

Review

Clinical Guidelines of the Italian Society of Periodontology for the Reconstructive Surgical Treatment of Angular Bony Defects in Periodontal Patients

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Background: The purpose of these clinical guidelines, commissioned by the Italian Society of Periodontology and compiled with the tools and instructions of the Appraisal of Guidelines for Research and Evaluation (AGREE) collaboration, was to determine, in terms of efficacy, complications, and patient opinions, the most appropriate surgical techniques for periodontal patients with infrabony defects ≥ 3 mm.

Methods: Results published in the literature concerning open flap debridement (OFD), guided tissue regeneration (GTR) using a bioabsorbable or non-resorbable membrane, regeneration of periodontal tissues using enamel matrix derivative (EMD), and bone or bone substitute grafts were searched (electronically and manually) and compared. The following variables were analyzed: number of teeth lost, variation in clinical attachment level (CAL gain), variation in probing depth (PD reduction), variation in gingival recession, variation in bony defect depth (bone gain), complications, and the functional and esthetic satisfaction of the patients. Literature searches were performed selecting randomized clinical trials (RCTs) and systematic reviews (SRs) of RCTs published through December 31, 2006 with ≥ 1 year of follow-up. The full text of the selected SRs and RCTs were analyzed using checklists for qualitative evaluation according to the Scottish Intercollegiate Guidelines Network (SIGN) method.

Results: For the drafting of these guidelines, it was decided to accept the results of two SRs that compared OFD versus GTR, OFD versus EMD, and GTR versus EMD. With regard to efficacy, GTR and EMD can yield better results than OFD in terms of CAL gain (1.22 mm [P value < 0.0001] and 1.20 mm [P value < 0.0001], respectively), reduction of PD (1.21 mm [$P = 0.0004$] and 0.77 mm [$P = 0.0001$], respectively), and bone gain (1.39 and 1.08 mm, respectively) after ≥ 1 year of follow-up. The available data are insufficient for an evaluation of bone or bone substitute grafts. The data in the literature are also insufficient for answering questions about complications and patient opinions.

Conclusions: The evidence reported in the literature indicates that it is advisable to treat infrabony defects ≥ 3 mm by OFD, GTR, and EMD. Further studies on these topics should be encouraged. There is a need for well-conducted RCTs that report data on complications and patient opinions. *J Periodontol* 2008; 79:2219-2232.

KEY WORDS

Alveolar bone loss; bone substitutes; enamel matrix proteins; guided tissue regeneration; guidelines; periodontitis.

Periodontitis is an infectious disease of the gums and tissue surrounding the teeth that can occur in various forms. According to recent studies, advanced forms of periodontitis affect 5% to 15% of the population aged 35 to 44 years, whereas aggressive forms strike ~2% of all adolescents.¹ In the United States, 50% of the population has bleeding gums, and 35% has periodontitis.^{2,3}

Periodontitis is an opportunistic infectious disease associated with some bacterial populations present in dental plaque that are capable of triggering an inflammatory response in the periodontal tissues of susceptible subjects.⁴ Under normal conditions, there is an equilibrium between host and bacteria; however, some conditions can alter this balance in favor of bacterial aggression.⁴ Some risk factors (smoking, diabetes,

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interleukin-1 genetic polymorphism, and familiarity) can aggravate the inflammatory process.⁵ Progression of the disease can lead to the destruction of the periodontal supporting tissues, with loss of connective tissue attachment and alveolar bone, manifesting itself clinically through the development of recessions and/or pockets.⁶

As the disease progresses, symptoms may include bleeding gums, periodontal abscesses, increased tooth mobility due to the loss of bone support, tooth migration, exposure of the root surface, and tooth loss.^{7,8}

Treatment of periodontitis calls for, first of all, controlling the cause (causal therapy), i.e., reducing the bacterial load on the tooth by mechanical treatment above and below the gum (scaling and root planing), pharmacologic treatment (local and/or general) when indicated, and instructing and motivating the patient in home oral hygiene techniques.^{8,9}

After causal treatment, the periodontal patient usually presents a reduction in dental plaque and in bleeding on probing (the clinical symptom of inflammation of periodontal tissues) and a decrease in probing depth (PD).

The pockets remaining after causal treatment are ecologic niches that facilitate the formation of subgingival biofilm. They can lead to progression of the disease despite professional maintenance therapy and good patient compliance with oral hygiene practices.¹⁰ In these cases, periodontal therapy calls for additional surgical treatment to reduce or eliminate the pockets and the associated bony defects to make it easier and simpler for the patient to remove plaque on his or her own.

Various surgical approaches have been proposed for the treatment of residual defects, with different indications for different defects. In particular, for infrabony or angular defects (the result of vertical destruction of the bone adjacent to the tooth caused by the disease) ≥ 3 mm, the current literature offers five techniques: opening a surgical flap to remove the granulation tissue adjacent to and inside the bony defect as well as any hard (tartar) and soft (biofilm) residue that may be on the root surface (open flap debridement [OFD]);¹¹ guided tissue regeneration (GTR) using a bioabsorbable or non-resorbable membrane;¹² tissue regeneration using enamel matrix derivatives (amelogenin [EMD]);¹³ filling the defect with bone or bone substitute grafts;¹⁴ and a combined approach (membrane, amelogenin, and bone or bone substitute grafts).⁸

Good patient compliance, in terms of oral hygiene at home, and periodic follow-up and maintenance visits are fundamental for the success of these treatments: without them the periodontal tissues can be soon recolonized by the bacterial populations that caused the disease.¹⁵

These clinical guidelines, commissioned by the Italian Society of Periodontology (SIdP), Florence, Italy,

complied with the tools and instructions of the Appraisal of Guidelines for Research and Evaluation (AGREE) Collaboration.¹⁶ The guidelines were developed by multidisciplinary development groups and based on a systematic review of the evidence of best practice following a standard methodology designed to balance scientific rigor with an open and consultative approach. The aim of these clinical guidelines was to determine which surgical techniques are most appropriate for periodontal patients with infrabony defects ≥ 3 mm.

The key clinical issues included:

Efficacy: Which surgical technique is the most appropriate among OFD, GTR, EMD, and bone or bone substitute grafts, and what are the expected clinical outcomes in periodontal patients who have already successfully undergone causal therapy?

Complications: What are the potential adverse reactions following OFD, GTR, EMD, and bone or bone substitute graft procedures?

Patient opinions: What is the level of patient satisfaction from the functional and esthetic standpoints following OFD, GTR, EMD, and bone or bone substitute grafts?

MATERIALS AND METHODS

Development of the Guidelines

Five authors (UP, MN, RR, FC, and GP) were chosen by SIdP and the Committee on Intersociety Coordination of the Italian Dental Societies, Urbino, Italy, to develop the clinical guidelines. At the same time, internal (ME and GC) and external (PC) reviewers were identified.

When the first draft of the manuscript was completed, it underwent the two internal reviewers' judgment to reach an agreement on the guidelines. If reaching unanimity was difficult, final agreement was obtained by a discussion involving all members of the research team. Subsequently, the guidelines were sent to the external reviewer for the definitive agreement.

Who Benefits From the Guidelines

General dentists, dental hygienists, general medical practitioners, dental specialists (periodontists), patients, and members of commercial organizations will benefit from the guidelines.

Updates

The guidelines will be updated at least every 3 years or when requested by SIdP. The guidelines will also be tested in some hospital and/or university settings and in some private practices selected by SIdP to verify user satisfaction (health professionals and patients). The data collected will be published on the society's Web site to update the guidelines. These guidelines will be published on the Web site of the SIdP as part of the services offered to members, patients, and visitors in general.

