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CLINICAL REVIEW

Absorbable Collagen Membranes for Periodontal Regeneration: A Systematic Review

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ABSTRACT

Guided tissue regeneration (GTR) with bioabsorbable collagen membranes (CM) is commonly used for the treatment of periodontal defects. The objective of this systematic review of randomized clinical trials was to assess the clinical efficacy of GTR procedures with CM, with or without bone substitutes, in periodontal infrabony defects compared with that of open flap debridement (OFD) alone. Primary outcomes were tooth loss and gain in clinical attachment level (CAL). Screening of records, data extraction, and risk-of-bias assessments were performed by two reviewers. Weighted mean differences were estimated by random effects meta-analysis. We included 21 reports on 17 trials. Risk of bias was generally high. No data were available for the primary outcome tooth loss. The summary treatment effect for change in CAL for GTR with CM compared with OFD was 1.58 mm (95% CI, 1.27 to 1.88). Despite large between-trial heterogeneity ($I^2 = 75\%$, $p < .001$), all trials favored GTR over OFD. No differences in treatment effects were detected between trials of GTR with CM alone and trials of GTR with CM in combination with bone substitutes (p for interaction, .31). GTR with CM, with or without substitutes, may result in improved clinical outcomes compared with those achieved with OFD alone. Our findings support GTR with CM for the treatment of infrabony periodontal defects.

KEY WORDS: periodontal disease(s)/periodontitis, surgery, meta-analysis, biomaterial(s), guided tissue regeneration, clinical studies/trials.

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INTRODUCTION

Infrabony periodontal osseous defects represent a frequent sequela of periodontitis (Papapanou and Tonetti, 2000). Guided tissue regeneration (GTR) regenerates connective tissue attachment (*i.e.*, forming cementum by inserting collagen fibers and periodontal ligament) and alveolar bone in periodontal defects. A mechanical barrier prevents or retards the apical migration of the gingival epithelium and allows periodontal ligament and bone tissue to selectively repopulate the root surface during healing (Nyman *et al.*, 1982; Gottlow *et al.*, 1986; Stahl *et al.*, 1990).

A systematic review that evaluated the effects of GTR with both non-bioabsorbable and bioabsorbable membranes showed that GTR improved attachment gain, reduced pocket depth, and resulted in less gingival recession and more hard-tissue fill than did open flap debridement (OFD) alone (Needleman *et al.*, 2006). The different barrier types [expanded polytetrafluoroethylene (ePTFE) barrier, collagen-derived or polymeric bioabsorbable barrier type] exhibited no significant differences in results (Murphy and Gunsolley, 2003).

However, a second surgical procedure is necessary to remove non-bioabsorbable membranes, and this increases the risk that newly formed tissues will be compromised. Moreover, flap elevation for membrane removal may result in crestal bone resorption (Pihlstrom *et al.*, 1983) and decrease coverage of the newly formed tissue, thus interrupting the healing process (Tonetti *et al.*, 1993, 1996). The use of non-bioabsorbable membranes increases risk of membrane exposure and bacterial colonization and thus may inhibit healing (Nowzari *et al.*, 1995). Bioabsorbable membranes, including collagen membranes (CM), have been developed for, and used in, GTR to prevent these problems.

Human histological studies have provided evidence that treatment of infrabony defects, with CM with or without the addition of bone substitutes, improves periodontal regeneration (Parodi *et al.*, 1997; Camelo *et al.*, 1998; Sculean *et al.*, 2004). Combining CM with bone substitutes may prevent the barrier from collapsing, especially in non-contained infrabony defects, and may thus ensure space maintenance (Bunyaratavej and Wang, 2001).

The goal of this systematic review was to assess the clinical, radiographic, and safety outcomes of GTR with absorbable CM, alone or in association with bone substitutes, as compared with those achieved with OFD alone. We also aimed at assessing whether the variations between trials could be explained by characteristics of the procedure or by biases affecting individual trials.

METHODS

We followed a standard protocol for all review steps. We included randomized or *quasi*-randomized controlled trials (RCTs) with patients who displayed infrabony periodontal defects around single- or multi-rooted teeth. We excluded studies that addressed only furcation defects. We considered trials that compared GTR with bioabsorbable CM, with or without the application of bone substitutes and other bio-active materials, with OFD alone. Primary outcomes were tooth loss and change in clinical attachment level (CAL). Secondary outcomes were change in probing pocket depth (PPD), change in gingival recession (REC), radiographic hard-tissue fill, clinical hard-tissue fill (bone sounding, re-entry surgeries), and post-operative complications (membrane exposure, infection).

Literature Search

We searched electronic databases, without language restrictions: Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE through Ovid (from inception to January 8, 2013) (see Appendix Tables 1 and 2 for search algorithms). This was complemented by a hand search of the *Journal of Periodontology, Journal of Clinical Periodontology*, and *Journal of Periodontal Research* up to January 2013 and reviews of bibliographies of all relevant systematic review articles and included trial reports. In addition, we contacted GTR experts with the request to indicate any report we had not captured in our online and hand searches. We did not seek unpublished data.

Trial Selection, Data Collection, and Risk-of-Bias Assessment

Titles and abstracts of the search results were screened independently in duplicate (CS, GES). We considered only reports with available full text, and those were independently assessed by two review authors (CS, GES), who determined their eligibility. Disagreements were resolved by consensus or discussion with a third reviewer (AS). If several reports described the same trial, we chose the most recent report or most complete report as the main report. Remaining reports were checked for complementary data on clinical outcomes, descriptions of study participants, or design characteristics.

Data were extracted independently by two reviewers (CS, AR) and entered into a Web-based extraction form. We collected the following information: patient characteristics (sex, average age, periodontal diagnosis, smoking status); tooth-related characteristics (infrabony defect configuration); type of bioabsorbable CM used; type of bone substitute material applied, if applicable; surgical flap design; post-operative care provided (including post-operative systemic antibiotics); enrollment in supportive periodontal treatment (SPT); clinical outcome variables at baseline and longest follow-up observation (tooth retention, CAL, PPD, REC, x-ray hard-tissue level, clinical hard-tissue level); post-operative complications (membrane exposure, infection); trial size, trial design, trial duration (defined as time from surgical intervention until end of follow-up); and number of study centers (single vs. multicenter). We considered concealment of allocation, blinding of patients, surgeons, and those performing outcome assessment, according to current guidelines of the Cochrane Handbook (Higgins *et al*., 2011). We determined if analyses were conducted according to the intention-to-treat principle, and if we could detect selective outcome reporting or other biases.

We considered allocation concealment to be adequate if the investigators responsible for patient selection were unable to predict which treatment was next before allocation. Central randomization and sequentially numbered, sealed, opaque envelopes were considered adequate methods. Concealment was judged to be associated with high risk of bias (ROB) if evidence of inadequate sequence generation was found. We decided that there was low risk of performance bias (Juni *et al*., 2001) if the treatment allocation was revealed to the surgeon only after mucoperiosteal flap elevation and defect debridement were completed. However, for split-mouth studies, both test and control sites would need to be prepared simultaneously to be considered at low risk of performance bias. If an attempt to blind patients was reported, we considered blinding of patients to be associated with low risk of bias. Blinding of outcome assessment was judged to result in low risk of bias if the investigators who performed the outcome assessment were explicitly reported to be blind.

