	4.3	ND	4.8 mm	ND	1.3	ND
Sculean et al., 2008[67]	Parallel	12	EMD (10)	4.1	<0.001	3.4	<0.001	ND	ND	0.7	<0.001
			GTR (10)	4.2	<0.001	3.2	<0.001	ND	ND	1.0	<0.001
			EMD + GTR (9)	4.3	<0.001	3.3	<0.001	ND	ND	1.0	<0.001
			OFD (9)	3.7	<0.001	2.0	<0.001	ND	ND	1.7	<0.001
		120	EMD (10)	4.6	NS	2.9	<0.001	ND	ND	0.7	NS
			GTR (10)	3.4	NS	2.8	<0.001	ND	ND	0.6	NS
			EMD + GTR (9)	3.6	NS	2.9	<0.001	ND	ND	0.6	NS
			OFD (9)	3.5	NS	1.8	<0.001	ND	ND	1.7	NS

Table 2. (continued)

Controlled Clinical Studies Using Access Flap and GTR Approaches

Study	Study Design	Time (months)	Treatment (n defects)	Mean PD Change (mm)	*P*	Mean CAL Change (mm)	*P*	Mean Linear Bone Fill	*P*	Mean REC Change (mm)*	*P*
Pretzl et al., 2008[82]	Paired	12	GTR-R (15)	4.4	ND	3.3	0.001	ND	ND	ND	ND
		12	GTR-NR (15)	4.7	ND	3.4	<0.001	ND	ND	ND	ND
		120	GTR-R (8)	4.2	ND	3.5	0.005	2.7 mm	0.02	ND	ND
		120	GTR-NR (8)	2.4	ND	1.5	0.02	0.8 mm	0.04	ND	ND
Pretzl et al., 2009[83]	Paired	12	GTR-R1 (15)	4.3	<0.001	3.89	<0.001	1.73 mm	0.01	ND	ND
		12	GTR-R2 (15)	5.16	<0.001	4.06	<0.001	2.11 mm	0.006	ND	ND
		120	GTR-R1 (11)	3.16	0.004	2.44	0.004	3.72 mm	NS	ND	ND
		120	GTR-R2 (11)	3.16	<0.001	2.44	0.002	3.49 mm	0.02	ND	ND
Nygaard-Østby et al., 2010[84]	Paired	9	BG (20)	2.9	<0.05	2.5	<0.05	1.9 mm	NS	0.4	NS
		9	BG + GTR (20)	3.2	<0.05	2.5	<0.05	2.5 mm	<0.05	0.6	NS
		120	BG (13)	2.7	<0.05	2.2	<0.05	1.3 mm	NS	0.6	NS
		120	BG + GTR (13)	4.2	<0.05	3.8	<0.05	3.9 mm	<0.05	0.7	NS
Nickles et al., 2009[85]	Parallel	12	OFD (17)	3.71	ND	3.47	ND	ND	ND	ND	ND
		12	GTR (18)	4.14	ND	3.67	ND	ND	ND	ND	ND
		120	OFD (17)	4.41	ND	3.41	ND	2.03 mm	0.002	ND	ND
		120	GTR (18)	4.25	ND	2.89	ND	1.69 mm	0.02	ND	ND
	Paired	12	OFD (10)	3.60	ND	3.60	ND	ND	ND	ND	ND
		12	GTR (10)	3.95	ND	3.50	ND	ND	ND	ND	ND
		120	OFD (10)	4.40	ND	3.65	ND	2.15 mm	0.01	ND	ND
		120	GTR (10)	4.15	ND	2.85	ND	1.30 mm	NS	ND	ND

R = resorbable; NR = non-resorbable; BG = bone graft; PPF = papilla preservation flap; nonS = non-smoker; S = smoker; Ext = extraction; FPD = fixed partial denture; ND = not defined; NS = not significant.
* Negative values indicate gain.

Table 3.

Controlled Clinical Studies Using Conservative and Minimally Invasive Surgical Approaches

Study	Study Design	Time (months)	Treatment (n defects)	Mean PD Change (mm)	*P*	Mean CAL Change (mm)	*P*	Mean Linear Bone Fill	*P*	Mean REC Change (mm)	*P*
Cortellini and Tonetti, 2007[53]	Case series	12	MIST + EMD (40)	5.2	<0.001	4.9	<0.001	77.6%	ND	0.4	0.02
Cortellini and Tonetti, 2007[58]	Case series	12	MIST + EMD (13)	4.8	<0.001	4.8	<0.001	88.7%	ND	0.1	NS
Cortellini et al., 2008[55]	Case series	12	MIST + EMD (40)	4.6	<0.001	4.4	<0.001	83%	ND	0.2	0.04
Cortellini et al., 2009[56]	Case series	12	MIST + EMD (40)	5.2	<0.001	4.9	<0.001	77.6%	ND	0.4	0.02
Cortellini and Tonetti, 2011[52]	Parallel	12	M-MIST (15) M-MIST + EMD (15) M-MIST + EMD + BG (15)	3.1 3.4 3.3	<0.001 <0.001 <0.001	4.1 4.1 3.7	<0.001 <0.001 <0.001	77% 71% 78%	NS NS NS	0.3 0.2 0.2	NS NS NS
Cortellini and Tonetti, 2009[54]	Case series	12	M-MIST + EMD (15) MIST + EMD (5)	4.6 5.0	<0.001 <0.001	4.5 4.8	<0.001 <0.001	75.5% ND	ND ND	0.07 0.2	NS
Cosyn et al., 2012[88]	Case series	12	MIST/M-MIST + BG (84)	3.5	ND	3.1	ND	53%	ND	0.5	ND
Harrel et al., 2005[89]	Case series	11	MIS + EMD (160)	3.56	0.002	3.57	0.01	ND	ND	0.01	ND
Harrel et al., 1999[90]	Case series	21.7	MIS + BG (194)	4.58	<0.001	4.87	<0.001	ND	ND	ND	ND
Harrel et al., 2010[91]	Case series	72	MIS + EMD (142)	3.78	0.03	3.7	NS	ND	ND	0.0	ND
Trombelli et al., 2012[92]	Parallel	6	SFA (14) DFA (14)	5.2 3.9	<0.001	4.5 3.4	<0.001	ND	ND	0.7 0.5	0.006 ND
Trombelli et al., 2010[75]	Parallel	6	SFA + GTR (12) SFA (12)	5.3 5.3	<0.001 <0.001	4.7 4.4	<0.001 <0.001	ND ND	ND ND	0.4 0.8	NS 0.005
Trombelli et al., 2009[87]	Case series	6–14	SFA/GTR (10)	5.2	<0.001	4.8	<0.001	ND	ND	0.4	NS
Wachtel et al., 2003[93]	Split-mouth	6	Microsurgery + EMD (26)	3.3	<0.05	2.8	<0.05	ND	ND	0.5	<0.05
		6	Microsurgery (26)	2.2	<0.05	2.0	<0.05	ND	ND	0.2	NS
		12	Microsurgery + EMD (26)	3.9	<0.05	3.6	<0.05	ND	ND	0.3	NS
		12	Microsurgery (26)	2.11	<0.05	1.7	<0.05	ND	ND	0.4	NS

Table 3. (continued)

Controlled Clinical Studies Using Conservative and Minimally Invasive Surgical Approaches

Study	Study Design	Time (months)	Treatment (n defects)	Mean PD Change (mm)	*P*	Mean CAL Change (mm)	*P*	Mean Linear Bone Fill	*P*	Mean REC Change (mm)	*P*
Ribeiro et al., 2011[94]	Parallel	6	MIST (14)	3.51	<0.05	2.85	<0.05	ND	ND	0.48	NS
			MINST (13)	3.13	<0.05	2.56	<0.05	ND	ND	0.45	NS
Ribeiro et al., 2011[95]	Parallel	6	MIST (15)	3.55	<0.05	8.21	<0.05	0.95	<0.05	0.54	NS
			MIST + EMD (15)	3.56	<0.05	9.21	<0.05	1.52	<0.05	0.46	NS
Mishra et al., 2013[96]	Parallel		MIST (12)	3.82	NS	2.64	NS	1.85 mm	NS	0.55	NS
			MIST-rhPDGF-BB (12)	4.18		3.0		1.89 mm		0.82	
Fickl et al., 2009[97]	Split-mouth	6	Microsurgery (35)	2.1	<0.001	1.6	<0.002	0.7	0.04	0.5	0.02
		6	Microsurgery + EMD (35)	3.5	<0.001	2.7	<0.002	1.4	0.39	0.6	0.003
		12	Microsurgery (35)	2.4	<0.001	1.7	<0.001	1.1	<0.001	0.7	0.002
		12	Microsurgery + EMD (35)	4.2	<0.001	3.7	<0.001	2.5	<0.001	0.5	0.008
Zucchelli et al., 2002[40]	Parallel	12	EMD + SPP (30)	5.1	<0.05	4.2	<0.05	ND	ND	1.0	<0.05
			GTR + SPP (30)	6.5	<0.05	4.9	<0.05	ND	ND	1.6	<0.05
			SPP/access flap (30)	4.5	<0.05	2.6	<0.05	ND	ND	1.9	<0.05
Nibali et al., 2011[98]	Case series	12–18	Non-surgical therapy (126)	Buccal: 2.24	<0.001	1.42	<0.001	ND	ND	MB or DB: 0.8	<0.001
				Lingual: 2.29	<0.001	1.5	<0.001	ND	ND	ML or DL: 0.8	<0.001

BG = bone graft; DFA = double-flap approach; MINST = minimally invasive non-surgical technique; SFA = single-flap approach; SPP = simplified papilla preservation; ND = not defined; NS = not significant; MB = mesio-buccal; DB = disto-buccal; ML = mesio-lingual; DL = disto-lingual.

Table 4.