Inclusion Criteria for Drafting the Guidelines

The objectives and inclusion criteria were organized using PICO,¹⁷ a worksheet assessment that uses four categories (Patient characteristics, Interventions to investigate, Comparison of interventions, and considered Outcomes variables) for breaking down and converting the issues to investigate and the information sought into specific, precise questions. According to PICO, a well-structured research strategy calls for at least four questions that define the characteristics of the patient (patient or population [P]), the treatments to investigate (intervention [I]), the comparisons among the identified treatments (comparison [C]), and the outcome variables considered important for the evaluation of the results (outcomes [O]).¹⁷

Patient identification. Patient identification included patients presenting angular bony defects ≥ 3 mm (measured from the bone crest to the most apical point of the defect) without involvement of furcations, who were diagnosed clinically, radiographically, and/or intraoperatively and were followed for ≥ 12 months after the procedure to correct the angular defect.

Compared surgical techniques. The results published in the literature concerning the following surgical techniques were searched and compared: OFD, including open flap curettage, access flap surgery, modified Widman flap, and papilla preservation flap surgery; GTR using a bioabsorbable or non-resorbable membrane; regeneration of periodontal tissues using amelogenin (EMD); and bone or bone substitute grafts.

Data concerning the techniques were sought for the following comparisons: OFD versus GTR; OFD versus EMD; OFD versus bone or bone substitute grafts; GTR versus EMD; GTR versus bone or bone substitute grafts; and EMD versus bone or bone substitute grafts.

Results concerning combinations of the above treatments (e.g., bone graft beneath a membrane) were not taken into consideration because the literature available on these techniques is still scanty and very heterogeneous, and it would be difficult to determine the contributions of the single techniques to the overall results.

Outcomes for professional reference. The following variables were taken into consideration: number of teeth lost over time; variation in clinical attachment level (CAL gain); variation in PD (PD gain); variation in gingival recession (Rec); variation in the bony defect depth (bone gain), from the bone crest to the most apical point of the defect, measured intraoperatively or by x-ray; complications; and adverse reactions.

Outcomes for patients. The following variables were considered: level of functional satisfaction and level of esthetic satisfaction.

Other inclusion or exclusion criteria. Only systematic reviews of the literature (SRs) of randomized clinical trials (RCTs) and RCTs were selected for these guidelines. The trial follow-up was ≥ 12 months. The reference period included literature published through December 31, 2006. For statistical analyses, the RCTs that treated more than one site in a single patient were excluded if they did not take into account the existence of non-independent sites (patient effect).

Scientific Sources: Identification

An electronic search of the literature through the end of 2006 was conducted on the following databases: MEDLINE (PubMed), Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials (CENTRAL). The electronic search covered SRs and RCTs. The electronic search on MEDLINE via PubMed was conducted on April 12, 2007 using the search strategy shown in Table 1.

The electronic search on the Cochrane database was conducted on April 12, 2007 using the search strategy shown in Table 2.

In addition to the electronic search, two reviewers (Drs. Gloria Iachetti and Luisa Guidi, Department of Periodontology, University of Florence) conducted a hand search of the literature published from January 1, 2001 to December 31, 2006 in the following journals: *Journal of Periodontology*, *Journal of Clinical*

Table 1.
Search Strategy in MEDLINE (April 12, 2007)

1. Periodontal Pocket/surgery [MeSH] OR Periodontal Pocket/therapy [MeSH]
2. Alveolar Bone Loss/surgery [MeSH] OR Alveolar Bone Loss/therapy [MeSH]
3. Intra bony defect* [Tw]
4. Infra bony defect* [Tw]
5. Intrabony defect* [Tw]
6. Infrabony defect* [Tw]
7. OR/1 through 6
8. Open Flap for Debridement [Tw] OR Open Flap Curettage [Tw] OR Modified Widman Flap [Tw] OR Open Clean-out [Tw]
9. Guided Tissue Regeneration [Tw] OR Guided-Tissue-Regeneration [Tw] OR Periodontal Regeneration [Tw] OR GTR [Tw]
10. Amelogenin [Tw] OR Emdogain [Tw] OR Enamel Matrix Derivative [Tw] OR Enamel Matrix Protein [Tw] OR Dental Enamel Protein [Tw]
11. Bone Graft [Tw] OR Autogenous Bone Graft [Tw] OR Allogenic Bone Graft [Tw]
12. OR/8 through 10
13. 7 AND 12
Limits:
Type of article: meta-analysis and review or RCT
Through December 31, 2006
Humans or animals: humans

MeSH = medical subject heading; Tw = text word.

Table 2.**Search Strategy in Cochrane Database of Systematic Reviews and CENTRAL (April 12, 2007)**

<ol style="list-style-type: none"> 1. Intra bony [Tw] OR Infra bony [Tw] OR Intraony [Tw] OR Infrabony [Tw] 2. Open Flap for Debridement [Tw] OR Open Flap Curettage [Tw] OR Modified Widman Flap [Tw] OR Open Clean-out [Tw] 3. Guided Tissue Regeneration [Tw] OR Guided-Tissue-Regeneration [Tw] OR Periodontal Regeneration [Tw] OR GTR [Tw] 4. Amelogenin [Tw] OR Emdogain [Tw] OR Enamel Matrix Derivative [Tw] OR Enamel Matrix Protein [Tw] OR Dental Enamel Protein [Tw] 5. Bone Graft [Tw] OR Autogenous Bone Graft [Tw] OR Allogenic Bone Graft [Tw] 6. OR/2-5 7. 1 AND 6
<p>Limits:</p> <p>Reviews and RCTs Through December 31, 2006</p>

Tw = text word.

Periodontology, Journal of Periodontal Research, International Journal of Prosthetic and Restorative Dentistry, and Periodontology 2000. Furthermore, SRs and RCTs were sought in the bibliographies of the selected studies.

The primary objective of the literature search was to evaluate SRs of RCTs that met the inclusion criteria. If more than one SR was published on the same subject by the same authors, the most recent SR was selected. The search also sought out any RCTs dated after the publication of the selected SRs.

In the event that no SR meeting the inclusion criteria was found, the RCTs were evaluated directly. In the event of more than one RCT conducted on the same test population, the RCT with the longest follow-up was considered. The RCTs that treated more than one site in the same patient were excluded if the statistical analysis did not take into account the presence of non-independent sites.

Scientific Sources: Selection

Two independent researchers (MN and UP) analyzed the complete texts of the selected reviews according to the method of the Scottish Intercollegiate Guidelines Network (SIGN) that calls for the use of checklists prepared specifically for the qualitative evaluation of SRs with meta-analyses.¹⁸

Working independently, five researchers (MN, RR, and Drs. Gloria Iachetti, Luisa Guidi, and Iana Mervelt, Department of Periodontology, University of Florence) analyzed the full texts of the selected RCTs according to the SIGN method that calls for the use of checklists for the qualitative evaluation of RCTs.¹⁸

At the conclusion of the independent analyses, the researchers compared their evaluations with the aim of reaching agreement. If reaching unanimity was dif-

ficult, the final results were obtained after a discussion involving all members of the research team.

RESULTS

The electronic search yielded 261 publications on RCTs via MEDLINE and 194 publications about RCTs in the Cochrane database. Further, 184 SRs and reviews of the literature were found on MEDLINE, and three SRs were located in the Cochrane database. The hand search starting from 2001 did not yield any additional articles beyond those found with the electronic search.

Subsequently, reading the abstracts of all reviews found (184 MEDLINE and three Cochrane) made it possible to select nine¹⁹⁻²⁷ that concerned the surgical techniques under consideration.

At this point, by reading the full texts of the nine selected reviews we accepted the results of two SRs^{26,27} for the drafting of these guidelines. Seven reviews were excluded because three^{19,21,25} were not systematic, two^{22,24} were not SRs of just RCTs, and two^{20,23} had follow-ups <12 months and did not specify the depths of the infrabony defects treated.

Of the two SRs that were analyzed, Esposito et al.,²⁶ which permitted comparisons of OFD versus EMD and EMD versus GTR, was judged to have a very low risk for bias according to the SIGN checklist method (SIGN code: 1++). The review by Needleman et al.,²⁷ which offered a comparison between OFD and GTR, was also judged to have a very low risk for bias (SIGN code: 1++).