Statistical analyses were considered adequate if all randomized patients were included in the analysis according to the intention-to-treat principle (Rutjes *et al*., 2012). Trials were considered to have a high risk of selective reporting bias if we identified 1 or more outcome measures in published reports for which results were not reported. We used a cut-off of 25 patients *per* group in case of parallel designs and 25 patients overall in case of split-mouth designs, to distinguish between small and moderate-to-large trials. This sample size yields a power of 80% to detect a biologically large difference between groups of 0.8 standard deviations, with a two-sided alpha of 0.05. We also examined how defects were ascertained as another source of bias. If multiple sites were measured, but only the deepest defect at baseline was considered in the analysis, we judged this to result in low risk of bias. If whole-tooth means were used, we judged this to be associated with high risk of bias, since this resulted in a dilution of potential effects and a bias toward the null.

Data Synthesis and Analysis

We used results from intention-to-treat analyses at the longest follow-up, whenever reported. We calculated weighted mean differences (WMDs) in changes from baseline between experimental and control groups for clinical outcomes. Effect sizes were used if at least 1 trial expressed change values in percentages, when other trial(s) expressed results in millimeters. Here, the differences in mean change from baseline across treatment groups were divided by the pooled standard deviation. An effect size of -0.20 standard deviation units was considered a small difference between experimental and control groups, an effect size of -0.50 was a moderate difference, and an effect size of -0.80 a large difference (Cohen, 1988). If differences in mean changes were unavailable, we used the reported baseline and follow-up values to approximate them. If some of the required data were unavailable, we used the approximations previously described (Reichenbach *et al.*, 2007). We expressed binary outcomes as risk ratios (RR) and excluded comparisons with zero events in both groups in the analyses (Sweeting *et al.*, 2004). In studies that used a split-mouth design in which more than 1

tooth contributed to a single treatment arm, we adjusted the standard errors as follows:

$$standard\ error \bullet \sqrt{\frac{number\ of\ teeth}{number\ of\ patients}}.$$

If a report provided clinical outcome data for more than 1 site, we pooled the estimates of treatment effects within the trial to prevent it from being too heavily weighted in the overall analyses.

We used a standard inverse-variance random-effects model to summarize the estimates of treatment effects across trials to account fully for between-study variance. We quantified between-study variance using the I^2 statistic (Higgins *et al.*, 2003), which describes the percentage of variation across trials attributable to heterogeneity rather than chance, and the corresponding Chi^2 test. I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high between-trial heterogeneity, although the precision of trials included in the meta-analysis must be considered for interpretation of I^2 values (Rücker *et al.*, 2008).

For the primary outcome, the association between trial size and treatment effects was investigated in funnel plots. We plotted WMDs on the vertical axis against their standard errors on the horizontal axis. We assessed asymmetry by the asymmetry coefficient. We used the difference in size of WMDs *per* unit increase in standard error (Sterne and Egger, 2001), which is mainly a surrogate for sample size.

In all analyses, we differentiated between the 2 kinds of GTR: CM with and without bone substitutes. For the outcome CAL gain, we performed stratified analyses by risk-of-bias items: concealment of allocation; blinding of patients, surgeons, and outcome assessors; analysis in accordance with the intention-to-treat principle; selective outcome reporting; and other bias. We also evaluated the following trial characteristics: type of CM (cross-linked *vs*. native CM), protocol-mandated use of antibiotics, percentage of smokers at baseline, and percentage of defects with three-wall involvement. We used uni-variable random-effects meta-regression models to determine if these factors were associated with estimates of treatment effect (Thompson and Sharp, 1999). All statistical analyses were done in STATA version 12.1 (StataCorp, College Station, TX, USA). All *p* values are two-sided.

RESULTS

Description of Studies

We identified 2,713 references, of which 46 were potentially eligible. Of the 46, 25 reports did not meet our inclusion criteria (see flow diagram in Appendix Fig. 1 and excluded reports in Appendix Table 3). The remaining 21 eligible reports described 17 trials with 35 arms and 507 patients (Blumenthal and Steinberg, 1990; Chung *et al.*, 1990; Quteish and Dolby, 1992; al-Arrayed *et al*., 1995; Camargo *et al.*, 2000, 2005; Lekovic *et al.*, 2001; Sculean *et al.*, 2003, 2005, 2007; Tonetti *et al.*, 2004; Vouros *et al.*, 2004; Heitz-Mayfield *et al.*, 2006; Linares *et al.*, 2006; Paolantonio *et al*., 2008, 2010; Boynuegri *et al.*, 2009; Sowmya *et al*., 2010; Trombelli *et al.*, 2010; Singh *et al.*, 2012a,b). The mean ages of patients ranged from 41 to 51 yrs, and the average percentage of women, if reported, ranged from 29% to 70%. The number of patients randomized *per* trial ranged from 10 to 124. Smokers were explicitly included in 5 studies, were excluded in 7 studies and were not reported in 5 of the remaining studies. Six trials explicitly included patients with chronic periodontitis only. Ten trials reported morphology of

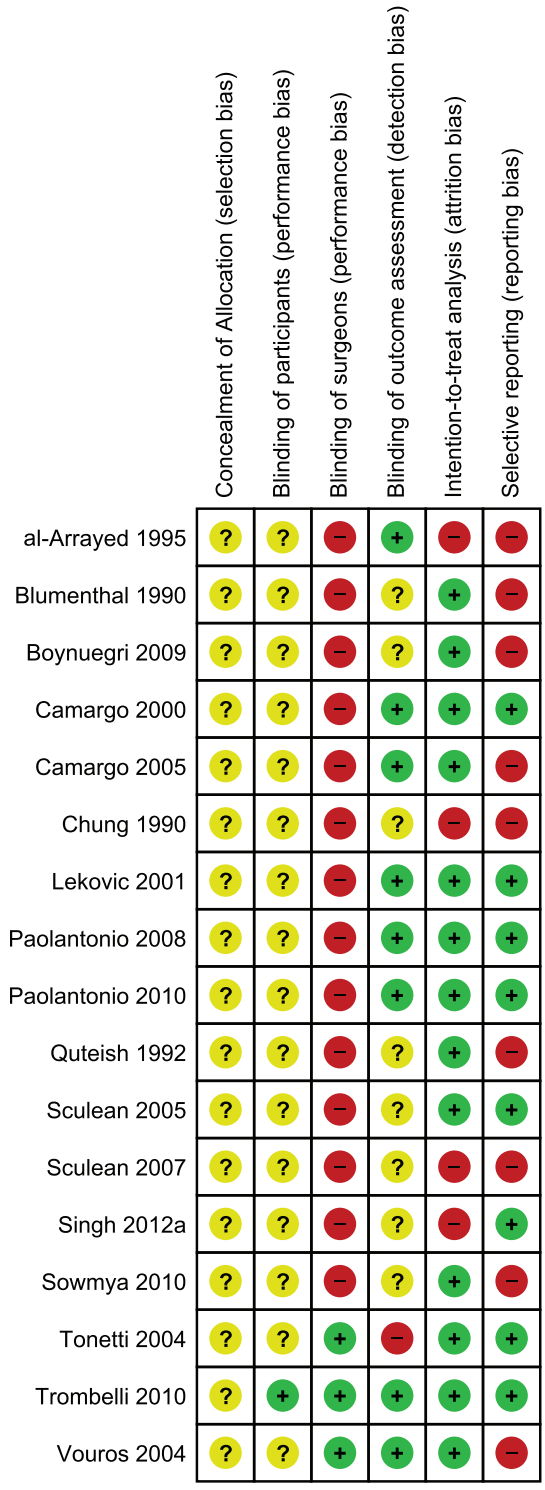

Figure 1. Methodological characteristics of included trials. (+) low risk of bias, (?) unclear, and (–) high risk of bias on a specific item.