Controlled Clinical Studies Comparing Treatment of Intrabony Defects With OFD With or Without EMD

Study	Time (months)	Study Design	Treatments (n defects)	PD Change (mm)	*P*	CAL Change (mm)	*P*	Linear Bone/Bone Fill	*P*
Heijl et al., 1997[137]	8	Split-mouth	EMD (34)	3.3	<0.01	2.1	<0.01	0.9 mm	<0.001
			OFD (34)	2.6		1.5		–0.1 mm	
	16		EMD (34)	3.3	<0.01	2.3	<0.01	2.2 mm	<0.001
			OFD (34)	2.6		1.7		–0.2 mm	
	36		EMD (34)	3.1	<0.01	2.2	<0.01	2.6 mm	<0.001
			OFD (34)	2.3		1.7		0	
Pontoriero et al., 1999[118]	12	Split-mouth	EMD (10)	4.4	<0.001	2.9	<0.001	ND	
			OFD (10)	3.5		1.8			
Silvestri et al., 2000[127]	12	Parallel	EMD (10)	4.8	<0.01	4.5	<0.01	ND	
			OFD (10)	1.4		1.2			
Okuda et al., 2000[146]	12	Split-mouth	EMD (18)	3.00	<0.05	1.72	<0.05	ND	
			OFD (18)	2.22		0.83			
Froum et al., 2001[144]	12	Split-mouth	EMD (53)	4.94	<0.001	4.28	<0.001	3.83 mm 74.0%	<0.001
			OFD (31)	2.24		2.65		1.47 mm 22.7%	
Sculean et al., 2001[126]	12	Parallel	EMD (14)	4.6	<0.05	3.4	<0.05	ND	
			OFD (14)	3.3		1.7			
Sculean et al., 2004[80]	60		EMD (14)	4.3	<0.001	2.9	<0.05	ND	
			OFD (14)	2.7		1.3			
Tonetti et al., 2002[47]	12	Parallel	EMD (83)	3.9	<0.02	3.1	<0.01	ND	
			OFD (83)	3.3		2.5			
Zucchelli et al., 2002[40]	12	Parallel	EMD (30)	5.1	<0.01	4.2	<0.01	ND	
			OFD (30)	4.5		2.6			
Parodi et al., 2004[147]	12	Case series	EMD (16)	4.18	<0.01	3.12	<0.01	ND	
	36		EMD (16)	4.94		4.20			
Francetti et al., 2004[143]	12	Parallel	EMD (12)	4.71	<0.05	4.14	<0.05	2.96 mm	<0.05
			OFD (12)	2.57		2.29		1.44 mm	
	24		EMD (12)	4.86	<0.05	4.29	<0.05	3.44 mm	<0.05
			OFD (12)	3.00		2.71		1.84 mm	
Rösing et al., 2005[148]	12	Split mouth	EMD (14)	4.17	NS	2.01	NS	0.94 mm	NS
			OFD (14)	4.39		2.16		0.91 mm	

Table 4. (continued)
Controlled Clinical Studies Comparing Treatment of Intrabony Defects With OFD With or Without EMD

Study	Time (months)	Study Design	Treatments (n defects)	PD Change (mm)	*P*	CAL Change (mm)	*P*	Linear Bone/Bone Fill	*P*
Grusovin and Esposito, 2009[145]	12	Parallel	EMD (15)	4.2	NS	3.4	NS	2.5	NS
			OFD (15)	3.9		3.3		2.5	
Chambrone et al., 2010[142]	12	Parallel	EMD	4.00	NS	3.46	NS	ND	
			OFD	3.49		3.65			
	24		EMD	4.21	<0.05	5.69	NS	ND	
			OFD	3.28		5.24			

NS = not significant.

with OFD. Subsequently, 13 additional studies evaluated the efficacy of EMD versus OFD, with the majority confirming that OFD followed by EMD application resulted in substantial improvements in clinical measurements and bone fill with EMD in the management of intrabony defects (Table 4)[40,47,80,118,126,127,137,142-148] (SORT level A). Neither postoperative antibiotics[149] nor EDTA root conditioning improved the clinical outcome of EMD therapy.[150,151]

EMD versus GTR. Of the 11 studies comparing the clinical management of intrabony defects with EMD versus GTR, all but one failed to show any significant difference (Table 5)[40,62,66,80,110,117,118,125-129,142-148] (SORT level A). The noted exception was an RCT that compared the two therapeutic modalities in deep, non-contained intrabony defects.[62] In these defects, GTR with titanium reinforcement was superior. The latter results suggest that, in situations in which defect configuration is broad or lacking in wall containment, a supported barrier membrane may be critical in the success of EMD-associated regeneration. Additionally, no added clinical advantage was observed when EMD was combined with GTR.[80,117,126]

EMD alone versus EMD used in combined therapy. There are several studies in which EMD has been used in combined therapy (Table 6).[71,78,109,111-116,119-124,130-132,152-155] Histologic evidence of periodontal regeneration has been demonstrated when EMD is used in combination with autogenous bone, a bovine-derived natural bone mineral (NBM),[††] bioactive glass,[‡‡] NBM + PRP, nanocrystalline hydroxyapatite (NHA), or biphasic calcium phosphate.[7,136,156-158] The majority of the studies indicate no added benefits in either clinical and radiographic gains when EMD is used with the addition of graft materials.[71,78,109,111,113,114,119-124,152-155] These updated studies confirmed the conclusions of meta-analyses of RCTs that there are few additional benefits of EMD when used in conjunction with other regenerative materials/approaches[159] (SORT level A). The exceptions are limited reports that indicate that improved PD, CAL, and/or bone fill is achievable when EMD augments the effect of bone grafts[112,131] or bone graft enhances the effects of EMD.[115,116,132]

In summary, EMD is a semipurified protein preparation from developing porcine teeth that contains a mixture of low-molecular-weight proteins. Although there were initial concerns about the poorly characterized nature of this preparation, recent reports suggest that the mixture may work

†† Bio-Oss, Geistlich Pharma North America, Princeton, NJ.
‡‡ PerioGlas, NovaBone, Jacksonville, FL.

Table 5.

Controlled Clinical Studies Comparing Treatment of Intrabony Defects With EMD Versus GTR

Study	Time (months)	Study Design	Treatments (n defects)	PD Change (mm)	*P*	CAL Change (mm)	*P*	Linear Bone/Bone Fill	*P*
Pontoriero et al., 1999[118]	12	Split-mouth	EMD (10) GTR (30)	4.4 4.5	NS	2.9 3.1	NS	ND	
Silvestri et al., 2000[127]	12	Parallel	EMD (10) GTR (10)	4.8 5.9	NS	4.5 4.8	NS	ND	
Sculean et al., 2001[126]	12	Parallel	EMD (14) GTR (14) EMD + GTR (14)	4.1 4.2 4.3	NS	3.4 3.1 3.4	NS	ND	
Sculean et al., 2004[80]	60	Parallel	EMD (14) GTR (14) EMD + GTR (14)	4.3 3.9 4.0	NS	2.9 2.7 2.6	NS	ND	
Zucchelli et al., 2002[40]	12	Parallel	EMD (30) GTR (30)	5.1 6.5	<0.01	4.2 4.9	<0.01	ND	
Minabe et al., 2002[117]	12	Parallel	EMD (22) GTR (23) EMD + GTR (24)	5.4 4.6 5.0	NS	3.0 3.0 3.2	NS	40% 35% 49%	NS
Silvestri et al., 2003[128]	12	Parallel	EMD (49) GTR (49)	5.3 5.6	NS	4.1 4.3	NS	ND	
Sanz et al., 2004[66]	12	Parallel	EMD (35) GTR (32)	3.8 3.3	NS	3.1 2.5	NS	ND	
Sipos et al., 2005[129]	12	Split-mouth	EMD (12) GTR (12)	2.86 3.02	NS	1.28 1.65	NS	1.63 mm 1.58 mm	NS
Sculean et al., 2006[125]	12	Split-mouth	EMD (10) GTR (10)	4.1 4.6	NS	3.2 3.0	NS	ND	
	96	Split-mouth	EMD (10) GTR (10)	3.4 3.7	NS	2.8 2.9	NS	ND	
Crea et al., 2008[110]	12	Parallel	EMD (19) GTR (20)	3.5 3.5	NS	2.9 2.5	<0.05	50.5% 57.0%	NS
	36	Parallel	EMD (19) GTR (20)	3.1 3.2	NS	2.4 2.0	<0.05	58.8% 53.7%	NS
Siciliano et al., 2011[62]	12	Parallel	EMD (20) GTR (20)	2.9 5.5	<0.001	2.4 4.1	<0.001	ND	

NS = not significant.

Table 6.

Controlled Clinical Studies Comparing Treatment of Intrabony Defects With EMD Versus Combined Therapy

Study	Time (months)	Study Design	Treatments (n defects)	PD Change (mm)	*P*	CAL Change (mm)	*P*	Linear Bone/Bone Fill	*P*
Guida et al., 2007[111]	12	Parallel	EMD (14) EMD + AB (14)	5.6 5.1	NS	4.6 4.9	NS	ND	
Yilmaz et al., 2010[131]	12	Parallel	EMD (20) EMD + AB (20)	4.6 5.6	<0.01	3.4 4.2	<0.01	2.8 mm 3.9 mm	<0.001
Gurinsky et al., 2004[112]	6	Parallel	EMD (34) EMD + DFDBA (33)	4.0 3.6	NS	3.2 3.0	NS	2.6 mm/55.3% 3.7 mm/74.9%	<0.001
Hoidal et al., 2008[113]	6	Parallel	DFDBA (20) EMD + DFDBA (17)	2.45 2.56	NS	1.63 1.47	NS	2.33/47.3% 1.91 mm/46.3%	NS
Rosen and Reynolds, 2002[119]	6	Case series	EMD + DFDBA (10) EMD–FDBA (12)	8.4 8.9	NS NS	9.2 9.1	NS NS	ND ND	
Al Machot et al., 2014[152]	12	Parallel	EMD (19) NHA (19)	3.2 2.6		2.0 1.5	ND ND	1.6 mm 1.6 mm	NS
Lekovic et al., 2000[116]	6	Split-mouth	EMD (21) EMD + NBM (21)	1.91 3.43	<0.001	1.72 3.13	<0.001	1.33 mm/28.9%) 3.82 mm/81.3%	<0.001
Scheyer et al., 2002[120]	6	Split-mouth	NBM (17) EMD–NBM (17)	3.9 4.2	NS	3.7 3.8	NS	3.0 mm/67.0% 3.2 mm/63.3%	NS
Sculean et al., 2002[123]	12	Parallel	NBM (16) EMD-NBM (16)	6.5 5.7	NS	4.9 4.7	NS	ND	
Velasquez-Plata et al., 2002[130]	6	Split-mouth	EMD (16) EMD + NBM (16)	3.8 4.0	NS	2.9 3.4	NS	3.1 mm/64.9% 4.0 mm/76.9%	NS for bone fill <0.05 for bone fill
Zucchelli et al., 2003[132]	12	Parallel	EMD (30) EMD + NBM (30)	5.8 6.2	NS	4.9 5.8	<0.01	4.3 mm 5.3 mm	<0.01
Sculean et al., 2005[122]	12	Parallel	EMD (15) EMD + NBM (15)	4.5 4.2	NS	3.9 3.2	NS	ND	
Sculean et al., 2002[121]	12	Parallel	EMD (14) EMD + BG (14)	4.22 4.15	NS	3.07 3.22	NS	ND	
Sculean et al., 2005[124]	12	Parallel	EMD (12) EMD + BG (13)	4.5 4.2	NS	3.9 3.2	NS	ND	