The search of RCTs published after the reference period of the two selected SRs and the reading of the respective abstracts resulted in three RCTs.²⁸⁻³⁰ They were excluded because two^{29,30} also reported data on infrabony defects <3 mm, and the statistical analysis in the other²⁸ did not take into account the dependency among the sites in the same patient.

Comparisons of surgical techniques that were not found through the SRs (bone or bone substitute grafts versus OFD or GTR or EMD) were searched by reading the abstracts of all studies found through the electronic and hand searches of the literature and bibliographies of the articles. This search identified 58³¹⁻⁸⁸ RCTs that permitted a comparison between OFD and bone or bone substitute grafts. A full reading of the 58 selected RCTs made it possible to include the results of one⁸³ in the drafting of the guidelines. Fifty-seven RCTs were excluded; two RCTs^{80,81} tested a combination of treatments, three RCTs^{82,84,85} dealt with comparisons of other types

of treatments not covered by these guidelines, one RCT⁸⁶ reported data on patients included in previous studies, five RCTs^{31,35,38,49,79} were not RCTs (no or inadequate randomization), two RCTs^{43,87} reported data on infrabony defects ≤ 3 mm and/or involved furcations, seven RCTs^{29,45,51,56,60,62,64} treated defects < 3 mm, 14 RCTs^{34,37,44,55,59,61,63,65,68-70,72,74,75} did not specify the magnitude of the infrabony defects treated, seven RCTs^{33,40,50,66,71,76,77} had follow-ups < 12 months, and one RCT⁷³ had a variable follow-up ranging from 9 to 13 months. In 14 RCTs,^{32,36,41,42,46-48,52,53,57,58,67,78,88} the statistical analysis did not take into account the dependency among sites in the same patient, and one RCT⁵⁴ only reported radiographic data that could not be interpreted (Table 3).

The only RCT included in the evaluation for the guidelines⁸³ that permitted a comparison between OFD and grafts of polylactide/polyglycolide (PLA/PGA) copolymer was judged at high risk for bias according to the SIGN checklist (SIGN code: 1-).

In the end, two SRs^{26,27} made it possible to compare the results for the following techniques: OFD versus GTR,²⁷ OFD versus EMD,²⁶ and GTR versus EMD.²⁶ However, the fact that many RCTs that tested bone or bone substitute grafts did not meet the inclusion criteria for these guidelines (usually because of the insufficient follow-up or for having treated infrabony defects of unstated size or < 3 mm) and that just one RCT⁸³ had a high risk for bias (SIGN code: 1-) made it impossible to compare OFD versus bone or bone substitute grafts.

Finally, it was not possible to obtain data that permitted comparisons of GTR versus bone or bone substitute grafts and EMD versus bone or bone substitute grafts.

Description of the Studies

In an SR of RCTs^{55,89-104} with ≥ 12 months of follow-up, Needleman et al.²⁷ (Table 4) conducted:

1) A meta-analysis of 16 studies^{55,89-96,98-104} that showed a statistically significant CAL gain of 1.22 mm (95% confidence interval [CI]: 0.80 to 1.64 mm; $P < 0.0001$) for GTR versus OFD.

2) A meta-analysis of 11 studies^{55,93,94,96,98-104} that showed a statistically significant reduction in PD of 1.21 mm (95% CI: 0.53 to 1.88 mm; $P = 0.0004$) for GTR versus OFD.

3) A meta-analysis of nine studies^{55,93,94,98,99,101-104} that showed a statistically significant increase in gingival recession of 0.26 mm (95% CI: 0.08 to 0.43 mm; $P = 0.005$) for OFD versus GTR.

4) A meta-analysis of three studies^{55,89,93} that showed a statistically significant increase in bone levels at the second operation (non-resorbable membrane) of 1.39 mm (95% CI: 1.08 to 1.71 mm) for GTR over OFD.

A sensitivity analysis conducted by Needleman et al.²⁷ on only three studies with allocation concealment and a masked examiner showed a statistically non-significant advantage in CAL gain of 0.41 mm (95% CI: -0.33 to 1.08 mm) for GTR over OFD.

In general, healing with GTR and OFD occurred without any particular complications, other than exposure of the membrane in GTR in 20%⁹⁰ to 68%⁹⁴ of the treated sites. The differences in the materials used, especially between bioabsorbable and non-resorbable membranes, in the treated sites were negligible. In any case, this complication frequently required more appointments for maintenance and the use of systemic antibiotics.

A multicenter RCT¹⁰² that was part of the studies included in this SR²⁷ reported that there were no statistically significant differences in the prevalence of postoperative pain between GTR and OFD; $> 50\%$ of the patients did not report this adverse reaction. Among the patients who experienced pain, the intensity was described with a visual analog scale (VAS) value of 28.1 ± 20 after GTR and 26.4 ± 17.6 after OFD (0 = no pain and 100 = unbearable pain). The pain lasted for an average of 14.1 ± 15.6 hours in the GTR group and 24.7 ± 39 hours in the OFD group ($P = 0.103$). Furthermore, 53.6% of the patients in the GTR group and 51.8% of the patients in the OFD group reported postoperative discomfort. Of the patients who underwent GTR and OFD, 35.7% and 32.1%, respectively, reported that the treatment prevented them from conducting normal daily activities for 2.7 ± 2.3 days (GTR) and 2.4 ± 1.3 days (OFD) ($P = 0.74$). In both groups, the treatment interfered with work in 25% of the patients. Recreational activities were hindered in 8.9% of the patients treated with GTR and in 7.1% of the patients treated with OFD. Postoperative edema was prevalent in week 1, mainly among the group of patients treated with GTR ($P = 0.01$). Hematoma was infrequent during week 1 and specifically was observed in 7.3% and 5.4% of the patients treated with GTR and OFD, respectively.

At postoperative week 3, the percentage of sites with membrane exposure was 53.6%. However, the difference in clinical attachment gain at the 1-year follow-up between patients with exposed and unexposed membranes was not statistically significant (3.7 ± 1.8 mm for the exposed sites and 3.3 ± 2.6 mm for the unexposed sites; $P = 0.246$).

Finally, Needleman et al.²⁷ did not find data on teeth lost over time or the patients' level of functional and esthetic satisfaction.

Esposito et al.²⁶ (Tables 5 and 6) conducted an SR of 13 RCTs^{98,100,103,105-114} with a follow-up ≥ 12 months with the aim of comparing the use of EMD to OFD, GTR, and bone or bone substitute grafts. With

Table 3.
OFD Versus Bone or Bone Substitute Grafts: Excluded RCTs

Study	Reason for Exclusion*
Radhakrishnan and Anusuya, 2004 ⁸⁰ Tonetti et al., 2004 ⁸¹	Combined treatments
Hanna et al., 2004 ⁸² Bender et al., 2005 ⁸⁴ Nevins et al., 2005 ⁸⁵	Comparisons of treatments not covered by these clinical guidelines
Sarment et al., 2006 ⁸⁶	Patient data included in previous studies
Ellegaard and Løe, 1971 ³¹ Pearson et al., 1981 ³⁵ Sanders et al., 1983 ³⁸ Hiatt et al., 1986 ⁴⁹ Nevins et al., 2003 ⁷⁹	Not RCT (randomization lacking or inadequate)
Mabry et al., 1985 ⁴³ Camargo et al., 2006 ⁸⁷	Data given on infrabony defects ≤ 3 mm and/or on furcations
Mellonig, 1984 ³⁹ Renvert et al., 1985 ⁴⁵ Krejci et al., 1987 ⁵¹ Yukna, 1990 ⁵⁶ Galgut et al., 1992 ⁶⁰ Borghetti et al., 1993 ⁶² Mora and Ouhayoun, 1995 ⁶⁴	Infrabony defects < 3 mm
Altieri et al., 1979 ³⁴ Movin and Borring-Moller, 1982 ³⁷ Kenney et al., 1985 ⁴⁴ Blumenthal and Steinberg, 1990 ⁵⁵ Shahmiri et al., 1992 ⁵⁹ Meadows et al., 1993 ⁶¹ Yukna, 1994 ⁶³ Masters et al., 1996 ⁶⁵ Zamet et al., 1997 ⁶⁸ Flemmig et al., 1998 ⁶⁹ Brown et al., 1998 ⁷⁰ Froum et al., 1998 ⁷² Schulz et al., 2000 ⁷⁴ Rosenberg et al., 2000 ⁷⁵	Entity of infrabony defect not specified
Froum et al., 1976 ³³ Chodroff and Ammons, 1984 ⁴⁰ Louise et al., 1987 ⁵⁰ Kim et al., 1996 ⁶⁶ Yukna et al., 1998 ⁷¹ Park et al., 2001 ⁷⁶ Han et al., 2002 ⁷⁷	Follow-up < 12 months
Ong et al., 1998 ⁷³	Follow-up ranged from 9 to 13 months