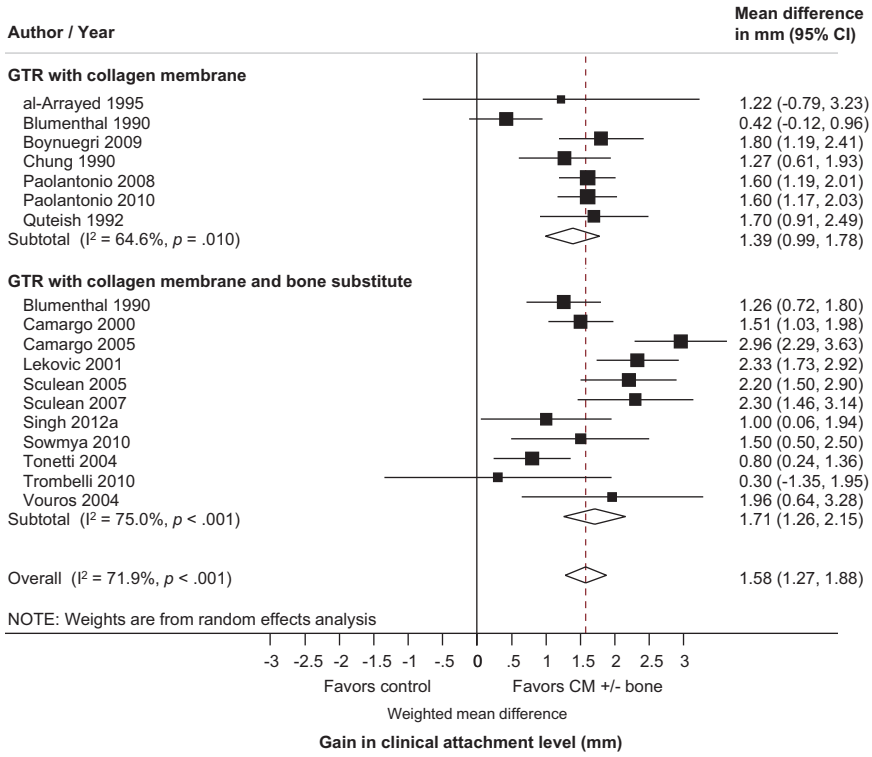

Figure 2. Forest plot of weighted mean differences in gain in clinical attachment level expressed in mm in 18 comparisons from 17 trials.

infrabony defects: 1 trial considered three-wall defects only, and in 1 trial most infrabony lesions showed a three-wall configuration; in 8 trials, the majority of infrabony lesions represented two-wall defects. Two trials explicitly reported that some infrabony defects displayed the concomitant presence of furcation lesions. Initial furcation involvement (degree I) was present in 4 out of 38 defects in the trial by al-Arrayed *et al.* (1995) and in 4 out of 52 defects in Quteish and Dolby (1992), with equal distribution of furcation-involved defects in both trial arms. Nine trials used a parallel group design, and the remaining trials used a split-mouth design. Eight trials had follow-up durations of 6 mos, 1 trial had a follow-up period of 9 mos, 7 trials had a follow-up period of one yr, and 1 trial reported outcomes up to 60 mos. All studies were conducted in a single-center university setting except for 1 trial, which was multi-centric, conducted at a university and in private practices.

Six trials tested OFD against CM alone, 10 trials tested OFD against CM and bone substitutes, and 1 trial tested OFD against CM with and without bone substitutes. Porcine-derived CM were used in 7 trials, human CM were tested in 4 trials, and 4 trials evaluated non-porcine-derived xenogen CM. Two trials did not declare the origin of membranes used. Thirteen trials used sulcular incisions on the mucoperiosteal flap to access the infrabony defect, 3 applied papilla preservation techniques, and 1 trial did not report on flap design. Appendix Tables 4 and 5 list further clinical trial characteristics.

Fig. 1 and Appendix Table 6 present the methodological characteristics of trials. In none of the trials was the concealment of allocation described in sufficient detail to allow for any judgment on the potential risk of bias. Only 2 trials stated that randomization envelopes were used, but the trialists did not describe whether these were opaque and consecutively numbered (Tonetti *et al.*, 2004; Vouros *et al.*, 2004). One trial reported blinding of patients, 2 trials reported adequate blinding of surgeons (*i.e.*, revealing treatment code only after the preparation of mucoperiosteal flaps and defect debridement), and 8 out of 17 trials reported blinding of outcome assessors. Thirteen trials had analyzed all patients according to the intention-to-treat principle, and 2 trials had sample sizes considered sufficiently large for clinically important treatment effects of 0.8 standard deviation units to be detected. Eight trials addressed all outcomes mentioned in the methods section in either the results or discussion section, but in the remaining 9 trials, selective outcome reporting was found for 1 or more outcomes.

Effects of Interventions

Tooth loss

None of the trials explicitly assessed tooth loss as an outcome. One trial incidentally reported 2 lost teeth, both in the OFD trial arm: 1 was extracted on request by the patient due to lack of improvement in tooth mobility, the other due to an accident (Tonetti *et al.*, 2004).

Gain in clinical attachment level (CAL)

All included trials reported on change in attachment level. The overall analysis (Fig. 2) shows that GTR with bioabsorbable CM had a greater mean CAL gain compared with OFD, as indicated by a mean difference of 1.58 mm (95% CI, 1.27 to 1.88). An I^2 of 71.9% indicated a high degree of between-trial heterogeneity (p for heterogeneity < .001; Fig. 2), and an inspection of the funnel plot suggested a lack of non-significant results from small trials in the white area (Appendix Fig. 2). Subgroup analysis of trials reporting on CM alone showed a WMD in gain in CAL of 1.39 mm (95% CI, 0.99 to 1.78), whereas the combination of CM and bone substitutes yielded a WMD of 1.71 mm (95% CI, 1.26 to 2.15) when compared with OFD only. Differences between the two subgroups were not statistically significant (p for interaction, .31).

Fig. 3 shows results from stratified analyses. Estimates varied to some extent, according to types of different characteristics, but CIs overlapped considerably between strata, and p values for interaction were all negative. Thirteen trials contributed to the analysis of a linear association between the percentage of smokers and gain in CAL, and 11 trials contributed to the analysis on an association between the percentage of three-wall involvement and gain in CAL. We found little