Table 6. (continued)

Controlled Clinical Studies Comparing Treatment of Intrabony Defects With EMD Versus Combined Therapy

Study	Time (months)	Study Design	Treatments (n defects)	PD Change (mm)	*P*	CAL Change (mm)	*P*	Linear Bone/Bone Fill	*P*
Sculean et al., 2007[71]	48	Parallel	EMD (12) EMD + BG (13)	4.2 4.1	NS	3.4 3.4	NS	ND	
Kuru et al., 2006[115]	8	Split-mouth	EMD (26) EMD + BG (26)	5.03 5.73	<0.05	4.06 5.17	<0.05	2.15 mm 2.76 mm	<0.05
Jepsen et al., 2008[114]	6	Parallel	EMD (35) EMD + BCP (38)	2.55 1.93	NS	1.83 1.31	NS	2.07 mm 2.01 mm	NS
Döri et al., 2005[78]	12	Parallel	EMD + NBM (12) EMD + β-TCP (12)	4.5 4.8	NS NS	3.1 3.7	NS NS	ND ND	
Döri et al., 2013[153]	120	Parallel	EMD + NBM (11) EMD + β-TCP (12)	3.9 4.0		3.1 3.0	NS		
Döri et al., 2008[154]	12	Parallel	EMD + NBM + PRP (13) EMD + NBM + PRP (13) EMD + NBM (12)	6.0 5.7 5.0	NS NS NS	5.0 4.8 4.3	NS NS NS	ND ND ND	
Döri et al., 2013[155]	60	Parallel	EMD + NBM + PRP (12) EMD (19)	4.9 3.9	NS	4.3 3.7	NS	ND ND	
Bokan et al., 2006[109]	12	Parallel	EMD + β-TCP (19) OFD (19)	4.1 3.8	NS	4.0 2.1	NS	ND ND	

AB = autogenous bone; NHA = nanocrystalline hydroxyapatite; NBM = natural bone mineral; BG = bioglass; BCP = biphasic calcium phosphate; β-TCP = beta tricalcium phosphate; NS = not significant.

synergistically on multiple levels to enhance periodontal regeneration.[138] When applied to root surfaces, the proteins are absorbed into the hydroxyapatite and collagen fibers of the root surface, in which they induce cementum formation followed by periodontal regeneration. Clinical use of EMD can generally be characterized as safe with excellent clinical healing and limited complications. EMD alone or in combination with graft materials provide clinical outcome and long-term clinical stability comparable with GTR.[67,71,80,137,160,161] Although characterization of the EMD preparation remains incomplete, the challenge, as with allografts, is to provide a consistent batch of EMD, so the regenerative response is predictable.

rhPDGF-BB

rhPDGF-BB has been shown to enhance periodontal regeneration.[162] Clinical application of the recombinant form of this growth factor indicates that it can promote regeneration of bone, ligament, and cementum.[27,31] Two RCTs using rhPDGF-BB have been reported (Table 7).[163,164] The first study was a prospective, masked, RCT to evaluate the safety and efficacy of rhPDGF-BB used in conjunction with synthetic β-tricalcium phosphate (β-TCP).[164] This study demonstrated that the use of rhPDGF-BB was safe and effective in the treatment of intrabony periodontal defects. Although improvements in PD and CAL were not significantly superior to grafted (control) intrabony defects, there was significant improvement in bone formation and accelerated wound healing as depicted by "the area under the curve" when grafted with rhPDGF-BB + β-TCP. Follow-up studies showed that the improved bone fill and linear bone growth continued to improve over 36 months, reaching maximal statistical significant bone fill after 24 months.[134,135] In a report of a subset of this study population, after 5 years, the use of rhPDGF-BB resulted in a stable, physiologic attachment in the presence of good patient compliance.[165] When deterioration of the regenerative result was present, it was associated with patients' smoking habits and poor compliance with supportive periodontal care.[165] The second multicenter RCT confirmed after 6 months not only improved bone fill but significant improvement of PD and CAL as well.[163]

In summary, rhPDGF-BB can be safely used with therapeutic results comparable with other regenerative approaches (SORT level A). The unique advantages of this system are that no barrier membrane is required and there is consistency in the concentration of rhPDGF-BB delivered to a regenerative site, which would suggest more consistent clinical results.

THE RELATIONSHIP OF REGENERATIVE TREATMENT TO ENDODONTIC AND ORTHODONTIC THERAPY

Recent studies confirm that endodontically treated teeth with no evidence of pulpal or periapical pathology respond favorably to regenerative therapy.[62-64] The regenerative outcomes of teeth with severe bone loss approaching the root apex were reported recently in a study that evaluated 22 of 25 teeth requiring endodontic therapy 3 months before GTR surgery.[57] Statistically significant reductions in PD and gains in CAL documented at 1 year were maintained for 5 years. However, no RCTs were identified on the relationship between regenerative treatment and endodontic treatment. Therefore, the best-practice management approach is based on one retrospective study[63] and two case series[166,167] that reported no adverse influence of root canal treatment on the periodontal regenerative outcome (SORT level C).

In reviewing the relationship between regenerative treatment and orthodontic treatment, there are several case reports/series describing the treatment of intrabony defects by means of orthodontic therapy, alone or in combination with periodontal therapy.[168-176] Additionally, one RCT was identified that evaluated the effect of periodontal regeneration combined with orthodontic treatment on clinical parameters in intrabony defects as discussed below.[177]

Case series/reports have documented improvement of intrabony defects with orthodontic tooth movement alone, including bodily movement into intrabony defects;[169,172,173] extrusive movement, such as a mesially tilted tooth with 1- or 2-wall intrabony defect;[168,170,171] and orthodontic intrusion.[174-176] Moreover, case reports suggest no adverse effects of orthodontic movement of teeth that had previously undergone regenerative therapy for intrabony defects.[178-180]

Recently, the first RCT evaluated the role of combined periodontal regenerative orthodontic treatment of 2- or 3-wall intrabony defects.[177] In this clinical trial, 47 patients were randomized into orthodontic extrusive force with pretreatment grafting of EMD + DFDBA plus orthodontic extrusion (test group) or EMD + DFDBA grafting alone (control group). After 1 year, both groups had improved PD, CAL, and bone fill; however, the test sites had significantly greater mean increase in open probing CAL in 2-wall intrabony defects than controls (SORT level C).

Patient Preferences and Clinical Outcomes

Patient options for regenerative approaches have increased. Personal and religious preferences can be respected as the clinician offers the appropriate regenerative modalities. The advent of GTR, EMD, rhPDGF, and LAR permits patients to select non–tissue

Table 7.

Controlled Clinical Studies Comparing Treatment of Intrabony Defects With rhPDGF-BB + β-TCP Versus β-TCP Alone

Study	Time (months)	Study Design	Treatments (n defects)	PD Change (mm)	*P*	CAL Change (mm)	*P*	Linear Bone/Bone Fill	*P*
Nevins et al., 2005[164]	6	Parallel	rhPDGF–β-TCP (60)	4.43	NS	3.8	NS	2.6 mm/7%	<0.001
			β-TCP (59)	4.20		3.5		0.9 mm/18%	
			rhPDGF–β-TCP non-smoker (18)	ND				60%	<0.001
			rhPDGF–β-TCP non-smoker (12)	ND				16%	
			β-TCP smoker (12)	ND				39%	NS
			β-TCP smoker (11)	ND				25%	
			rhPDGF–β-TCP 1- to 2-wall defect (40)	ND				53%	<0.001
			rhPDGF–β-TCP 3-wall/Cir defect (42)	ND		4.8	NS	4.3	
			β-TCP 1- to 2-wall defect (12)	ND				65%	<0.001
			β-TCP 3-wall/Cir defect (11)	ND				21%	
Nevins et al., 2013[135]	12		rhPDGF–β-TCP (43)	4.46	NS	3.80	NS	2.88 mm/60%	<0.001
			β-TCP (45)	4.08		3.65		1.42 mm/33%	
	24		rhPDGF–β-TCP (29)	4.49	NS	4.09	NS	3.32 mm/68%	<0.001
			β-TCP (29)	3.80		3.31		1.81 mm/42%	
	36		rhPDGF–β-TCP (27)	4.57	NS	4.31			NS
			β-TCP (28)	4.14		3.44			
	12		rhPDGF–β-TCP non-smoker	ND				2.85 mm/62%	<0.001
			rhPDGF–β-TCP smoker	ND				1.0 mm/27%	
	24		rhPDGF–β-TCP non-smoker	ND				3.60 mm/72%	<0.001
			rhPDGF–β-TCP smoker	ND				1.00 mm/25%	
	36		rhPDGF–β-TCP non-smoker	ND				3.75 mm/82%	<0.001
			rhPDGF–β-TCP smoker	ND				1.45 mm/30%	
Jayakumar et al., 2011[163]	6	Parallel	rhPDGF–β-TCP (27)	4.3	<0.005	3.7	<0.005	3.7 mm/65.6%	<0.01 LBG
			β-TCP (27)	3.2		2.8		2.8 mm/47.5%	<0.004 % BF

Cir = circumferential; NS = not significant; LBG = linear bone growth; BF = bone fill.