Table 3. (continued)
OFD Versus Bone or Bone Substitute Grafts: Excluded RCTs

Study	Reason for Exclusion*
Carraro et al., 1976 ³² Rabalais et al., 1981 ³⁶ Yukna et al., 1984 ⁴¹ Meffert et al., 1985 ⁴² Yukna et al., 1985 ⁴⁶ Yukna et al., 1986 ⁴⁷ Schrad and Tussing, 1986 ⁴⁸ Yukna, 1989 ⁵² Yukna et al., 1989 ⁵³ Nery et al., 1990 ⁵⁷ Galgut et al., 1991 ⁵⁸ Kilic et al., 1997 ⁶⁷ Mengel et al., 2003 ⁷⁸ Mengel et al., 2006 ⁸⁸	The statistical analysis did not take the number of independent sites into account (patient effect)
Galgut, 1990 ⁵⁴	Radiographic data could not be interpreted

* Some studies were excluded for more than one reason.

regard to the comparison between EMD and OFD, they conducted:

1) A meta-analysis of eight studies^{98,100,103,105,107,109,111,114} that showed a statistically significant CAL gain of 1.20 mm (95% CI: 0.71 to 1.69 mm; $P < 0.0001$) with EMD.

2) A meta-analysis of eight studies^{98,100,103,105,107,109,111,114} that showed a statistically significant reduction in PD of 0.77 mm (95% CI: 0.54 to 1.00 mm; $P = 0.0001$) with EMD.

3) A meta-analysis of five studies^{98,100,103,107,109} that did not show statistically significant differences in increased gingival recession for either surgical technique: 0.04 mm greater for OFD (95% CI: -0.32 to 0.40 mm; $P = 0.8$).

4) A meta-analysis of two studies^{105,114} (that reported radiographic measurements of bone level) which showed a greater, though not statistically significant, bone gain for the EMD group versus the OFD group of 1.08 mm (95% CI: -0.72 to 2.89 mm; $P = 0.2$).

A further sensitivity analysis extrapolated only two studies^{105,114} with a lower risk of bias. In this case, the differences between EMD and OFD were smaller: CAL gain with EMD was 0.56 mm greater (95% CI: 0.14 to 0.98 mm) than with OFD, and PD reduction was 0.58 mm greater with EMD versus OFD.

With regard to tooth loss over time, Esposito et al.²⁶ reported that the data were insufficient, and the few events reported had been caused by prostheses. With regard to complications and adverse reactions, there were no particular events in the analyzed trials other than adverse reactions caused by postoperative

Table 4.**SR of Needleman et al.²⁷: Results of the GTR Versus OFD Comparison**

Variables	Estimate	95% CI	P Value	Studies (n)
Teeth lost	–	–	–	–
CAL gain better for GTR	1.22 mm*	0.80 to 1.64 mm	<0.0001	16
PD reduction better for GTR	1.21 mm	0.53 to 1.88 mm	0.0004	11
Rec (greater for OFD)	–0.26 mm	–0.08 to –0.43 mm	0.005	9
Bone gain better for GTR [†]	1.39 mm	1.08 to 1.71 mm	–	3
Complications	Exposed membrane (GTR)			
Esthetic satisfaction	–			
Functional satisfaction	–			

– = no data.

Characteristics of study: SR of RCT; follow-up ≥12 months; and comparison of GTR versus OFD.

Sign code: 1++.

* 0.41 mm from three RCTs with low risk for bias.

† Data recorded at the second surgical procedure (to remove membrane).

Table 5.**SR of Esposito et al.²⁶: Results of the EMD Versus OFD Comparison**

Variables	Estimate	95% CI	P Value	Studies (n)
Teeth lost	–	–	–	–
CAL gain better for EMD	1.20 mm*	0.71 to 1.69 mm	<0.0001	8
PD reduction better for EMD	0.77 mm [†]	0.54 to 1.00 mm	0.0001	8
Rec (greater for OFD)	–0.04 mm	–0.40 to 0.32 mm	0.80	5
Bone gain better for EMD [‡]	1.08 mm	–0.72 to 2.89 mm	0.20	2
Complications	No difference in postoperative discomfort			
Esthetic satisfaction better for EMD	1.00	–5.42 to 7.42	0.84	1
Functional satisfaction	–			

– = no data.

Characteristics of the study: SR of RCT; follow-up ≥12 months; and comparisons of EMD versus OFD, GTR, and bone or bone substitute grafts.

Sign code: 1++.

* 0.56 mm from two RCTs with low risk for bias.

† 0.58 mm from two RCTs with low risk for bias.

‡ Data obtained from radiographs.

antibiotic therapy. There was no difference in postoperative discomfort (intensity, duration, need for analgesics, edema, hematoma, wound healing, and radicular hypersensitivity), measured with a VAS, for the two techniques (EMD and OFD) in one study.¹¹³ With regard to patient satisfaction with the cosmetic results, the investigators reported on only one trial,¹¹³ which did not cite any statistically significant differences between EMD and OFD (estimate 1.00 [VAS] better for EMD; 95% CI: –5.42 to 7.42; $P = 0.84$).

With regard to functional satisfaction, at the 1-year follow-up in the same study¹¹³ there were high levels of patient satisfaction with the functional results (chewing ability, gingival health, ability to speak, and ease of oral hygiene), and there were no statistically significant differences between the two patient groups (EMD and OFD). The advantages most frequently cited by the patients were the possibility of keeping their teeth and maintaining or increasing chewing ability, whereas the costs of the treatments and the need for many check-ups were considered the main disadvantages.

In the comparison between EMD and GTR, Esposito et al.²⁶ conducted:

1) A meta-analysis of five studies^{99,100,103,110,112} that showed a statistically non-significant CAL gain of 0.20 mm (95% CI: –0.59 to 0.20 mm; $P = 0.3$) for GTR versus amelogenin EMD.

2) A meta-analysis of five studies^{99,100,103,110,112} that showed a statistically non-significant reduction of PD of 0.49 mm (95% CI: –1.23 to 0.26 mm; $P = 0.2$) for GTR versus EMD.

3) A meta-analysis of four studies^{99,100,103,112} that showed a statistically significant increase in gingival recession that was 0.39 mm greater for GTR (95% CI: 0.13 to 0.66 mm; $P = 0.003$).

None of the RCTs reported comparison data on the teeth lost over time, variations in bone level, or patient satisfaction (functional and esthetic) for the two techniques.

With regard to complications and adverse reactions, Esposito et al.²⁶ reported information from four studies;^{98,100,103,110} there were no statistically significant differences in postoperative infections

between EMD and GTR (relative risk, 0.20; 95% CI: 0.01 to 4.09; $P = 0.3$). There were two cases of abscesses and some membrane exposure in the GTR group.

Another multicenter trial¹¹² reported postoperative complications without differentiating between minor (such as flap dehiscence) and major (such as an abscess) events. There were two (6%) complications in the EMD group and 32 (100%) complications in the GTR group. The difference was statistically significant (relative risk, 0.06; 95% CI: 0.02 to 0.24; $P = 0.00005$).