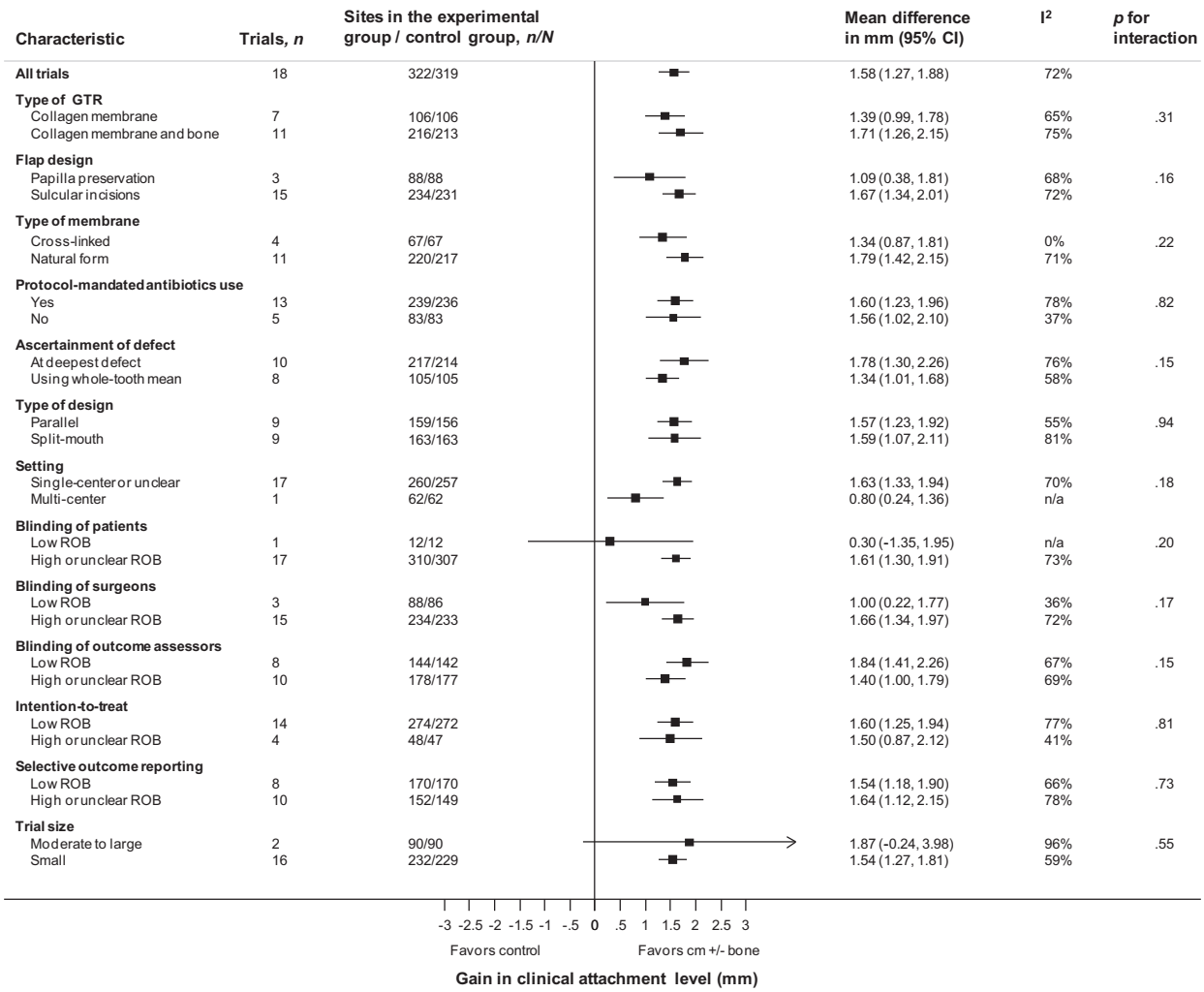

Figure 3. Results of stratified analyses of the gain in clinical attachment level. Note: n/a = not applicable.

evidence for a linear association between these characteristics and treatment effect (p from meta-regression, .43 and .81, respectively).

Probing pocket depth (PPD) reduction

Sixteen studies reported on changes in probing pocket depths. The analysis (Fig. 4) suggested that GTR with bioabsorbable CM had a greater mean reduction in PPD than did OFD, with a WMD of 1.52 mm (95% CI, 1.18 to 1.86). Subgroup analysis of studies showed that GTR with CM alone reduced PPD 1.66 mm more than did OFD (95% CI, 0.99 to 2.33) on average, while the combination of GTR with bone substitutes reduced PPD by 1.44 mm (95% CI, 1.04 to 1.85, p for interaction, .56).

Gingival recession (Rec)

Twelve studies assessed gingival recession as an outcome. The pooled estimate revealed no statistically significant difference between GTR (with or without the application of bone substitutes) and OFD (Fig. 5). The overall WMD was -0.06 (95% CI, -0.18 to 0.06). Treatment effects appeared more pronounced with GTR and bone substitution than with GTR alone, with a borderline p for interaction of .056.

Clinical and radiographic hard-tissue fill (HTF)

Fig. 6A shows results from meta-analyses of all the 8 studies that contributed outcomes for clinical hard-tissue fill. The results demonstrated that GTR improved clinical HTF over OFD, with a WMD of 2.22 mm (95% CI, 1.54 to 2.90). The combination of GTR and bone substitutes was associated with larger treatment effects than with GTR alone (p for interaction, .004). Radiographic hard-tissue fill was assessed in 4 trials, with an overall effect size of 2.35 standard deviation units (95% CI, 1.68 to 3.03). No differences were detected between GTR with CM alone and GTR with CM in combination with bone substitutes, when compared with OFD (p for interaction, .70) (Fig. 6B).

Post-operative complications: wound infection and membrane exposure

Thirteen trials reported that no wound infections had occurred, neither in experimental groups (216 teeth in 192 patients) nor in

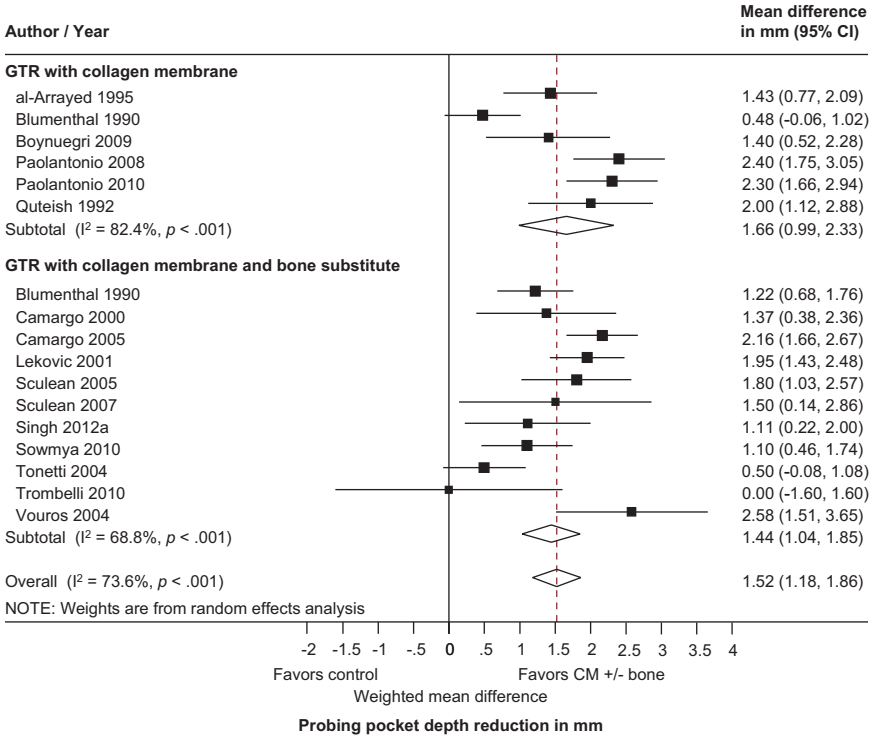

Figure 4. Forest plot of weighted mean differences in probing pocket depth reduction expressed in mm in 17 comparisons from 16 trials.