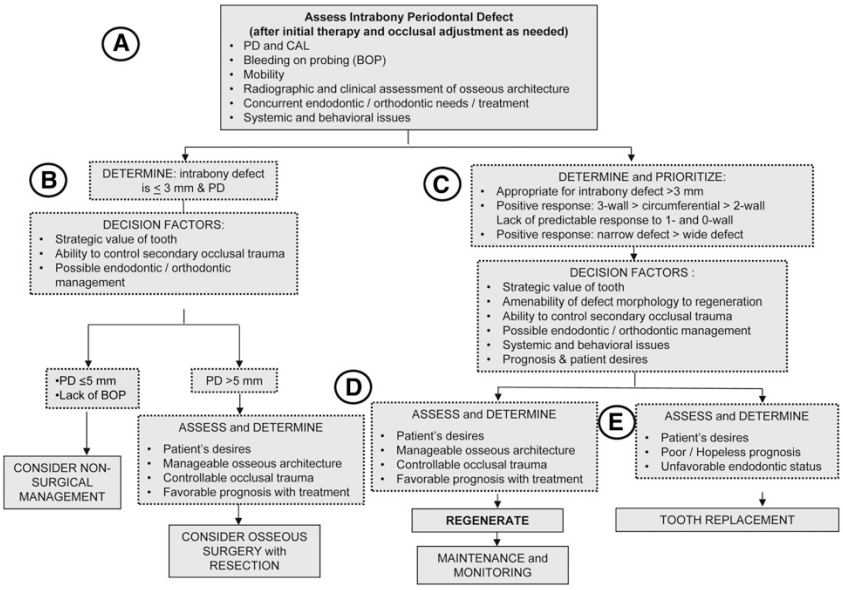

Figure 2.
Decision tree for the management of intrabony defects. A/B/C/D/E are explained in paragraph "Summary With Decision Tree to Guide Clinicians in Their Patient Management."

banked and non-porcine regenerative options. Historically, when DFDBA was the only regenerative approach, options, such as bioactive glass, β-TCP, and ceramics were reasonable alternatives.[15] Although these grafting procedures healed by the formation of the long junctional epithelium, long-term clinical stability was possible.[15] Now, these materials are used primarily as scaffolding agents to support regenerative approaches in wide/large intrabony defects.[15,115,116,131,132]

Clinical outcomes for both GTR and conservative/minimally invasive procedures continue to demonstrate therapeutic value for the periodontal patient (Tables 2 and 3). The majority of GTR studies report 12-month clinical results,[11,51,57,62,72-74,76-78,80-83,85] although 5- and 10-year results are now available (Table 2).[57,67,76-85] These reports document maintainable and significantly reduced PD and gains in CAL compared with pretreatment levels. Conversely, because of the more recent introduction of minimally invasive/conservative flap procedures, very few long-term (>5 years) studies or comparisons with OFD are available.[91] The great majority of articles present 6- to 12-month results, demonstrating statistically significant reductions in PD and gains in CAL (Table 2).[40,52-56,58,75,87-90,92-98] However, Harrel et al.[91] concluded that the therapeutic benefits of combining MIS and EMD at 12 months remained stable at 6 years (Table 2). Of note, REC values for conservative/minimally invasive procedures tend to be lower than those reported for access flap surgery/GTR (Tables 2 and 3), suggesting that minimally invasive techniques are better suited for areas requiring preservation of esthetics. Nevertheless, it is important to consider that the presence of either a non-supportive defect anatomy (OR = 58.8) or thin-scalloped gingival biotype (OR = 76.9) was identified as a risk factor for REC on the midfacial aspect.[88] These findings have significant implications in the esthetic zone, in which minimizing REC is paramount.

Silvestri et al.[39] evaluated tooth survival outcomes up to 16 years after GTR. A 90% tooth survival rate was observed at 13 years, and post-surgical CAL gains were maintained at 82% for 11 years. Prognosis was negatively influenced by smoking and lack of oral hygiene maintenance. Indeed, results from a Kaplan-Meier analysis, correlating survival rate and smoking status over time, indicated that survival rates in smokers decreased at a faster rate beginning 5 years after surgery; log-rank testing showed that both smoking status and poor compliance with oral hygiene programs were significantly correlated with tooth loss.[39] Cortellini and Tonetti[50] retrospectively evaluated tooth survival after GTR treatment up to 16 years and concluded that tooth retention and clinical improvements can be maintained long term in most patients. Of note, 96% of patients exhibited tooth survival >10 years, with smokers contributing the most lost teeth. Consistent with the latter finding, the probability of losing ≥2 mm of regenerated CAL was also shown to be significantly higher in smokers than in non-smokers.[50]

DISCUSSION

The goal of this systematic review is to update research findings since the last consensus reviews on the efficacy of bone replacement grafts and GTR.[15,16] Focus was on determinants for regenerative success, new approaches for periodontal regeneration of intrabony defects, and the relationship of periodontal regeneration to endodontic or orthodontic therapy. These findings were presented above. To bring clinical relevance to this body of information, clinical

scenarios are addressed based on the information and are reviewed below.

Clinical Scenario 1: What New Regenerative Approaches Are There for Regeneration of Intrabony Defects?

In this review, the use of biologics in the form of EMD and rhPDGF-BB + β-TCP can also be added to the list of available periodontal regenerative approaches. The overall conclusion is that a beneficial result may be seen as early as 6 months, but the maximal regenerative results are not achieved until 1 or 2 years later. Compared with OFD, EMD appears to support greater improvements in both hard (defect fill) and soft tissue parameters (CAL and PD), whereas rhPDGF-BB + β-TCP may support greater improvements with defect fill. The volume of bone fill for both of these biologics is comparable with those associated with DFDBA and GTR approaches. Although there is proof of principle for the use of laser as a regenerative approach,[30] there is an absence of data available to define the predictability, frequency, and level of clinical improvement that can be achieved with this approach. Minimally invasive approaches, with or without the addition of biomaterials, represent viable techniques in the treatment of intrabony defects. These require microsurgical instruments and magnification to perform accurately. Studies indicate lower REC values compared with access flap/GTR approaches.

Clinical Scenario 2: What Level of Evidence Addresses the Decision When Selecting the Most Appropriate Surgical Approach for Regeneration of an Intrabony Defect?

The goal of evidence-based dentistry is to help practitioners provide their patients with optimal care.[181] This concept is based on integrating sound research evidence with personal clinical expertise and patient values to determine the best course of treatment. Although inclusion of studies evaluated included only those materials that fulfill the criteria of histologic evidence of periodontal regeneration, it should be appreciated that this definition is problematic and becoming more difficult to meet for ethical reasons. Furthermore, although one of the inclusion criteria was based on histologic evidence of periodontal regeneration, the treatment decision is never based on histology but rather on clinical determinants (as outlined in Fig. 2) and long-term stability (≥3 years). The latter is difficult to achieve because of the limited number of study participants included in most of these studies. Nevertheless, clinical evidence substantiates that periodontal regeneration of intrabony defects is possible with the use of autogenous bone, DFDBA, GTR, EMD, and rhPDGF-BB + β-TCP. Furthermore, this review and previous consensus reports substantiate that these approaches support comparable improvements in clinical parameters and bone fill.[15,16] Given the research evidence, the selection of a regenerative approach is dependent on the clinical expertise and experience of the clinician and the patient's desires. Although there are justifiable reasons for strategic extraction,[182] current evidence demonstrates that long-term stable results are achievable with periodontal regeneration. The ability to delay extraction by gaining more time through periodontal regeneration should always be considered as an option. This gained time may allow for advances in implant dentistry, such as the following: 1) newer technologies to enhance osseointegration; 2) more predictable treatment strategies for peri-implantitis; and 3) improved methodology to address increasing esthetic and functional demands of implant dentistry. Implant dentistry is rapidly changing and improving; as such, prolonging tooth survival through regeneration appears to be a defensible and prudent consideration.

Clinical Scenario 3: What Are the General Principles of a Good Regenerative Approach?

Regenerative therapy represents a proven method to improve clinical parameters, periodontal prognosis, and tooth retention. Achieving therapeutic goals in periodontal regeneration necessitates the incorporation of sound clinical judgment and emphasis on control of patient-centered variables both preoperatively and postoperatively. Surgical experience and clinician skill should align with techniques that maximize the biologic potential of the surgical site, including space maintenance and wound stabilization. Tooth stabilization appears to benefit periodontal regenerative outcomes, whereas endodontically treated teeth respond in a similar manner as vital teeth in periodontal regenerative outcomes. Conservative/minimally invasive techniques appear to result in less REC postoperatively. These approaches may be better suited for esthetically sensitive areas, although long-term studies have yet to confirm the short-term (1-year) outcomes.

Summary With Decision Tree to Guide Clinicians in Their Patient Management

A decision tree is provided to show an overview of clinical determinants that should be considered for the best-practice management of intrabony defects (Fig. 2). As with any therapeutic procedure, consideration must be given to a patient's desires and expectations, as well as behavioral and systemic issues. This along with the clinical determinants will dictate whether therapy should be performed for

posterior teeth (Fig. 2A). Exceptions to this decision tree may be in the maxillary anterior esthetic zone in which maintenance versus strategic extraction may need to be considered. For posterior teeth, if the intrabony defect is narrow and ≤3 mm in open PD, conventional osseous surgery may be most appropriate and predictable for posterior teeth (Fig. 2B). Debridement of the narrow defect is often adequate to achieve clinical improvement, whereas ostectomy can be performed on the broader crestal aspect of the defect. Should the defect be broad and >3 mm in open PD, one should consider periodontal regeneration (Fig. 2C). Assessment of defect morphology and the patient's clinical and systemic-behavioral determinants is critical for regenerative success. Consideration of this in addition to the patient's desires will define the selection of the regenerative approach (Fig. 2D). Although the clinician and the patient together decide on the appropriate material, the management of the defect is based more on the osseous architecture. Narrow 3-wall defects are easily managed by a variety of regenerative approaches, whereas broad, deep 2-wall defects may require combination therapy that provides scaffolding support to prevent tissue collapse into the defect. Long-term stability is possible, but the individual outcome is influenced by smoking and compliance with periodontal maintenance and monitoring. Should patient-related or clinical determinants be unfavorable for periodontal regeneration, then consideration, if appropriate, might be given to strategic extraction and placement of an implant-supported prosthesis (Fig. 2E).

REVIEWERS' CONCLUSIONS

The reviewers' conclusions are the following: 1) The use of biologics (EMD and rhPDGF-BB + β-TCP) generally increase bone fill and improve CAL and reduce PD compared with OFD procedures in the treatment of intrabony defects. These improvements are comparable with those found with DFDBA and GTR regenerative approaches. 2) Histologic evidence of regeneration has been demonstrated with laser therapy, but there are no data that define the clinical effectiveness and predictability of this approach. 3) Clinical outcomes will be most significantly influenced by patient behaviors, surgical approach, and much less by tooth and site characteristics. 4) Long-term studies indicate that the clinical results achieved with regenerative therapy are maintainable up to 10 years, even in severely compromised teeth. Regenerative therapy is capable of improving tooth prognosis.

ACKNOWLEDGMENTS

Dr. Nares has received lecture fees from DENTSPLY (York, Pennsylvania). Dr. Reynolds has received research funding from Millennium Dental Technologies (Cerritos, California) and Zimmer Dental (Carlsbad, California), and is an unpaid consultant for LifeNet Health (Virginia Beach, Virginia). Dr. Kao reports no conflicts of interest related to this review. The 2014 Regeneration Workshop was hosted by the American Academy of Periodontology (AAP) and supported in part by the AAP Foundation, Geistlich Pharma North America, Colgate-Palmolive, and the Osteology Foundation.