Table 6.**SR of Esposito et al.²⁶: Results of the GTR Versus EMD Comparison**

Variables	Estimate	95% CI	P Value	Studies (n)
Teeth lost	–	–	–	–
CAL gain better for GTR	0.20 mm	–0.20 to 0.59 mm	0.3	5
PD reduction better for GTR	0.49 mm	–0.26 to 1.23 mm	0.2	5
Rec (greater for GTR)	0.39 mm	0.13 to 0.66 mm	0.003	4
Bone gain	–	–	–	–
Complications				
Postoperative infections (greater for GTR)	0.20*	0.01 to 4.09	0.3	4
All complications (greater for GTR)	0.06*	0.02 to 0.24	0.00005	1
Esthetic satisfaction		–		
Functional satisfaction		–		

– = no data.

Characteristics of study: SR of RCT; follow-up ≥ 12 months; and comparisons of EMD versus OFD, GTR, and bone or bone substitute grafts.

Results of the comparison of EMD versus bone or bone substitute grafts: no RCT found; sign code: 1++.

* Relative risk.

Esposito et al.²⁶ did not find any RCT with details of the comparison between EMD and bone or bone substitute grafts.

With regard to the comparison between bone or bone substitute grafts and OFD, a clinical trial conducted by Minenna et al.⁸³ on 32 patients with infrabony defects ≥ 4 mm made it possible to compare the clinical results of therapy using PLA/PGA copolymer graft (16 patients with one treated site each) to OFD (16 patients with one treated site each) after 1 year of follow-up.

Not a single tooth had been lost 12 months after the treatments. Compared to OFD, the PLA/PGA copolymer achieved a CAL gain of 0.2 mm (statistically non-significant), a PD reduction of 0.7 mm (statistically non-significant), and 0.5 mm greater recession (statistically non-significant). The investigators did not report data about variations in the magnitude of the bony defect, complications, or patient satisfaction levels (functional and esthetic).

GUIDE TO EVIDENCE LEVELS AND STRENGTH OF THE RECOMMENDATIONS (TABLE 7)

In accordance with the suggestions of SIGN,¹⁸ the recommendations in these guidelines distinguish between those supported by strong evidence and those based on trials of lower scientific value. It is important to bear in mind that the grading of a recommendation is not related to the importance of the recommendation itself, but to the strength of the supporting scientific trials.

The recommendations are classified by evidence level and strength of the recommendations in accordance with the guidelines of the United States Agency for Health Care Policy and Research,¹¹⁵ amended and introduced in 2000.¹¹⁶

The evidence levels are rated by four (Arabic) numerals and ++, +, and – signs (decreasing levels of evidence: 1⁺⁺, 1⁺, 1[–], 2⁺⁺, 2⁺, 2[–], 3, 4). The strength of the recommendations is classified in four levels indicated by letters (decreasing strength levels) from A to D.

The evidence level of a recommendation refers to the probability that specific knowledge is obtained from studies with low risk for bias. The strength of the recommendations refers to the probability that transferring them to clinical practice can promote improvement in the health of the population for which the recommendation was made.

RECOMMENDATIONS

Efficacy

Which surgical techniques among OFD, GTR, EMD, and bone or bone substitute grafts are the best, and what are the expected clinical results of the treatment of infrabony defects ≥ 3 mm in patients who have already undergone successful causal treatment?

All of the surgical techniques that we compared (OFD, GTR, and EMD) proved to be capable of increasing CAL, reducing PD, and promoting an increase in bone at the treated site(s).

There is evidence in the literature that at the 1-year follow-up, GTR techniques favor greater CAL increases of 1.22 mm (statistically significant), greater reduction in PD of 1.21 mm (statistically significant), less increase in gingival recession of 0.26 mm (statistically significant), and greater increases in bone levels of 1.39 mm (statistically significant) with respect to simple access surgery for debridement of the lesion (OFD)²⁷ (evidence level: 1⁺⁺; strength of the recommendation: A).

At the 1-year follow-up, there is evidence in the literature that EMD can favor a greater increase in CAL of 1.20 mm (statistically significant), a greater reduction in PD of 0.77 mm (statistically significant), less increase in gingival recession of 0.04 mm (statistically non-significant), and a greater increase in bone level of 1.08 mm (statistically non-significant) compared to simple access surgery for debridement of the lesion (OFD)²⁶ (evidence level: 1⁺⁺; strength of the recommendation: A).

Table 7.
SIGN Grading System¹⁸

Levels of Evidence	
1 ⁺⁺	High-quality meta-analyses, SRs, or RCTs, or RCTs with a very low risk for bias
1 ⁺	Well-conducted meta-analyses, SRs, of RCTs, or RCTs with a low risk for bias
1 ⁻	Meta-analyses, SRs of RCTs, or RCTs with a high risk for bias
2 ⁺⁺	High-quality SRs of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2 ⁺	Well-conducted case-control or cohort studies with a low risk for confounding, bias, or chance and a moderate probability that the relationship is causal
2 ⁻	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g., case report, case series
4	Expert opinion
Grades of Recommendations	
A	At least one meta-analysis, SR, or RCT rated as 1 ⁺⁺ and directly applicable to the target population; or an SR of RCTs or a body of evidence consisting principally of studies rated as 1 ⁺ , directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2 ⁺⁺ , directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1 ⁺⁺ or 1 ⁺
C	A body of evidence including studies rated as 2 ⁺ , directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2 ⁺⁺
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2 ⁺

At the 1-year follow-up, there is evidence in the literature that GTR techniques are capable of guaranteeing results that are essentially comparable to EMD in terms of CAL increase (0.20 mm for GTR; statistically non-significant), PD reduction (0.49 mm for GTR; statistically non-significant), and increased gingival recession (0.39 mm; statistically significant)²⁶ (evidence level: 1⁺⁺; strength of the recommendation: A).

On the basis of the inclusion criteria for these guidelines and the studies available in the literature, there are insufficient data for comparing the results of bone or bone substitute grafts to those obtained with OFD,

GTR, and EMD in the treatment of deep infrabony defects ≥ 3 mm in periodontal patients who have already undergone successful causal treatment.

Therefore, it is advisable to treat vertical bony defects ≥ 3 mm with OFD, GTR, or EMD techniques. GTR and EMD show better results than surgical access flaps for debridement in terms of mean CAL gain, mean reduction of PD, and mean bone increment at the 1-year follow-up (evidence level: 1⁺⁺; strength of the recommendation: A).

However, this statement must be viewed with extreme caution because it seems limited by the observation that when the RCTs with a lower risk for bias are analyzed, the differences in the treatments decrease, as in Needleman et al.²⁷ for the comparison between GTR and OFD, in which the CAL gains in favor of GTR are reduced and become statistically non-significant (0.41 mm) and in Esposito et al.²⁶ for the comparison between EMD and OFD, in which the values for CAL gain and PD reduction in favor of amelogenin EMD are halved (0.56 and 0.58 mm, respectively). Also, the studies are often very heterogeneous, and most of the RCTs had a short follow-up (~12 months).

Furthermore, the choice of one technique over another should take into account the cost/benefit ratio for the patient from biologic and economic standpoints; the fact that GTR, EMD, and bone or bone substitute grafts are usually used to treat one site at a time, whereas OFD is generally used to treat more than one site at one time; the anatomic characteristics of the site to be treated (e.g., number of walls and depth and angle of the bony defect); the strategic importance of the site to be treated; the professional's experience; the ease of performing one technique over another; and the postoperative comfort of the patient.

There are insufficient data from randomized studies to permit an evaluation of all of these factors; therefore, such studies should be encouraged.

Complications

What are the possible adverse reactions following treatment of deep infrabony defects ≥ 3 mm by OFD, GTR, EMD, and bone or bone substitute grafts?

In general, only a few trials report these data, and the available data are scanty. Therefore, the data available in the literature are insufficient for answering the question.

In any event, with regard to the comparison between GTR and OFD, one RCT¹⁰² did not report any significant differences concerning complications other than postoperative edema, which was more frequent among patients treated with GTR ($P = 0.01$) (evidence level: 1⁺).