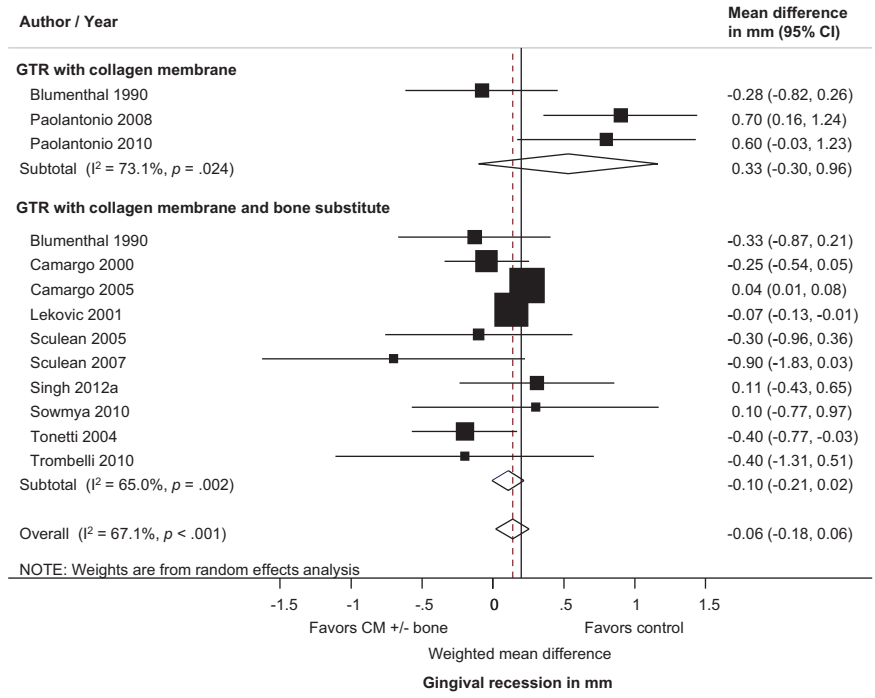

Figure 5. Forest plot of weighted mean differences in gingival recession expressed in mm in 13 comparisons from 12 trials.

control groups (216 teeth in 193 patients). Membrane exposure was reported in 3 trials of CM alone and occurred in a median of 24% of patients (range, 0% to 29%), and in 9 trials of CM with bone substitute, with a median percentage of patients with membrane exposure of 11% (range, 0% to 43%) (Appendix Fig. 3).

DISCUSSION

The present meta-analysis showed that, in infrabony defects, GTR with bioabsorbable CM barriers, either alone or in association with bone substitutes, yielded more beneficial effects than OFD for our primary outcome CAL gain. The overall weighted mean difference was 1.58 mm. However, there were no data available for the other primary outcome, "tooth loss". Analysis of secondary outcomes demonstrated that reduction of PPD was greater in GTR with CM compared with OFD (WMD of 1.52 mm), as was the increase in clinical and radiographic defect fill, which showed WMDs of 2.22 mm and 2.35 mm, respectively. We did not detect differences between experimental and control interventions for gingival recession change. In addition, we stratified the analysis by the use of bone substitutes in the experimental group (trials of GTR with CM alone *vs*. trials of GTR with CM and bone substitutes). Even though the effects of CM were larger in trials with, as compared with trials without bone substitutes, the non-significant *p* value for interaction indicated that this difference could be a chance finding. This information may bear clinical relevance, since it indicates that GTR with the combination of CM and bone substitutes may not additionally improve the outcomes compared with the use of CM alone and is in agreement with findings from previous systematic reviews (Murphy and Gunsolley, 2003). Nonetheless, caution is indicated, since the majority of the defects in our meta-analysis were self-contained (*e.g.*, they displayed a two- to three-wall configuration), thus possibly preventing membrane collapse and diminishing the need for space-maintaining bone substitutes. Although our meta-regression analysis did not show any association between morphology and treatment outcomes, such an association cannot be ruled out. Previous studies have suggested that non-contained (*e.g.*, displaying one-wall configuration) infrabony defects may yield better clinical outcomes with the combination of CM and bone substitutes (Paolantonio, 2002; Cortellini and Tonetti, 2005). Regarding adverse healing outcomes, no study observed wound infections

in the post-surgical phase in either treatment groups. In contrast, of the 11 trials that reported on membrane exposure, 7 observed this kind of untoward event. Taken together, these findings indicate that, despite the fact that treatment of infrabony periodontal defects by means of GTR with CM (with or without bone substitutes) resulted in superior clinical outcomes compared with those achieved with OFD alone, we still cannot ascertain whether this regenerative approach may indeed prevent tooth loss.

Factors that have been repeatedly suggested to have a potential influence on wound-healing are membrane exposure and subsequent bacterial colonization (Selvig *et al.*, 1992; Nowzari *et al.*, 1995; Ling *et al.*, 2003). However, in the present study, it was not feasible to analyze the effect of membrane exposure on clinical outcomes, because subgroup outcome data were not available in the trials. However, the present findings are in agreement with those from a previous systematic review (Needleman *et al.*, 2006), which failed to demonstrate an effect of barrier exposure on healing, despite frequently reported exposure.

There are several other limitations. The included trials were generally of poor methodological quality and reporting. None of the included trials reported on the number of patients screened for inclusion. Most studies failed to report on the time point of communicating treatment allocation to surgeons. Only 3 studies of parallel design reported this. Therefore, we are uncertain about performance bias causing an overestimation of treatment effects if surgeons consciously or unconsciously performed better at flap preparation and defect debridement in experimental groups than in control groups. We generally found a high degree of heterogeneity, which we were unable to explain. This means that the true magnitude of treatment effects remains unclear. Inspection of the funnel plot suggested a selective lack of non-significant results for small trials with large standard errors. This is likely to have introduced bias due to small study effects, even though the funnel plot did not satisfy the conventional criteria for asymmetry.