REFERENCES

1. Bowers G, Felton F, Middleton C, et al. Histologic comparison of regeneration in human intrabony defects when osteogenin is combined with demineralized freeze-dried bone allograft and with purified bovine collagen. *J Periodontol* 1991;62:690-702.
2. Bowers GM, Chadroff B, Carnevale R, et al. Histologic evaluation of new attachment apparatus formation in humans. Part III. *J Periodontol* 1989;60:683-693.
3. Yukna RA, Mellonig JT. Histologic evaluation of periodontal healing in humans following regenerative therapy with enamel matrix derivative. A 10-case series. *J Periodontol* 2000;71:752-759.
4. Mellonig JT. Enamel matrix derivative for periodontal reconstructive surgery: Technique and clinical and histologic case report. *Int J Periodontics Restorative Dent* 1999;19:8-19.
5. Yukna R, Salinas TJ, Carr RF. Periodontal regeneration following use of ABM/P-1 5: A case report. *Int J Periodontics Restorative Dent* 2002;22:146-155.
6. Mellonig JT. Human histologic evaluation of a bovine-derived bone xenograft in the treatment of periodontal osseous defects. *Int J Periodontics Restorative Dent* 2000;20:19-29.
7. Sculean A, Windisch P, Keglevich T, Chiantella GC, Gera I, Donos N. Clinical and histologic evaluation of human intrabony defects treated with an enamel matrix protein derivative combined with a bovine-derived xenograft. *Int J Periodontics Restorative Dent* 2003;23:47-55.
8. Mellonig JT, Valderrama MdelP, Cochran DL. Histological and clinical evaluation of recombinant human platelet-derived growth factor combined with beta tricalcium phosphate for the treatment of human Class III furcation defects. *Int J Periodontics Restorative Dent* 2009;29:169-177.
9. Ridgway HK, Mellonig JT, Cochran DL. Human histologic and clinical evaluation of recombinant human platelet-derived growth factor and beta-tricalcium phosphate for the treatment of periodontal intraosseous defects. *Int J Periodontics Restorative Dent* 2008;28:171-179.
10. Patel RA, Wilson RF, Palmer RM. The effect of smoking on periodontal bone regeneration: A systematic review and meta-analysis. *J Periodontol* 2012;83:143-155.

11. Stavropoulos A, Mardas N, Herrero F, Karring T. Smoking affects the outcome of guided tissue regeneration with bioresorbable membranes: A retrospective analysis of intrabony defects. *J Clin Periodontol* 2004;31:945-950.
12. Yilmaz S, Cakar G, Ipci SD, Kuru B, Yildirim B. Regenerative treatment with platelet-rich plasma combined with a bovine-derived xenograft in smokers and non-smokers: 12-month clinical and radiographic results. *J Clin Periodontol* 2010;37: 80-87.
13. Palmer RM, Wilson RF, Hasan AS, Scott DA. Mechanisms of action of environmental factors — Tobacco smoking. *J Clin Periodontol* 2005;32(Suppl. 6): 180-195.
14. Cortellini P, Paolo G, Prato P, Tonetti MS. Long-term stability of clinical attachment following guided tissue regeneration and conventional therapy. *J Clin Periodontol* 1996;23:106-111.
15. Reynolds MA, Aichelmann-Reidy ME, Branch-Mays GL, Gunsolley JC. The efficacy of bone replacement grafts in the treatment of periodontal osseous defects. A systematic review. *Ann Periodontol* 2003;8: 227-265.
16. Murphy KG, Gunsolley JC. Guided tissue regeneration for the treatment of periodontal intrabony and furcation defects. A systematic review. *Ann Periodontol* 2003;8:266-302.
17. Needleman I, Tucker R, Giedrys-Leeper E, Worthington H. Guided tissue regeneration for periodontal intrabony defects — A Cochrane Systematic Review. *Periodontol 2000* 2005;37:106-123.
18. Aichelmann-Reidy ME, Reynolds MA. Predictability of clinical outcomes following regenerative therapy in intrabony defects. *J Periodontol* 2008;79:387-393.
19. Koop R, Merheb J, Quirynen M. Periodontal regeneration with enamel matrix derivative in reconstructive periodontal therapy: A systematic review. *J Periodontol* 2012;83:707-720.
20. Esposito M, Grusovin MG, Papanikolaou N, Coulthard P, Worthington HV. Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects. A Cochrane systematic review. *Eur J Oral Implantol* 2009;2:247-266.
21. Sculean A, Nikolidakis D, Schwarz F. Regeneration of periodontal tissues: Combinations of barrier membranes and grafting materials — Biological foundation and preclinical evidence: A systematic review. *J Clin Periodontol* 2008;35(Suppl. 8):106-116.
22. Esposito M, Coulthard P, Thomsen P, Worthington HV. Enamel matrix derivative for periodontal tissue regeneration in treatment of intrabony defects: A Cochrane systematic review. *J Dent Educ* 2004;68: 834-844.
23. Giannobile WV, Somerman MJ. Growth and amelogenin-like factors in periodontal wound healing. A systematic review. *Ann Periodontol* 2003;8:193-204.
24. Reynolds MA, Aichelmann-Reidy ME, Branch-Mays GL. Regeneration of periodontal tissue: Bone replacement grafts. *Dent Clin North Am* 2010;54: 55-71.
25. Cortellini P, Labriola A, Tonetti MS. Regenerative periodontal therapy in intrabony defects: State of the art. *Minerva Stomatol* 2007;56:519-539.
26. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 2009;6:e1000097.
27. Camelo M, Nevins ML, Schenk RK, Lynch SE, Nevins M. Periodontal regeneration in human Class II furcations using purified recombinant human platelet-derived growth factor-BB (rhPDGF-BB) with bone allograft. *Int J Periodontics Restorative Dent* 2003;23:213-225.
28. Heijl L. Periodontal regeneration with enamel matrix derivative in one human experimental defect. A case report. *J Clin Periodontol* 1997;24:693-696.
29. Majzoub Z, Bobbo M, Atiyeh F, Cordioli G. Two patterns of histologic healing in an intrabony defect following treatment with enamel matrix derivative: A human case report. *Int J Periodontics Restorative Dent* 2005;25:283-294.
30. Nevins ML, Camelo M, Schupbach P, Kim SW, Kim DM, Nevins M. Human clinical and histologic evaluation of laser-assisted new attachment procedure. *Int J Periodontics Restorative Dent* 2012; 32:497-507.
31. Nevins M, Camelo M, Nevins ML, Schenk RK, Lynch SE. Periodontal regeneration in humans using recombinant human platelet-derived growth factor-BB (rhPDGF-BB) and allogenic bone. *J Periodontol* 2003;74:1282-1292.
32. Sculean A, Donos N, Windisch P, et al. Healing of human intrabony defects following treatment with enamel matrix proteins or guided tissue regeneration. *J Periodontal Res* 1999;34:310-322.
33. Newman MG, Weyant R, Hujoel P. JEBDP improves grading system and adopts strength of recommendation taxonomy grading (SORT) for guidelines and systematic reviews. *J Evid Based Dent Pract* 2007;7: 147-150.
34. Chang PC, Chung MC, Wang YP, et al. Patterns of diabetic periodontal wound repair: A study using micro-computed tomography and immunohistochemistry. *J Periodontol* 2012;83:644-652.
35. Shirakata Y, Eliezer M, Nemcovsky CE, et al. Periodontal healing after application of enamel matrix derivative in surgical supra/infrabony periodontal defects in rats with streptozotocin-induced diabetes. *J Periodontal Res* 2013:49:93-101.
36. Um YJ, Jung UW, Kim CS, et al. The influence of diabetes mellitus on periodontal tissues: A pilot study. *J Periodontal Implant Sci* 2010;40:49-55.
37. Trombelli L, Kim CK, Zimmerman GJ, Wikesjö UM. Retrospective analysis of factors related to clinical outcome of guided tissue regeneration procedures in intrabony defects. *J Clin Periodontol* 1997;24:366-371.
38. Eickholz P, Hörr T, Klein F, Hassfeld S, Kim TS. Radiographic parameters for prognosis of periodontal healing of infrabony defects: Two different definitions of defect depth. *J Periodontol* 2004;75: 399-407.
39. Silvestri M, Rasperini G, Milani S. 120 infrabony defects treated with regenerative therapy: Long-term results. *J Periodontol* 2011;82:668-675.
40. Zucchelli G, Bernardi F, Montebugnoli L, De SM. Enamel matrix proteins and guided tissue regeneration with titanium-reinforced expanded polytetrafluoroethylene membranes in the treatment of infrabony