For the comparison between EMD and OFD, Esposito et al.²⁶ reported that there were no particular events in

the trials that they analyzed other than adverse reactions caused by postoperative antibiotic therapy. No difference in postoperative discomfort between the two techniques was reported in one RCT¹¹³ (evidence level: 1⁺).

With regard to the comparison between EMD and GTR, Esposito et al.²⁶ reported on four studies.^{98,100,103,110} There was no statistically significant difference between EMD and GTR in terms of postoperative infections (evidence level: 1⁺⁺). There were two cases of abscesses and some membrane exposure in the GTR group, whereas there were no postoperative infections or other adverse reactions in the EMD group.

It is important to mention that the investigators reported on one multicenter trial¹¹² that described postoperative complications without differentiating between minor (e.g., flap dehiscence) and major (e.g., abscess) ones. There were two (6%) complications in the EMD group and 32 (100%) complications in the GTR group. The difference was statistically significant ($P < 0.0001$) (evidence level: 1⁺).

No data were found on other comparisons between treatment methods; further studies are needed.

Patient Opinions

What is the level of patient satisfaction from functional and esthetic standpoints with the results of OFD, GTR, EMD, and bone or bone substitute grafts after treatment of deep infrabony defects of ≥ 3 mm?

The data in the literature are insufficient; therefore, the question cannot be answered.

Only one trial¹¹³ reported statistically non-significant differences between EMD and OFD in terms of patient perceptions of functional and esthetic satisfaction (evidence level: 1⁺). Further studies on these aspects should be encouraged and conducted.

SUMMARY OF THE RECOMMENDATIONS

Efficacy

Which surgical technique (OFD, GTR, EMD, or bone or bone substitute grafts) is most recommendable, and what are the predicted clinical results for the treatment of infrabony defects ≥ 3 mm in periodontal patients who have already undergone causal treatment?

Answer: It is advisable to treat vertical bony defects ≥ 3 mm with OFD, GTR, or EMD (evidence level: 1⁺⁺; strength of the recommendation: A). GTR and EMD can yield better results than OFD in terms of CAL gain, reduction of PD, and bone gain after 1 year of follow-up (evidence level: 1⁺⁺; strength of the recommendation: A). The available data are insufficient for an evaluation of bone or bone substitute grafts after 1 year.

Complications

What are the possible adverse reactions following treatment of infrabony defects ≥ 3 mm with OFD, GTR, EMD, or bone or bone substitute grafts?

Answer: The data in the literature are insufficient for answering the question. One study¹¹² reported more postoperative complications for GTR compared to EMD (1⁺). Further studies on these aspects should be encouraged and conducted.

Patient Opinions

What is the level of patient satisfaction from esthetic and functional standpoints with the results of OFD, GTR, EMD, and bone or bone substitute grafts after treatment of infrabony defects ≥ 3 mm?

Answer: There are insufficient data in the literature to answer the question. One study¹¹³ suggested that there are no differences in patient functional and esthetic perceptions following treatment with OFD and EMD (1⁺). Further studies should be encouraged and conducted.

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REFERENCES

- Peterson P. The World Oral Health Report 2003. Available at: http://www.who.int/oral_health/media/en/orh_report03_en.pdf. Accessed February 5, 2007.
- Albandar JM, Brunelle JA, Kingman A. Destructive periodontal disease in adults 30 years of age and older in the United States 1988-1994. *J Periodontol* 1999;70:13-29.
- Albandar JM. Periodontal diseases in North America. *Periodontol 2000* 2002;29:31-69.
- Socransky SS, Haffajee AD. The bacterial etiology of destructive periodontal disease: Current concepts. *J Periodontol* 1992;63(Suppl. 4):322-331.
- Nunn ME. Understanding the etiology of periodontitis: An overview of periodontal risk factors. *Periodontol 2000* 2003;32:11-23.
- Renvert S, Persson GR. A systematic review on the use of residual probing depth, bleeding on probing and furcation status following initial periodontal therapy to predict further attachment and tooth loss. *J Clin Periodontol* 2002;29:82-89.
- American Academy of Periodontology. The pathogenesis of periodontal disease (position paper). *J Periodontol* 1999;70:457-470.

8. Committee on Intersociety Coordination of the Italian Dental Societies (CIC). *Guidelines in Dentistry* (in Italian). Promo Leader Service, Florence, Italy; 2003: 131-156.
9. Van der Weijden GA, Timmerman MF. A systematic review on the clinical efficacy of subgingival debridement in the treatment of chronic periodontitis. *J Clin Periodontol* 2002;29(Suppl. 3):55-71.
10. Claffey N, Egelberg J. Clinical indicators of probing attachment loss following initial periodontal treatment in advanced periodontitis patients. *J Clin Periodontol* 1995;22:690-696.
11. Kirkland O. The suppurative periodontal pus pocket; its treatment by the modified flap operation. *J Am Dent Assoc* 1931;18:1462-1470.
12. Nyman S, Gottlow J, Karring T, Lindhe J. The regenerative potential of the periodontal ligament. An experimental study in the monkey. *J Clin Periodontol* 1982;9:257-265.
13. Heijl L. Periodontal regeneration with enamel matrix derivative in one human experimental defect. A case report. *J Clin Periodontol* 1997;24(9 Pt. 2):693-696.
14. Bowers GM, Vargo JW, Levy B, Emerson JR, Bergquist JJ. Histologic observations following the placement of tricalcium phosphate implants in human intrabony defects. *J Periodontol* 1986;57:286-287.
15. American Academy of Periodontology. Periodontal maintenance (position paper). *J Periodontol* 2003; 74:1395-1401.
16. The AGREE Collaboration. Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument. Available at: <http://www.agreecollaboration.org>. Accessed February 5, 2007.
17. Glossary of evidence-based terms. *J Evid Based Dent Pract* 2007;7:45-49.
18. Scottish Intercollegiate Guidelines Network (SIGN). A guideline developers' handbook. Available at <http://www.sign.ac.uk>. Accessed February 5, 2007.
19. Laurell L, Gottlow J, Zybutz M, Persson R. Treatment of intrabony defects by different surgical procedures. A literature review. *J Periodontol* 1998;69: 303-313.
20. Trombelli L, Heitz-Mayfield L, Needleman I, Moles D, Scabbia A. A systematic review of graft materials and biological agents for periodontal intraosseous defects. *J Clin Periodontol* 2002;29(Suppl. 3):117-135.
21. Kalpidis CDR, Ruben MP. Treatment of intrabony periodontal defects with enamel matrix derivative: A literature review. *J Periodontol* 2002;73:1360-1376.
22. Giannobile WV, Somerman MJ. Growth and amelogenin-like factors in periodontal wound healing. A systematic review. *Ann Periodontol* 2003;8:193-204.
23. 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: 227-264.
24. 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.
25. Venezia E, Goldstein M, Boyan BD, Schwartz Z. The use of enamel matrix derivative in the treatment of periodontal defects: A literature review and meta-analysis. *Crit Rev Oral Biol Med* 2004;15:382-402.
26. Esposito M, Grusovin MG, Coulthard P, Worthington HV. Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects. *Cochrane Database Syst Rev* 2005;CD003875.
27. Needleman IG, Worthington HV, Tucker RJ, Giedrys-Leeper E. Guided tissue regeneration for periodontal infra-bony defects. *Cochrane Database Syst Rev* 2006; CD001724.
28. Francetti L, Trombelli L, Lombardo G, et al. Evaluation of efficacy of enamel matrix derivative in the treatment of intrabony defects: A 24-month multicenter study. *Int J Periodontics Restorative Dent* 2005;25:461-473.
29. 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.
30. Sculean A, Schwarz F, Miliuskaite 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.
31. Ellegaard B, Loe H. New attachment of periodontal tissues after treatment of intrabony lesions. *J Periodontol* 1971;42:648-652.
32. Carraro JJ, Sznajder N, Alonso CA. Intraoral cancellous bone autografts in the treatment of infrabony pockets. *J Clin Periodontol* 1976;3:104-109.
33. Froum SJ, Ortiz M, Witkin RT, Thaler R, Scopp IW, Stahl SS. Osseous autografts. III. Comparison of osseous coagulum-bone blend implants with open curettage. *J Periodontol* 1976;47:287-294.
34. Altieri ET, Reeve CM, Sheridan PJ. Lyophilized bone allografts in periodontal intraosseous defects. *J Periodontol* 1979;50:510-519.
35. Pearson GE, Rosen S, Deporter DA. Preliminary observations on the usefulness of a decalcified, freeze-dried cancellous bone allograft material in periodontal surgery. *J Periodontol* 1981;52:55-59.
36. Rabalais ML Jr., Yukna RA, Mayer ET. Evaluation of durapatite ceramic as an alloplastic implant in periodontal osseous defects. I. Initial six-month results. *J Periodontol* 1981;52:680-689.
37. Movin S, Borring-Moller G. Regeneration of infrabony periodontal defects in humans after implantation of allogenic demineralized dentin. *J Clin Periodontol* 1982; 9:141-147.
38. Sanders JJ, Sepe WW, Bowers GM, et al. Clinical evaluation of freeze-dried bone allografts in periodontal osseous defects. Part III. Composite freeze-dried bone allografts with and without autogenous bone grafts. *J Periodontol* 1983;54:1-8.
39. Mellonig JT. Decalcified freeze-dried bone allograft as an implant material in human periodontal defects. *Int J Periodontics Restorative Dent* 1984;4:40-55.
40. Chodroff RE, Ammons WF. Periodontal repair after surgical debridement with and without cartilage allografts. *J Clin Periodontol* 1984;11:295-312.
41. Yukna RA, Mayer ET, Brite DV. Longitudinal evaluation of durapatite ceramic as an alloplastic implant in periodontal osseous defects after 3 years. *J Periodontol* 1984;55:633-637.
42. Meffert RM, Thomas JR, Hamilton KM, Brownstein CN. Hydroxylapatite as an alloplastic graft in the treatment of human periodontal osseous defects. *J Periodontol* 1985;56:63-73.