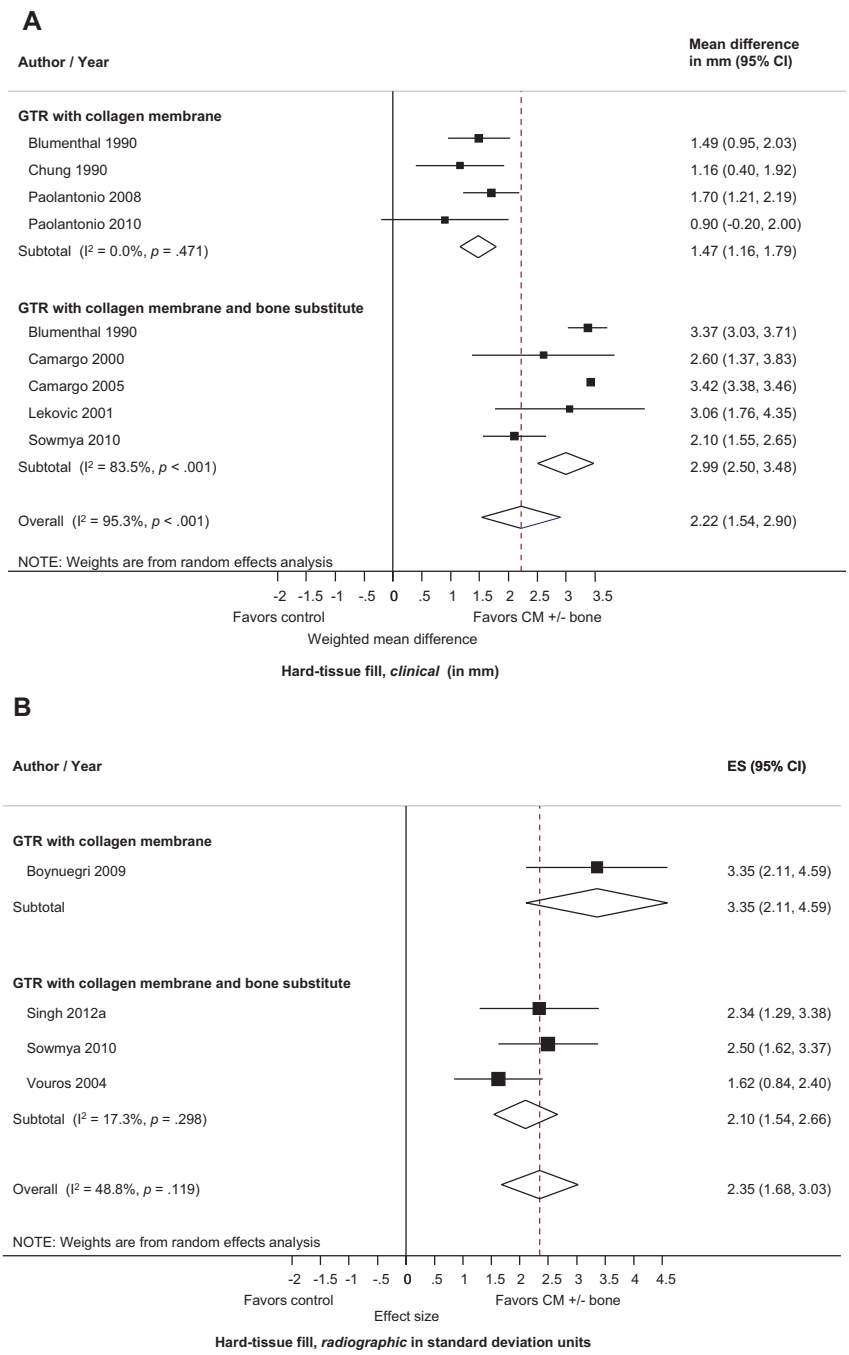

Figure 6. Forest plot of weighted mean differences in hard-tissue fill. **Panel A**: *clinical,* expressed in mm in 9 comparisons from 8 trials. **Panel B**: *radiographic,* expressed in standard deviation units in 4 trials.

It is unfortunate that none of the included trials reported on our primary outcome, "tooth loss". Only 1 of the included trials would have a sufficiently long follow-up of 5 yrs to allow for the clinically meaningful interpretation of effects of different treatments on tooth loss. All other trials were limited to a follow-up of 6 to 12 mos. When follow-up time is limited in clinical trials, surrogate endpoints, such as clinical attachment loss, are substitutes for true, patient-relevant clinical endpoints, such as tooth loss (Hujoel, 2004). However, unless additional long-term trials ascertain this outcome, it remains difficult in our view to understand whether CM indeed enhance tooth retention. Conversely, the inclusion of 5-year results from the trial by Sculean *et al.* (2007) could have biased results for the other primary outcome, CAL gain, toward the null, since changes in

CAL beyond 1 yr could be mainly a function of SPT rather than of the allocated interventions. A *post hoc* sensitivity analysis based on 1-year data from this trial showed much the same results, however (data available on request).

We were unable to satisfactorily address 2 clinically relevant questions: whether defect configuration (Tonetti *et al*., 1993) and whether smoking (Cortellini and Tonetti, 2004) affect regenerative treatment effects. Our preliminary results of aggregate level data do not point toward an association of treatment effects with these characteristics. However, we could have missed associations because of the ecological fallacy (Piantadosi *et al*., 1988). To address these issues properly, a meta-analysis of individual patient data, infeasible given the resource constraints, would be required to perform proper subgroup analyses in smokers and non-smokers and across different defect configurations.

This is the first systematic review to analyze the outcomes of GTR with CM as compared with OFD, without considering any other types of barrier membranes. Combining trials of different barrier membranes, Needleman *et al*. (2006) reported a weighted mean difference of 1.22 mm for our primary outcome of CAL gain (95% CI 0.80 to 1.64), favoring GTR procedures with membranes over OFD. Murphy and Gunsolley (2003) reported mean differences in CAL gain in a subgroup of trials with CM compared with OFD to be around 0.95 mm. Our estimate tends to be slightly more beneficial, but confidence intervals from our and previous meta-analyses overlap, which indicates that our results are compatible with those reported in previous publications.

In conclusion, GTR with CM, with or without bone substitutes, may lead to improved clinical outcomes compared with those achieved with OFD alone. Our meta-analysis lends support to this concept in the treatment of infrabony periodontal defects.

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REFERENCES

al-Arrayed F, Adam S, Moran J, Dowell P (1995). Clinical trial of cross-linked human type I collagen as a barrier material in surgical periodontal treatment. *J Clin Periodontol* 22:371-379.

Blumenthal N, Steinberg J (1990). The use of collagen membrane barriers in conjunction with combined demineralized bone-collagen gel implants in human infrabony defects. *J Periodontol* 61:319-327.

Boynuegri D, Ozcan G, Senel S, Uc D, Uraz A, Ogus E, *et al*. (2009). Clinical and radiographic evaluations of chitosan gel in periodontal intraosseous defects: a pilot study. *J Biomed Mater Res B Appl Biomater* 90:461-466.

Bunyaratavej P, Wang HL (2001). Collagen membranes: a review. *J Periodontol* 72:215-229.

Camargo PM, Lekovic V, Weinlaender M, Nedic M, Vasilic N, Wolinsky LE, *et al*. (2000). A controlled re-entry study on the effectiveness of bovine porous bone mineral used in combination with a collagen membrane of porcine origin in the treatment of intrabony defects in humans. *J Clin Periodontol* 27:889-896.

Camargo PM, Lekovic V, Weinlaender M, Vasilic N, Madzarevic M, Kenney EB (2005). A reentry study on the use of bovine porous bone mineral, GTR, and platelet-rich plasma in the regenerative treatment of intrabony defects in humans. *Int J Periodontics Restorative Dent* 25:49-59.

Camelo M, Nevins ML, Schenk RK, Simion M, Rasperini G, Lynch SE, *et al*. (1998). Clinical, radiographic, and histologic evaluation of human periodontal defects treated with Bio-Oss and Bio-Gide. *Int J Periodontics Restorative Dent* 18:321-331.

Chung KM, Salkin LM, Stein MD, Freedman AL (1990). Clinical evaluation of a biodegradable collagen membrane in guided tissue regeneration. *J Periodontol* 61:732-736.

Cohen J (1988). Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum.

Cortellini P, Tonetti MS (2004). Long-term tooth survival following regenerative treatment of intrabony defects. *J Periodontol* 75:672-678.

Cortellini P, Tonetti MS (2005). Clinical performance of a regenerative strategy for intrabony defects: scientific evidence and clinical experience. *J Periodontol* 76:341-350.

Gottlow J, Nyman S, Lindhe J, Karring T, Wennstrom J (1986). New attachment formation in the human periodontium by guided tissue regeneration. Case reports. *J Clin Periodontol* 13:604-616.

Heitz-Mayfield L, Tonetti MS, Cortellini P, Lang NP (2006). Microbial colonization patterns predict the outcomes of surgical treatment of intrabony defects. *J Clin Periodontol* 33:62-68.

Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003). Measuring inconsistency in meta-analyses. *BMJ* 327:557-560.

Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, *et al*. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928.

Hujoel PP (2004). Endpoints in periodontal trials: the need for an evidence-based research approach. *Periodontology* 2000 36:196-204.

Juni P, Altman DG, Egger M (2001). Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 323:42-46.

Lekovic V, Camargo PM, Weinlaender M, Kenney EB, Vasilic N (2001). Combination use of bovine porous bone mineral, enamel matrix proteins, and a bioabsorbable membrane in intrabony periodontal defects in humans. *J Periodontol* 72:583-589.

Linares A, Cortellini P, Lang NP, Suvan J, Tonetti MS (2006). Guided tissue regeneration/deproteinized bovine bone mineral or papilla preservation flaps alone for treatment of intrabony defects. II: Radiographic predictors and outcomes. *J Clin Periodontol* 33:351-358.

Ling LJ, Hung SL, Lee CF, Chen YT, Wu KM (2003). The influence of membrane exposure on the outcomes of guided tissue regeneration: clinical and microbiological aspects. *J Periodontal Res* 38:57-63.

Murphy KG, Gunsolley JC (2003). Guided tissue regeneration for the treatment of periodontal intrabony and furcation defects. A systematic review. *Ann Periodontol* 8:266-302.