defects: A comparative controlled clinical trial. *J Periodontol* 2002;73:3-12.
41. Klein F, Kim TS, Hassfeld S, et al. Radiographic defect depth and width for prognosis and description of periodontal healing of infrabony defects. *J Periodontol* 2001;72:1639-1646.
42. Parashis AO, Polychronopoulou A, Tsiklakis K, Tatakis DN. Enamel matrix derivative in intrabony defects: Prognostic parameters of clinical and radiographic treatment outcomes. *J Periodontol* 2012;83:1346-1352.
43. Cortellini P, Pini-Prato G, Tonetti M. Periodontal regeneration of human infrabony defects (V). Effect of oral hygiene on long-term stability. *J Clin Periodontol* 1994;21:606-610.
44. Heden G, Wennström J, Lindhe J. Periodontal tissue alterations following Emdogain treatment of periodontal sites with angular bone defects. A series of case reports. *J Clin Periodontol* 1999;26:855-860.
45. Machtei EE, Cho MI, Dunford R, Norderyd J, Zambon JJ, Genco RJ. Clinical, microbiological, and histological factors which influence the success of regenerative periodontal therapy. *J Periodontol* 1994;65:154-161.
46. Rosling B, Nyman S, Lindhe J, Jern B. The healing potential of the periodontal tissues following different techniques of periodontal surgery in plaque-free dentitions. A 2-year clinical study. *J Clin Periodontol* 1976;3:233-250.
47. Tonetti MS, Lang NP, Cortellini P, et al. Enamel matrix proteins in the regenerative therapy of deep intrabony defects. *J Clin Periodontol* 2002;29:317-325.
48. Tonetti MS, Pini-Prato G, Cortellini P. Periodontal regeneration of human intrabony defects. IV. Determinants of healing response. *J Periodontol* 1993;64:934-940.
49. Tonetti MS, Prato GP, Cortellini P. Factors affecting the healing response of intrabony defects following guided tissue regeneration and access flap surgery. *J Clin Periodontol* 1996;23:548-556.
50. Cortellini P, Tonetti MS. Long-term tooth survival following regenerative treatment of intrabony defects. *J Periodontol* 2004;75:672-678.
51. Cortellini P, Tonetti MS. Clinical performance of a regenerative strategy for intrabony defects: scientific evidence and clinical experience. *J Periodontol* 2005;76:341-350.
52. Cortellini P, Tonetti MS. Clinical and radiographic outcomes of the modified minimally invasive surgical technique with and without regenerative materials: A randomized-controlled trial in intrabony defects. *J Clin Periodontol* 2011;38:365-373.
53. Cortellini P, Tonetti MS. Minimally invasive surgical technique and enamel matrix derivative in intrabony defects. I: Clinical outcomes and morbidity. *J Clin Periodontol* 2007;34:1082-1088.
54. Cortellini P, Tonetti MS. Improved wound stability with a modified minimally invasive surgical technique in the regenerative treatment of isolated interdental intrabony defects. *J Clin Periodontol* 2009;36:157-163.
55. Cortellini P, Nieri M, Prato GP, Tonetti MS. Single minimally invasive surgical technique with an enamel matrix derivative to treat multiple adjacent intrabony defects: Clinical outcomes and patient morbidity. *J Clin Periodontol* 2008;35:605-613.
56. Cortellini P, Pini-Prato G, Nieri M, Tonetti MS. Minimally invasive surgical technique and enamel matrix derivative in intrabony defects: 2. Factors associated with healing outcomes. *Int J Periodontics Restorative Dent* 2009;29:257-265.
57. Cortellini P, Stalpers G, Mollo A, Tonetti MS. Periodontal regeneration versus extraction and prosthetic replacement of teeth severely compromised by attachment loss to the apex: 5-year results of an ongoing randomized clinical trial. *J Clin Periodontol* 2011;38:915-924.
58. Cortellini P, Tonetti MS. A minimally invasive surgical technique with an enamel matrix derivative in the regenerative treatment of intrabony defects: A novel approach to limit morbidity. *J Clin Periodontol* 2007;34:87-93.
59. Trejo PM, Weltman RL. Favorable periodontal regenerative outcomes from teeth with presurgical mobility: A retrospective study. *J Periodontol* 2004;75:1532-1538.
60. Carranza FA. Clinical diagnosis. In: Newman MG, Takei HH, Carrana FA, eds. *Carranza's Clinical Periodontology*. Philadelphia: W.B. Saunders Company; 2002:439-453.
61. Schulz A, Hilgers RD, Niedermeier W. The effect of splinting of teeth in combination with reconstructive periodontal surgery in humans. *Clin Oral Investig* 2000;4:98-105.
62. Siciliano VI, Andreuccetti G, Siciliano AI, Blasi A, Sculean A, Salvi GE. Clinical outcomes after treatment of non-contained intrabony defects with enamel matrix derivative or guided tissue regeneration: A 12-month randomized controlled clinical trial. *J Periodontol* 2011;82:62-71.
63. Needleman IG, Worthington HV, Giedrys-Leeper E, Tucker RJ. Guided tissue regeneration for periodontal infra-bony defects. *Cochrane Database Syst Rev* 2006;19:CD001724.
64. Parrish LC MT, Fong N, Mattson JS, Cerutis DR. Non-bioabsorbable vs. bioabsorbable membrane: Assessment of their clinical efficacy in guided tissue regeneration technique. A systematic review. *J Oral Sci* 2009;51:383-400.
65. Stoecklin-Wasmer C, Rutjes AW, da Costa BR, Salvi GE, Jüni P, Sculean A. Absorbable collagen membranes for periodontal regeneration: A systematic review. *J Dent Res* 2013;92:773-781.
66. Sanz M, Tonetti MS, Zabalegui I, et al. Treatment of intrabony defects with enamel matrix proteins or barrier membranes: Results from a multicenter practice-based clinical trial. *J Periodontol* 2004;75:726-733.
67. Sculean A, Kiss A, Miliauskaite A, Schwarz F, Arweiler NB, Hannig M. Ten-year results following treatment of intrabony defects with enamel matrix proteins and guided tissue regeneration. *J Clin Periodontol* 2008;35:817-824.
68. Machtei EE. The effect of membrane exposure on the outcome of regenerative procedures in humans: A meta-analysis. *J Periodontol* 2001;72:512-516.
69. Sowmya NK, Tarun Kumar AB, Mehta DS. Clinical evaluation of regenerative potential of type I collagen membrane along with xenogenic bone graft in the treatment of periodontal intrabony defects assessed with surgical re-entry and radiographic linear and

densitometric analysis. *J Indian Soc Periodontol* 2010;14:23-29.
70. Paolantonio M, Femminella B, Coppolino E, et al. Autogenous periosteal barrier membranes and bone grafts in the treatment of periodontal intrabony defects of single-rooted teeth: A 12-month reentry randomized controlled clinical trial. *J Periodontol* 2010;81:1587-1595.
71. Sculean A, Schwarz F, Chiantella GC, et al. Five-year results of a prospective, randomized, controlled study evaluating treatment of intrabony defects with a natural bone mineral and GTR. *J Clin Periodontol* 2007; 34:72-77.
72. Aimetti M, Romano F, Pigella E, Pranzini F, Debernardi C. Treatment of wide, shallow, and predominantly 1-wall intrabony defects with a bioabsorbable membrane: A randomized controlled clinical trial. *J Periodontol* 2005;76:1354-1361.
73. Bianchi AE, Bassetti A. Flap design for guided tissue regeneration surgery in the esthetic zone: The "whale's tail" technique. *Int J Periodontics Restorative Dent* 2009;29:153-159.
74. Tonetti MS, Cortellini P, Lang NP, et al. Clinical outcomes following treatment of human intrabony defects with GTR/bone replacement material or access flap alone. A multicenter randomized controlled clinical trial. *J Clin Periodontol* 2004;31:770-776.
75. Trombelli L, Simonelli A, Pramstraller M, Wikesjö UME, Farina R. Single flap approach with and without guided tissue regeneration and a hydroxyapatite biomaterial in the management of intraosseous periodontal defects. *J Periodontol* 2010; 81:1256-1263.
76. Stavropoulos A, Karring T. Five-year results of guided tissue regeneration in combination with deproteinized bovine bone (Bio-Oss) in the treatment of intrabony periodontal defects: A case series report. *Clin Oral Investig* 2005;9:271-277.
77. Stavropoulos A, Karring T. Long-term stability of periodontal conditions achieved following guided tissue regeneration with bioresorbable membranes: Case series results after 6-7 years. *J Clin Periodontol* 2004;31:939-944.
78. Döri F, Arweiler N, Gera I, Sculean A. Clinical evaluation of an enamel matrix protein derivative combined with either a natural bone mineral or beta-tricalcium phosphate. *J Periodontol* 2005;76:2236-2243.
79. Kim TS, Holle R, Hausmann E, Eickholz P. Long-term results of guided tissue regeneration therapy with non-resorbable and bioabsorbable barriers. II. A case series of infrabony defects. *J Periodontol* 2002;73: 450-459.
80. Sculean A, Donos N, Schwarz F, Becker J, Brecx M, Arweiler NB. Five-year results following treatment of intrabony defects with enamel matrix proteins and guided tissue regeneration. *J Clin Periodontol* 2004; 31:545-549.
81. Slotte C, Asklöw B, Lundgren D. Surgical guided tissue regeneration treatment of advanced periodontal defects: A 5-year follow-up study. *J Clin Periodontol* 2007;34:977-984.
82. Pretzl B, Kim TS, Holle R, Eickholz P. Long-term results of guided tissue regeneration therapy with non-resorbable and bioabsorbable barriers. IV. A case series of infrabony defects after 10 years. *J Periodontol* 2008;79:1491-1499.
83. Pretzl B, Kim TS, Steinbrenner H, Dörfer C, Himmer K, Eickholz P. Guided tissue regeneration with bioabsorbable barriers III 10-year results in infrabony defects. *J Clin Periodontol* 2009;36:349-356.
84. Nygaard-Østby P, Bakke V, Nesdal O, Susin C, Wikesjö UM. Periodontal healing following reconstructive surgery: Effect of guided tissue regeneration using a bioresorbable barrier device when combined with autogenous bone grafting. A randomized-controlled trial 10-year follow-up. *J Clin Periodontol* 2010;37: 366-373.
85. Nickles K, Ratka-Krüger P, Neukranz E, Raetzke P, Eickholz P. Open flap debridement and guided tissue regeneration after 10 years in infrabony defects. *J Clin Periodontol* 2009;36:976-983.
86. Harrel SK, Rees TD. Granulation tissue removal in routine and minimally invasive procedures. *Compend Contin Educ Dent* 1995;16:960, 962, 964 passim.
87. Trombelli L, Farina R, Franceschetti G, Calura G. Single-flap approach with buccal access in periodontal reconstructive procedures. *J Periodontol* 2009;80:353-360.
88. Cosyn J, Cleymaet R, Hanselaer L, De Bruyn H. Regenerative periodontal therapy of infrabony defects using minimally invasive surgery and a collagen-enriched bovine-derived xenograft: A 1-year prospective study on clinical and aesthetic outcome. *J Clin Periodontol* 2012;39:979-986.
89. Harrel SK, Wilson TG, Nunn ME. Prospective assessment of the use of enamel matrix proteins with minimally invasive surgery. *J Periodontol* 2005;76:380-384.
90. Harrel SK, Nunn ME, Belling CM. Long-term results of a minimally invasive surgical approach for bone grafting. *J Periodontol* 1999;70:1558-1563.
91. Harrel SK, Wilson TG Jr, Nunn ME. Prospective assessment of the use of enamel matrix derivative with minimally invasive surgery: 6-year results. *J Periodontol* 2010;81:435-441.
92. Trombelli L, Simonelli A, Schincaglia GP, Cucchi A, Farina R. Single-flap approach for surgical debridement of deep intraosseous defects: A randomized controlled trial. *J Periodontol* 2012;83:27-35.
93. Wachtel H, Schenk G, Böhm S, Weng D, Zuhr O, Hürzeler MB. Microsurgical access flap and enamel matrix derivative for the treatment of periodontal intrabony defects: A controlled clinical study. *J Clin Periodontol* 2003;30:496-504.
94. Ribeiro FV, Casarin RC, Palma MA, Júnior FH, Sallum EA, Casati MZ. Clinical and patient-centered outcomes after minimally invasive non-surgical or surgical approaches for the treatment of intrabony defects: A randomized clinical trial. *J Periodontol* 2011;82: 1256-1266.
95. Ribeiro FV, Casarin RC, Júnior FH, Sallum EA, Casati MZ. The role of enamel matrix derivative protein in minimally invasive surgery in treating intrabony defects in single-rooted teeth: A randomized clinical trial. *J Periodontol* 2011;82:522-532.
96. Mishra A, Avula H, Pathakota KR, Avula J. Efficacy of modified minimally invasive surgical technique in the treatment of human intrabony defects with or without use of rhPDGF-BB gel: A randomized controlled trial. *J Clin Periodontol* 2013;40:172-179.
97. Fickl S, Thalmair T, Kebschull M, Böhm S, Wachtel H. Microsurgical access flap in conjunction with enamel matrix derivative for the treatment of intrabony