43. Mabry TW, Yukna RA, Sepe WW. Freeze-dried bone allografts combined with tetracycline in the treatment of juvenile periodontitis. *J Periodontol* 1985;56:74-81.
44. Kenney EB, Lekovic V, Han T, Carranza FA Jr., Dimitrijevic B. The use of a porous hydroxylapatite implant in periodontal defects. I. Clinical results after six months. *J Periodontol* 1985;56:82-88.
45. Renvert S, Garrett S, Schallhorn RG, Egelberg J. Healing after treatment of periodontal intraosseous defects. III. Effect of osseous grafting and citric acid conditioning. *J Clin Periodontol* 1985;12:441-455.
46. Yukna RA, Harrison BG, Caudill RF, Evans GM, Mayer ET, Miller S. Evaluation of durapatite ceramic as an alloplastic implant in periodontal osseous defects. II. Twelve month reentry results. *J Periodontol* 1985;56:540-547.
47. Yukna RA, Cassingham RJ, Caudill RF, et al. Six month evaluation of Calcite (hydroxyapatite ceramic) in periodontal osseous defects. *Int J Periodontics Restorative Dent* 1986;6:34-45.
48. Schrad SC, Tussing GJ. Human allografts of iliac bone and marrow in periodontal osseous defects. *J Periodontol* 1986;57:205-210.
49. Hiatt WH, Lorato DC, Hiatt WR, Lindfors KW. The induction of new bone and cementum formation. V. A comparison of graft and control in sites in deep intrabony periodontal lesions. *Int J Periodontics Restorative Dent* 1986;6:8-21.
50. Louise F, Borghetti A, Simeone D, Gervasone V. 6-month clinical evaluation of the augmentation of intraosseous lesions with porous hydroxyapatite (Interpore 200) (in French). *J Parodontol* 1987;6:203-212.
51. Krejci CB, Bissada NF, Farah C, Greenwell H. Clinical evaluation of porous and nonporous hydroxyapatite in the treatment of human periodontal bony defects. *J Periodontol* 1987;58:521-528.
52. Yukna RA. Osseous defect responses to hydroxylapatite grafting versus open flap debridement. *J Clin Periodontol* 1989;16:398-402.
53. Yukna RA, Mayer ET, Amos S. A 5-year evaluation of durapatite ceramic alloplastic implants in periodontal osseous defects. *J Periodontol* 1989;60:544-551.
54. Galgut PN. Variations in healing of infrabony defects treated with ceramic bone-grafting material observed radiographically for a period of three years. *J Oral Implantol* 1990;16:173-182.
55. Blumenthal N, Steinberg J. The use of collagen membrane barriers in conjunction with combined demineralized bone-collagen gel implants in human infrabony defects. *J Periodontol* 1990;61:319-327.
56. Yukna RA. HTR polymer grafts in human periodontal osseous defects. I. 6-month clinical results. *J Periodontol* 1990;61:633-642.
57. Nery EB, Lee KK, Czajkowski S, et al. A Veterans Administration Cooperative Study of biphasic calcium phosphate ceramic in periodontal osseous defects. *J Periodontol* 1990;61:737-744.
58. Galgut PN, Verrier J, Waite IM, Linney A, Cornick DER. Computerized densitometric analysis of interproximal bone levels in a controlled clinical study into the treatment of periodontal bone defects with ceramic hydroxyapatite implant material. *J Periodontol* 1991;62:44-50.
59. Shahmiri S, Singh IJ, Stahl SS. Clinical response to the use of the HTR polymer implant in human intrabony lesions. *Int J Periodontics Restorative Dent* 1992;12:294-299.
60. Galgut PN, Waite IM, Brookshaw JD, Kingston CP. A 4-year controlled clinical study into the use of a ceramic hydroxylapatite implant material for the treatment of periodontal bone defects. *J Clin Periodontol* 1992;19:570-577.
61. Meadows CL, Gher ME, Quintero G, Lafferty TA. A comparison of polylactic acid granules and decalcified freeze-dried bone allograft in human periodontal osseous defects. *J Periodontol* 1993;64:103-109.
62. Borghetti A, Novakovitch G, Louise F, Simeone D, Fourel J. Cryopreserved cancellous bone allograft in periodontal intraosseous defects. *J Periodontol* 1993;64:128-132.
63. Yukna RA. Clinical evaluation of coralline calcium carbonate as a bone replacement graft material in human periodontal osseous defects. *J Periodontol* 1994;65:177-185.
64. Mora F, Ouhayoun JP. Clinical evaluation of natural coral and porous hydroxyapatite implants in periodontal bone lesions: Results of a 1-year follow-up. *J Clin Periodontol* 1995;22:877-884.
65. Masters LB, Mellonig JT, Brunsvold MA, Nummikoski PV. A clinical evaluation of demineralized freeze-dried bone allograft in combination with tetracycline in the treatment of periodontal osseous defects. *J Periodontol* 1996;67:770-781.
66. Kim CK, Choi EJ, Cho KS, Chai JK, Wikesjo UM. Periodontal repair in intrabony defects treated with a calcium carbonate implant and guided tissue regeneration. *J Periodontol* 1996;67:1301-1306.
67. Kilic AR, Efeoglu E, Yilmaz S. Guided tissue regeneration in conjunction with hydroxyapatite-collagen grafts for intrabony defects. A clinical and radiological evaluation. *J Clin Periodontol* 1997;24:372-383.
68. Zamet JS, Darbar UR, Griffiths GS, et al. Particulate bioglass as a grafting material in the treatment of periodontal intrabony defects. *J Clin Periodontol* 1997;24:410-418.
69. Flemmig TF, Ehmke B, Bolz K, et al. Long-term maintenance of alveolar bone gain after implantation of autolyzed, antigen-extracted, allogenic bone in periodontal intraosseous defects. *J Periodontol* 1998;69:47-53.
70. Brown GD, Mealey BL, Nummikosky PV, Bifano SL, Waldrop TC. Hydroxyapatite cement implant for regeneration of periodontal osseous defects in humans. *J Periodontol* 1998;69:146-157.
71. Yukna RA, Callan DP, Krauser JT, et al. Multi-center clinical evaluation of combination anorganic bovine-derived hydroxyapatite matrix (ABM)/cell binding peptide (P-15) as a bone replacement graft material in human periodontal osseous defects. 6-month results. *J Periodontol* 1998;69:655-663.
72. Froum SJ, Weinberg MA, Tarnow D. Comparison of bioactive glass synthetic bone graft particles and open debridement in the treatment of human periodontal defects. A clinical study. *J Periodontol* 1998;69:698-709.
73. Ong MM, Eber RM, Korsnes MI, et al. Evaluation of a bioactive glass alloplast in treating periodontal intrabony defects. *J Periodontol* 1998;69:1346-1354.
74. 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.
75. Rosenberg ES, Fox GK, Cohen C. Bioactive glass granules for regeneration of human periodontal defects. *J Esthet Dent* 2000;12:248-257.