Needleman IG, Worthington HV, Giedrys-Leeper E, Tucker RJ (2006). Guided tissue regeneration for periodontal infra-bony defects. *Cochrane Database Syst Rev* 2:CD001724.

Nowzari H, Matian F, Slots J (1995). Periodontal pathogens on polytetrafluoroethylene membrane for guided tissue regeneration inhibit healing. *J Clin Periodontol* 22:469-474.

Nyman S, Lindhe J, Karring T, Rylander H (1982). New attachment following surgical treatment of human periodontal disease. *J Clin Periodontol* 9:290-296.

Paolantonio M (2002). Combined periodontal regenerative technique in human intrabony defects by collagen membranes and anorganic bovine bone. A controlled clinical study. *J Periodontol* 73:158-166.

Paolantonio M, Perinetti G, Dolci M, Perfetti G, Tete S, Sammartino G, *et al*. (2008). Surgical treatment of periodontal intrabony defects with calcium sulfate implant and barrier versus collagen barrier or open flap debridement alone: a 12-month randomized controlled clinical trial. *J Periodontol* 79:1886-1893.

Paolantonio M, Femminella B, Coppolino E, Sammartino G, D'Arcangelo C, Perfetti G, *et al*. (2010). 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* 81:1587-1595.

Papapanou PN, Tonetti MS (2000). Diagnosis and epidemiology of periodontal osseous lesions. *Periodontol* 2000 22:8-21.

Parodi R, Carusi G, Santarelli G, Nanni F, Pingitore R, Brunel G (1997). Guided tissue regeneration employing a collagen membrane in a human periodontal bone defect: a histologic evaluation. *Int J Periodontics Restorative Dent* 17:282-291.

Piantadosi S, Byar DP, Green SB (1988). The ecological fallacy. *Am J Epidemiol* 127:893-904.

Pihlstrom BL, McHugh RB, Oliphant TH, Ortiz-Campos C (1983). Comparison of surgical and nonsurgical treatment of periodontal disease. A review of current studies and additional results after 61/2 years. *J Clin Periodontol* 10:524-541.

Quteish D, Dolby AE (1992). The use of irradiated-crosslinked human collagen membrane in guided tissue regeneration. *J Clin Periodontol* 19:476-484.

Reichenbach S, Sterchi R, Scherer M, Trelle S, Burgi E, Burgi U, *et al*. (2007). Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med* 146:580-590.

Rücker G, Schwarzer G, Carpenter JR, Schumacher M (2008). Undue reliance on I(2) in assessing heterogeneity may mislead. *BMC Med Res Methodol* 8:79.

Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S (2012). Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med* 157:180-191.

Sculean A, Berakdar M, Chiantella GC, Donos N, Arweiler NB, Brecx M (2003). Healing of intrabony defects following treatment with a bovine-derived xenograft and collagen membrane. A controlled clinical study. *J Clin Periodontol* 30:73-80.

Sculean A, Stavropoulos A, Windisch P, Keglevich T, Karring T, Gera I (2004). Healing of human intrabony defects following regenerative periodontal therapy with a bovine-derived xenograft and guided tissue regeneration. *Clin Oral Investig* 8:70-74.

Sculean A, Chiantella GC, Windisch P, Arweiler NB, Brecx M, Gera I (2005). Healing of intra-bony defects following treatment with a composite bovine-derived xenograft (Bio-Oss Collagen) in combination with a collagen membrane (Bio-Gide PERIO). *J Clin Periodontol* 32:720-724.

Sculean A, Schwarz F, Chiantella GC, Donos N, Arweiler NB, Brecx M, *et al*. (2007). Five-year results of a prospective, randomized, controlled study evaluating treatment of intra-bony defects with a natural bone mineral and GTR. *J Clin Periodontol* 34:72-77.

Selvig KA, Kersten BG, Chamberlain AD, Wikesjö UM, Nilvéus RE (1992). Regenerative surgery of intrabony periodontal defects using ePTFE barrier membranes: scanning electron microscopic evaluation of retrieved membranes versus clinical healing. *J Periodontol* 63:974-978.

Singh VP, Nayak DG, Uppoor AS, Shah D (2012a). Nano-crystalline hydroxyapatite bone graft combined with bioresorbable collagen membrane in the treatment of periodontal intrabony defects: a randomized controlled clinical trial. *J Indian Soc Periodontol* 16:562-568.

Singh VP, Nayak DG, Uppoor AS, Shah D (2012b). Clinical and radiographic evaluation of nano-crystalline hydroxyapatite bone graft (Sybograf) in combination with bioresorbable collagen membrane (Periocol) in periodontal intrabony defects. *Dent Res J (Isfahan)* 9:60-67.

Sowmya NK, Tarun Kumar AB, Mehta DS (2010). 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* 14:23-29.

Stahl SS, Froum S, Tarnow D (1990). Human histologic responses to guided tissue regenerative techniques in intrabony lesions. Case reports on 9 sites. *J Clin Periodontol* 17:191-198.

Sterne JA, Egger M (2001). Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 54:1046-1055.

Sweeting MJ, Sutton AJ, Lambert PC (2004). What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 23:1351-1375.

Thompson SG, Sharp SJ (1999). Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 18:2693-2708.

Tonetti MS, Pini-Prato G, Cortellini P (1993). Periodontal regeneration of human intrabony defects. IV. Determinants of healing response. *J Periodontol* 64:934-940.

Tonetti MS, Prato GP, Cortellini P (1996). Factors affecting the healing response of intrabony defects following guided tissue regeneration and access flap surgery. *J Clin Periodontol* 23:548-556.

Tonetti MS, Cortellini P, Lang NP, Suvan JE, Adriaens P, Dubravec D, *et al*. (2004). 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* 31:770-776.

Trombelli L, Simonelli A, Pramstraller M, Wikesjö UM, Farina R (2010). Single flap approach with and without guided tissue regeneration and a hydroxyapatite biomaterial in the management of intraosseous periodontal defects. *J Periodontol* 81:1256-1263.

Vouros I, Aristodimou E, Konstantinidis A (2004). Guided tissue regeneration in intrabony periodontal defects following treatment with two bioabsorbable membranes in combination with bovine bone mineral graft. A clinical and radiographic study. *J Clin Periodontol* 31:908-917.

CLINICAL REVIEW

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Absorbable Collagen Membranes for Periodontal Regeneration: A Systematic Review