defects: A controlled clinical trial. *J Clin Periodontol* 2009;36:784-790.
98. Nibali L, Pometti D, Tu YK, Donos N. Clinical and radiographic outcomes following non-surgical therapy of periodontal infrabony defects: A retrospective study. *J Clin Periodontol* 2011;38:50-57.
99. Cortellini P. Minimally invasive surgical techniques in periodontal regeneration. *J Evid Based Dent Pract* 2012;12(Suppl. 3):89-100.
100. Ribeiro FV, Nociti Júnior FH, Sallum EA, Sallum AW, Casati MZ. Use of enamel matrix protein derivative with minimally invasive surgical approach in intrabony periodontal defects: Clinical and patient-centered outcomes. *Braz Dent J* 2010;21:60-67.
101. Graziani F, Gennai S, Cei S, et al. Clinical performance of access flap surgery in the treatment of the intrabony defect. A systematic review and meta-analysis of randomized clinical trials. *J Clin Periodontol* 2012; 39:145-156.
102. Cortellini P, Carnevale G, Sanz M, Tonetti MS. Treatment of deep and shallow intrabony defects. A multicenter randomized controlled clinical trial. *J Clin Periodontol* 1998;25:981-987.
103. Cortellini P, Tonetti MS. Focus on intrabony defects: Guided tissue regeneration. *Periodontol 2000* 2000; 22:104-132.
104. Garrett S, Loos B, Chamberlain D, Egelberg J. Treatment of intraosseous periodontal defects with a combined adjunctive therapy of citric acid conditioning, bone grafting, and placement of collagenous membranes. *J Clin Periodontol* 1988;15: 383-389.
105. Esposito M, Grusovin MG, Papanikolaou N, Coulthard P, Worthington HV. Enamel matrix derivative (Emdogain(R)) for periodontal tissue regeneration in intrabony defects. *Cochrane Database Syst Rev* 2009;(4):CD003875.
106. Haney JM, Nilvéus RE, McMillan PJ, Wikesjö UM. Periodontal repair in dogs: Expanded polytetrafluoroethylene barrier membranes support wound stabilization and enhance bone regeneration. *J Periodontol* 1993;64:883-890.
107. Sigurdsson TJ, Hardwick R, Bogle GC, Wikesjö UM. Periodontal repair in dogs: Space provision by reinforced ePTFE membranes enhances bone and cementum regeneration in large supraalveolar defects. *J Periodontol* 1994;65:350-356.
108. Yen CC, Tu YK, Chen TH, Lu HK. Comparison of treatment effects of guided tissue regeneration on infrabony lesion between animal and human studies: A systemic review and meta-analysis. *J Periodontal Res* 2014;49:415-424.
109. Bokan I, Bill JS, Schlagenhauf U. Primary flap closure combined with Emdogain alone or Emdogain and Cerasorb in the treatment of intrabony defects. *J Clin Periodontol* 2006;33:885-893.
110. Crea A, Dassatti L, Hoffmann O, Zafiropoulos GG, Deli G. Treatment of intrabony defects using guided tissue regeneration or enamel matrix derivative: A 3-year prospective randomized clinical study. *J Periodontol* 2008;79:2281-2289.
111. Guida L, Annunziata M, Belardo S, Farina R, Scabbia A, Trombelli L. Effect of autogenous cortical bone particulate in conjunction with enamel matrix derivative in the treatment of periodontal intraosseous defects. *J Periodontol* 2007;78:231-238.
112. Gurinsky BS, Mills MP, Mellonig JT. Clinical evaluation of demineralized freeze-dried bone allograft and enamel matrix derivative versus enamel matrix derivative alone for the treatment of periodontal osseous defects in humans. *J Periodontol* 2004;75:1309-1318.
113. Hoidal MJ, Grimard BA, Mills MP, Schoolfield JD, Mellonig JT, Mealey BL. Clinical evaluation of demineralized freeze-dried bone allograft with and without enamel matrix derivative for the treatment of periodontal osseous defects in humans. *J Periodontol* 2008;79:2273-2280.
114. Jepsen S, Topoll H, Rengers H, et al. Clinical outcomes after treatment of intrabony defects with an EMD/synthetic bone graft or EMD alone: A multicentre randomized-controlled clinical trial. *J Clin Periodontol* 2008;35:420-428.
115. Kuru B, Yilmaz S, Argin K, Noyan U. Enamel matrix derivative alone or in combination with a bioactive glass in wide intrabony defects. *Clin Oral Investig* 2006;10:227-234.
116. Lekovic V, Camargo PM, Weinlaender M, Nedic M, Aleksic Z, Kenney EB. A comparison between enamel matrix proteins used alone or in combination with bovine porous bone mineral in the treatment of intrabony periodontal defects in humans. *J Periodontol* 2000;71:1110-1116.
117. Minabe M, Kodama T, Kogou T, et al. A comparative study of combined treatment with a collagen membrane and enamel matrix proteins for the regeneration of intraosseous defects. *Int J Periodontics Restorative Dent* 2002;22:595-605.
118. Pontoriero R, Wennström J, Lindhe J. The use of barrier membranes and enamel matrix proteins in the treatment of angular bone defects. A prospective controlled clinical study. *J Clin Periodontol* 1999;26: 833-840.
119. Rosen PS, Reynolds MA. A retrospective case series comparing the use of demineralized freeze-dried bone allograft and freeze-dried bone allograft combined with enamel matrix derivative for the treatment of advanced osseous lesions. *J Periodontol* 2002;73: 942-949.
120. Scheyer ET, Velasquez-Plata D, Brunsvold MA, Lasho DJ, Mellonig JT. A clinical comparison of a bovine-derived xenograft used alone and in combination with enamel matrix derivative for the treatment of periodontal osseous defects in humans. *J Periodontol* 2002;73:423-432.
121. Sculean A, Barbé G, Chiantella GC, Arweiler NB, Berakdar M, Brecx M. Clinical evaluation of an enamel matrix protein derivative combined with a bioactive glass for the treatment of intrabony periodontal defects in humans. *J Periodontol* 2002;73: 401-408.
122. Sculean A, Chiantella GC, Windisch P, Arweiler NB, Brecx M, Gera I. Healing of intrabony defects following treatment with a composite bovine-derived xenograft (Bio-Oss Collagen) in combination with a collagen membrane (Bio-Gide PERIO). *J Clin Periodontol* 2005;32:720-724.
123. Sculean A, Chiantella GC, Windisch P, Gera I, Reich E. Clinical evaluation of an enamel matrix protein derivative (Emdogain) combined with a bovine-derived xenograft (Bio-Oss) for the treatment of intrabony periodontal defects in humans. *Int J Periodontics Restorative Dent* 2002;22:259-267.

124. Sculean A, Pietruska M, Schwarz F, Willershausen B, Arweiler NB, Auschill TM. Healing of human intrabony defects following regenerative periodontal therapy with an enamel matrix protein derivative alone or combined with a bioactive glass. A controlled clinical study. *J Clin Periodontol* 2005;32:111-117.
125. Sculean A, Schwarz F, Miliauskaite A, et al. Treatment of intrabony defects with an enamel matrix protein derivative or bioabsorbable membrane: An 8-year follow-up split-mouth study. *J Periodontol* 2006;77:1879-1886.
126. Sculean A, Windisch P, Chiantella GC, Donos N, Brecx M, Reich E. Treatment of intrabony defects with enamel matrix proteins and guided tissue regeneration. A prospective controlled clinical study. *J Clin Periodontol* 2001;28:397-403.
127. Silvestri M, Ricci G, Rasperini G, Sartori S, Cattaneo V. Comparison of treatments of infrabony defects with enamel matrix derivative, guided tissue regeneration with a nonresorbable membrane and Widman modified flap. A pilot study. *J Clin Periodontol* 2000;27:603-610.
128. Silvestri M, Sartori S, Rasperini G, Ricci G, Rota C, Cattaneio V. Comparison of infrabony defects treated with enamel matrix derivative versus guided tissue regeneration with a non-resorbable membrane: A multicenter controlled clinical trial. *J Clin Periodontol* 2003;30:386-393.
129. Sipos PM, Loos BG, Abbas F, Timmerman MF, van der Velden U. The combined use of enamel matrix proteins and a tetracycline-coated expanded polytetrafluoroethylene barrier membrane in the treatment of intra-osseous defects. *J Clin Periodontol* 2005;32:765-772.
130. Velasquez-Plata D, Scheyer ET, Mellonig JT. Clinical comparison of an enamel matrix derivative used alone or in combination with a bovine-derived xenograft for the treatment of periodontal osseous defects in humans. *J Periodontol* 2002;73:433-440.
131. Yilmaz S, Cakar G, Yildirim B, Sculean A. Healing of two and three wall intrabony periodontal defects following treatment with an enamel matrix derivative combined with autogenous bone. *J Clin Periodontol* 2010;37:544-550.
132. Zucchelli G, Amore C, Montebugnoli L, De Sanctis M. Enamel matrix proteins and bovine porous bone mineral in the treatment of intrabony defects: A comparative controlled clinical trial. *J Periodontol* 2003;74:1725-1735.
133. Yukna RA, Carr RL, Evans GH. Histologic evaluation of an Nd:YAG laser-assisted new attachment procedure in humans. *Int J Periodontics Restorative Dent* 2007;27:577-587.
134. McGuire MK, Kao RT, Nevins M, Lynch SE. rhPDGF-BB promotes healing of periodontal defects: 24-month clinical and radiographic observations. *Int J Periodontics Restorative Dent* 2006;26:223-231.
135. Nevins M, Kao RT, McGuire MK, et al. Platelet-derived growth factor promotes periodontal regeneration in localized osseous defects: 36-month extension results from a randomized, controlled, double-masked clinical trial. *J Periodontol* 2013;84:456-464.
136. Sculean A, Chiantella GC, Arweiler NB, Becker J, Schwarz F, Stavropoulos A. Five-year clinical and histologic results following treatment of human intrabony defects with an enamel matrix derivative combined with a natural bone mineral. *Int J Periodontics Restorative Dent* 2008;28:153-161.
137. Heijl L, Heden G, Svärdström G, Ostgren A. Enamel matrix derivative (EMDOGAIN) in the treatment of intrabony periodontal defects. *J Clin Periodontol* 1997;24:705-714.
138. Kao RT, Murakami S, Beirne OR. The use of biologic mediators and tissue engineering in dentistry. *Periodontol 2000* 2009;50:127-153.
139. Sculean A, Alessandri R, Miron R, Salvi G, Bosshardt DD. Enamel matrix proteins and periodontal wound healing and regeneration. *Clin Adv Periodontics* 2011;1:101-117.
140. Sculean A, Windisch P, Keglevich T, Fabi B, Lundgren E, Lyngstadaas PS. Presence of an enamel matrix protein derivative on human teeth following periodontal surgery. *Clin Oral Investig* 2002;6:183-187.
141. Sculean A, Junker R, Donos N, Windisch P, Brecx M, Dünker N. Immunohistochemical evaluation of matrix molecules associated with wound healing following treatment with an enamel matrix protein derivative in humans. *Clin Oral Investig* 2003;7:167-174.
142. Chambrone D, Pasin IM, Chambrone L, Pannuti CM, Conde MC, Lima LA. Treatment of infrabony defects with or without enamel matrix proteins: A 24-month follow-up randomized pilot study. *Quintessence Int* 2010;41:125-134.
143. Francetti L, Del Fabbro M, Basso M, Testori T, Weinstein R. Enamel matrix proteins in the treatment of intrabony defects. A prospective 24-month clinical trial. *J Clin Periodontol* 2004;31:52-59.
144. Froum SJ, Weinberg MA, Rosenberg E, Tarnow D. A comparative study utilizing open flap debridement with and without enamel matrix derivative in the treatment of periodontal intrabony defects: a 12-month re-entry study. *J Periodontol* 2001;72:25-34.
145. Grusovin MG, Esposito M. The efficacy of enamel matrix derivative (Emdogain) for the treatment of deep infrabony periodontal defects: A placebo-controlled randomised clinical trial. *Eur J Oral Implantol* 2009;2:43-54.
146. Okuda K, Momose M, Miyazaki A, et al. Enamel matrix derivative in the treatment of human intrabony osseous defects. *J Periodontol* 2000;71:1821-1828.
147. Parodi R, Santarelli GA, Gasparetto B. Treatment of intrabony pockets with Emdogain: Results at 36 months. *Int J Periodontics Restorative Dent* 2004;24:57-63.
148. Rösing CK, Aass AM, Mavropoulos A, Gjermo P. Clinical and radiographic effects of enamel matrix derivative in the treatment of intrabony periodontal defects: A 12-month longitudinal placebo-controlled clinical trial in adult periodontitis patients. *J Periodontol* 2005;76:129-133.
149. Sculean A, Blaes A, Arweiler N, Reich E, Donos N, Brecx M. The effect of postsurgical antibiotics on the healing of intrabony defects following treatment with enamel matrix proteins. *J Periodontol* 2001;72:190-195.
150. Parashis AO, Tsiklakis K, Tatakis DN. EDTA gel root conditioning: Lack of effect on clinical and radiographic outcomes of intrabony defect treatment with