76. Park JS, Suh JJ, Choi SH, et al. Effects of pretreatment clinical parameters on bioactive glass implantation in intrabony periodontal defects. *J Periodontol* 2001;72:730-740.
77. Han J, Meng H, Xu L. Clinical evaluation of bioactive glass in the treatment of periodontal intrabony defects. *Zhonghua Kou Qiang Yi Xue Za Zhi* 2002;37:225-227.
78. Mengel R, Soffner M, Flores-de-Jacoby L. Bioabsorbable membrane and bioactive glass in the treatment of intrabony defects in patients with generalized aggressive periodontitis: Results of a 12-month clinical and radiological study. *J Periodontol* 2003;74:899-908.
79. 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.
80. Radhakrishnan S, Anusuya CN. Comparative clinical evaluation of combination anorganic bovine-derived hydroxyapatite matrix (ABM)/cell binding peptide (P-15) and open flap debridement (DEBR) in human periodontal osseous defects: A 6 month pilot study. *J Int Acad Periodontol* 2004;6:101-107.
81. 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.
82. Hanna R, Trejo PM, Weltman RL. Treatment of intrabony defects with bovine-derived xenograft alone and in combination with platelet-rich plasma: A randomized clinical trial. *J Periodontol* 2004;75:1668-1677.
83. Minenna L, Herrero F, Sanz M, Trombelli L. Adjunctive effect of a polylactide/polyglycolide copolymer in the treatment of deep periodontal intra-osseous defects: A randomized clinical trial. *J Clin Periodontol* 2005;32:456-461.
84. Bender SA, Rogalski JB, Mills MP, Arnold RM, Cochran DL, Mellonig JT. Evaluation of demineralized bone matrix paste and putty in periodontal intraosseous defects. *J Periodontol* 2005;76:768-777.
85. 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.
86. Sarment DP, Cooke JW, Miller SE, et al. Effect of rhPDGF-BB on bone turnover during periodontal repair. *J Clin Periodontol* 2006;33:135-140.
87. Camargo PM, Wolinsky LE, Ducar JP, et al. The effect of fibronectin and a bone xenograft on regenerative treatment: A feasibility study. *Compend Contin Educ Dent* 2006;27:560-568.
88. Mengel R, Schreiber D, Flores-de-Jacoby L. Bioabsorbable membrane and bioactive glass in the treatment of intrabony defects in patients with generalized aggressive periodontitis: Results of a 5-year clinical and radiological study. *J Periodontol* 2006;77:1781-1787.
89. Chung KM, Salkin LM, Stein MD, Freedman AL. Clinical evaluation of a biodegradable collagen membrane in guided tissue regeneration. *J Periodontol* 1990;61:732-736.
90. Cortellini P, Pini Prato G, Tonetti MS. Periodontal regeneration of human intrabony defects with titanium reinforced membranes. A controlled clinical trial. *J Periodontol* 1995;66:797-803.
91. Pritlove-Carson S, Palmer RM, Floyd PD. Evaluation of guided tissue regeneration in the treatment of paired periodontal defects. *Br Dent J* 1995;179:388-394.
92. Cortellini P, Pini Prato G, Tonetti MS. Periodontal regeneration of human intrabony defects with bioresorbable membranes. A controlled clinical trial. *J Periodontol* 1996;67:217-223.
93. Mora F, Etienne D, Ouhayoun JP. Treatment of interproximal angular defects by guided tissue regeneration: 1 year follow-up. *J Oral Rehabil* 1996;23:599-606.
94. Mayfield L, Söderholm G, Hallström H, et al. Guided tissue regeneration for the treatment of intraosseous defects using a bioabsorbable membrane. A controlled clinical study. *J Clin Periodontol* 1998;25:585-595.
95. Tonetti MS, Cortellini P, Suvan JE, et al. Generalizability of the added benefits of guided tissue regeneration in the treatment of deep intrabony defects. Evaluation in a multi-center randomized controlled clinical trial. *J Periodontol* 1998;69:1183-1192.
96. 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.
97. Kim CK, Chai JK, Cho KS, et al. Periodontal repair in intrabony defects treated with a calcium sulfate implant and calcium sulfate barrier. *J Periodontol* 1998;69:1317-1324.
98. 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.
99. Ratka-Kruger P, Neukrantz E, Raetzke P. Guided tissue regeneration procedure with bioresorbable membranes versus conventional flap surgery in the treatment of infrabony periodontal defects. *J Clin Periodontol* 2000;27:120-127.
100. 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.
101. Sculean A, Windisch P, Chiantella GC, Donos N, Brex 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.
102. Cortellini P, Tonetti MS, Lang NP, et al. The simplified papilla preservation flap in the regenerative treatment of deep intrabony defects: Clinical outcomes and postoperative morbidity. *J Periodontol* 2001;72:1702-1712.
103. 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.

104. Loos BG, Louwse PH, Van Winkelhoff AJ, et al. Use of barrier membranes and systemic antibiotics in the treatment of intraosseous defects. *J Clin Periodontol* 2002;29:910-921.
105. Heijl L, Heden G, Svardstrom G, Ostgren A. Enamel matrix derivative (EMDOGAIN) in the treatment of intrabony periodontal defects. *J Clin Periodontol* 1997;24:705-714.
106. Heijl L, Heden G, Svardstrom G, Ostgren A. EMDOGAIN in the treatment of intrabony periodontal defects. *J Dent Res* 1997;76(Spec. Abstr. Issue 1):292.
107. 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.
108. Okuda K, Miyazaki A, Momose M, Murata M, Yokoyama S, Yonezawa Y. Enamel matrix derivative (EMD) in the treatment of human intrabony periodontal osseous defects. *J Periodontol* 2000;71:1913.
109. 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.
110. Silvestri M, Sartori S, Rasperini G, Ricci G, Rota C, Cattaneo V. Comparison of intrabony defects treated with enamel matrix derivative versus guided tissue regeneration with a nonresorbable membrane. *J Clin Periodontol* 2003;30:386-393.
111. Francetti L, Del Fabbro M, Basso M, Testori R, Weinstein R. Enamel matrix proteins in the treatment of intra-bony defects. A prospective 24-month clinical trial. *J Clin Periodontol* 2004;31:52-59.
112. 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.
113. Tonetti MS, Fourmouis I, Suvan J, Cortellini P, Bragger U, Lang NP; European Research Group on Periodontology (ERGOPERIO). Healing, post-operative morbidity and patient perception of outcomes following regenerative therapy of deep intrabony defects. *J Clin Periodontol* 2004;31:1092-1098.
114. 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.
115. U.S. Department of Health and Human Services. *Acute Pain Management: Operative or Medical Procedures and Trauma*. Clinical Practice Guideline No. 1. AHCPR Publication No. 92-0023:107. Rockville, MD: Agency for Health Care Policy and Research, U.S. Department of Health and Human Services; 1993.
116. Scottish Intercollegiate Guidelines Network. Methodology Review Group. *Report on the Review of the Method of Grading Guideline Recommendations*. Edinburgh: SIGN; 1999.

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