enamel matrix derivative. *J Periodontol* 2006;77:103-110.
151. Sculean A, Berakdar M, Willershausen B, Arweiler NB, Becker J, Schwarz F. Effect of EDTA root conditioning on the healing of intrabony defects treated with an enamel matrix protein derivative. *J Periodontol* 2006;77:1167-1172.
152. Al Machot E, Hoffmann T, Lorenz K, Khalili I, Noack B. Clinical outcomes after treatment of periodontal intrabony defects with nanocrystalline hydroxyapatite (Ostim) or enamel matrix derivatives (Emdogain): A randomized controlled clinical trial. *Biomed Res Int* 2014;2014:786353.
153. Döri F, Arweiler NB, Szántó E, Agics A, Gera I, Sculean A. Ten-year results following treatment of intrabony defects with an enamel matrix protein derivative combined with either a natural bone mineral or a β-tricalcium phosphate. *J Periodontol* 2013;84:749-757.
154. Döri F, Nikolidakis D, Húszár T, Arweiler NB, Gera I, Sculean A. Effect of platelet-rich plasma on the healing of intrabony defects treated with an enamel matrix protein derivative and a natural bone mineral. *J Clin Periodontol* 2008;35:44-50.
155. Döri F, Arweiler N, Húszár T, Gera I, Miron RJ, Sculean A. Five-year results evaluating the effects of platelet-rich plasma on the healing of intrabony defects treated with enamel matrix derivative and natural bone mineral. *J Periodontol* 2013;84:1546-1555.
156. Cochran DL, Jones A, Heijl L, Mellonig JT, Schoolfield J, King GN. Periodontal regeneration with a combination of enamel matrix proteins and autogenous bone grafting. *J Periodontol* 2003;74:1269-1281.
157. Sculean A, Windisch P, Szendröi-Kiss D, et al. Clinical and histologic evaluation of an enamel matrix derivative combined with a biphasic calcium phosphate for the treatment of human intrabony periodontal defects. *J Periodontol* 2008;79:1991-1999.
158. Sculean A, Windisch P, Keglevich T, Gera I. Clinical and histologic evaluation of an enamel matrix protein derivative combined with a bioactive glass for the treatment of intrabony periodontal defects in humans. *Int J Periodontics Restorative Dent* 2005;25:139-147.
159. Tu YK, Woolston A, Faggion CM Jr. Do bone grafts or barrier membranes provide additional treatment effects for infrabony lesions treated with enamel matrix derivatives? A network meta-analysis of randomized-controlled trials. *J Clin Periodontol* 2010;37:59-79.
160. Rasperini G, Silvestri M, Ricci G. Long-term clinical observation of treatment of infrabony defects with enamel matrix derivative (Emdogain): Surgical reentry. *Int J Periodontics Restorative Dent* 2005;25:121-127.
161. Sculean A, Pietruska M, Arweiler NB, Auschill TM, Nemcovsky C. Four-year results of a prospective-controlled clinical study evaluating healing of intrabony defects following treatment with an enamel matrix protein derivative alone or combined with a bioactive glass. *J Clin Periodontol* 2007;34:507-513.
162. Lynch SE, Williams RC, Polson AM, et al. A combination of platelet-derived and insulin-like growth factors enhances periodontal regeneration. *J Clin Periodontol* 1989;16:545-548.
163. Jayakumar A, Rajababu P, Rohini S, et al. Multicentre, randomized clinical trial on the efficacy and safety of recombinant human platelet-derived growth factor with β-tricalcium phosphate in human intraosseous periodontal defects. *J Clin Periodontol* 2011;38:163-172.
164. Nevins M, Giannobile WV, McGuire MK, et al. Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: Results of a large multicenter randomized controlled trial. *J Periodontol* 2005;76:2205-2215.
165. Kao RT, Lynch SE. Stability of recombinant human platelet-derived growth factor-BB regenerated periodontal defects: Sixty month clinical and radiographic observations. *Clin Adv Periodontics* 2011;1:132-141.
166. Cortellini P, Tonetti MS. Evaluation of the effect of tooth vitality on regenerative outcomes in infrabony defects. *J Clin Periodontol* 2001;28:672-679.
167. Miranda de Santana CM, Santana RB. Influence of endodontic treatment inthe post-surgical healing of human class II furcation defects. *J Periodontol* 2013;84:51-57.
168. Brown IS. The effect of orthodontic therapy on certain types of periodontal defects. I. Clinical findings. *J Periodontol* 1973;44:742-756.
169. Cirelli JA, Cirelli CC, Holzhausen M, Martins LP, Brandão CH. Combined periodontal, orthodontic, and restorative treatment of pathologic migration of anterior teeth: A case report. *Int J Periodontics Restorative Dent* 2006;26:501-506.
170. Iino S, Taira K, Machigashira M, Miyawaki S. Isolated vertical infrabony defects treated by orthodontic tooth extrusion. *Angle Orthod* 2008;78:728-736.
171. Ingber JS. Forced eruption. I. A method of treating isolated one and two wall infrabony osseous defects-rationale and case report. *J Periodontol* 1974;45:199-206.
172. Kazandjian G, Scopp IW, Stahl S. Combined orthodontic-periodontal treatment of an infrabony defect. A case report. *J Periodontol* 1979;50:479-482.
173. Nevins M, Wise RJ. Use of orthodontic therapy to alter infrabony pockets. 2. *Int J Periodontics Restorative Dent* 1990;10:198-207.
174. Re S, Corrente G, Abundo R, Cardaropoli D. Orthodontic treatment in periodontally compromised patients: 12-year report. *Int J Periodontics Restorative Dent* 2000;20:31-39.
175. Re S, Corrente G, Abundo R, Cardaropoli D. The use of orthodontic intrusive movement to reduce infrabony pockets in adult periodontal patients: A case report. *Int J Periodontics Restorative Dent* 2002;22:365-371.
176. Steffensen B, Storey A. Effects of orthodontic intrusive forces in treatment of periodontally compromised incisors. Case report. *Int J Periodontics Restorative Dent* 1993;13:433-441.
177. Ogihara S, Wang HL. Periodontal regeneration with or without limited orthodontics for the treatment of 2- or 3-wall infrabony defects. *J Periodontol* 2010;81:1734-1742.
178. Ghezzi C, Masiero S, Silvestri M, Zanotti G, Rasperini G. Orthodontic treatment of periodontally involved teeth after tissue regeneration. *Int J Periodontics Restorative Dent* 2008;28:559-567.
179. Cardaropoli D, Re S, Manuzzi W, Gaveglio L, Cardaropoli G. Bio-Oss collagen and orthodontic movement

for the treatment of infrabony defects in the esthetic zone. *Int J Periodontics Restorative Dent* 2006;26: 553-559.
180. Ghezzi C, Vigano V, Francetti P, Zanotti G, Masiero S. Orthodontic treatment after induced periodontal regeneration in deep infrabony defects. *Clin Adv Periodontics* 2013;3:24-31.
181. Kao RT. The challenges of transferring evidence-based dentistry into practice. *J Evid Based Dent Pract* 2006;6:125-128.
182. Kao RT. Strategic extraction: A paradigm shift that is changing our profession. *J Periodontol* 2008;79:971-977.

Correspondence: Dr. Richard T. Kao, 10440 S. De Anza Blvd., #D-1, Cupertino, CA 95014. E-mail: richkao@sbcglobal.net.

Submitted November 18, 2013; accepted for publication March 31, 2014.