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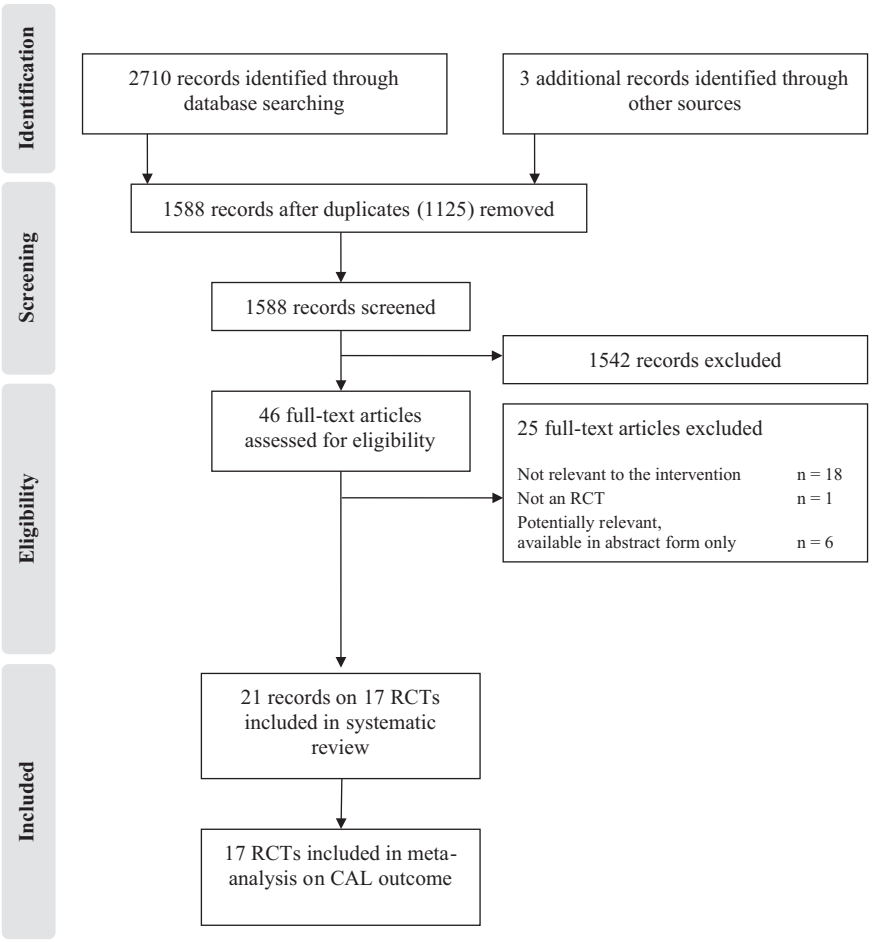
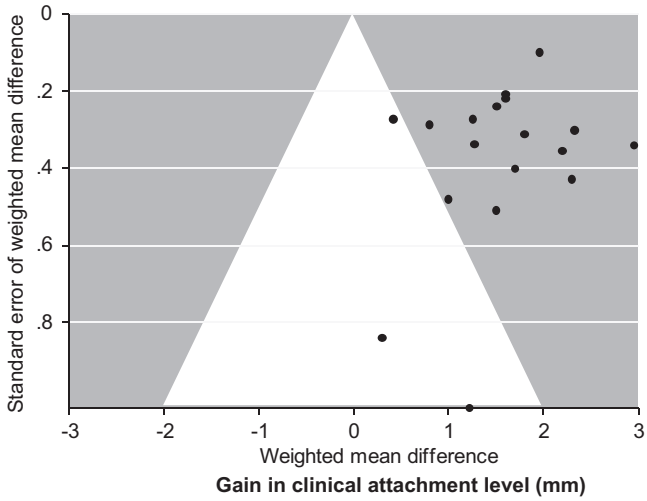
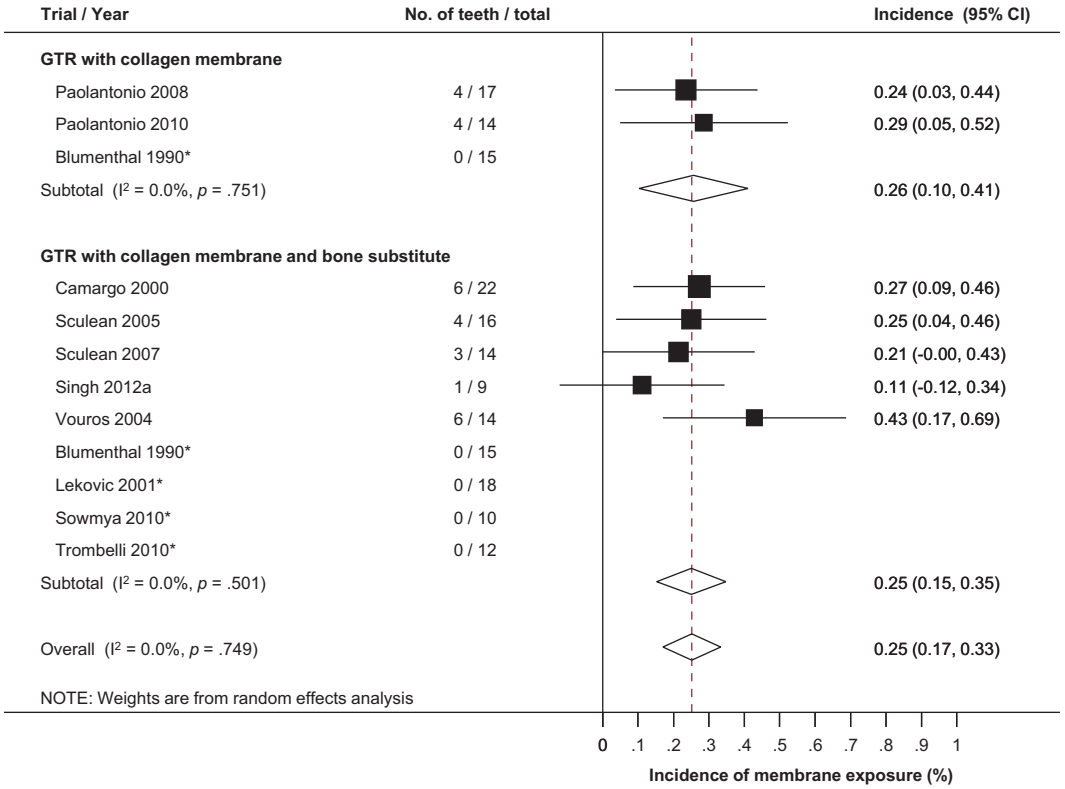
APPENDIX



Appendix Figure 1. Flow diagram. RCT = randomized, controlled trial; CAL = clinical attachment level.



Appendix Figure 2. Contour-enhanced funnel plot for effects on the gain of clinical attachment level. Contour areas display areas of significance at $p \leq .05$ (gray) and non-significance (white).



Appendix Figure 3. Incidence of membrane exposure. Note: *Comparisons with 0 events in both trial arms did not contribute to the analysis.

Appendix Table 1. Search Terms for MEDLINE and EMBASE

MEDLINE*	EMBASE*
Search terms related to periodontitis	**Search terms related to periodontitis**
1. in*ra*bon* defect*.mp.	1. exp periodontitis/ or exp periodontal disease/
2. in*ra-bon* defect*.mp.	2. in*ra*bon* defect*.mp.
3. intra-osseous.mp.	3. in*ra-bon* defect*.mp.
4. intraosseous.mp.	4. intra-osseous.mp.
5. (angular adj1 defect*).mp.	5. intraosseous.mp.
6. (vertical adj1 defect*).mp.	6. (angular adj1 defect*).mp.
7. exp periodontitis/	7. (vertical adj1 defect*).mp.
8. exp periodontal disease/	**Search terms related to guided tissue regeneration**
Search terms related to guided tissue regeneration	8. exp tissue regeneration/
9. exp tissue regeneration/	9. guided tissue regeneration.mp.
10. guided tissue regeneration.mp.	10. gtr.mp.
11. gtr.mp.	11. resorbable membrane*.mp.
12. barrier* membrane*.mp.	12. (resorbable adj10 membrane*).mp.
13. (resorbable adj10 membrane*).mp.	13. (periodontal adj5 regeneration).mp.
14. (bioabsorb$ adj10 membrane*).mp.	14. exp xenograft/
15. (periodontal adj5 regeneration).mp.	15. (collagen adj1 membrane*).mp.
16. exp xenograft/	16. collagen barrier*.mp.
17. (collagen adj1 membrane*).mp.	17. xenograft$.mp.
18. collagen barrier*.mp.	18. (bioabsorb$ adj10 membrane*).mp.
19. xenograft$.mp.	19. (bioabsorb$ adj10 barrier*).mp.
20. graft*.ti,ab.	20. barrier membrane*.mp.
21. bon* substitut*.mp.	21. exp bone graft/
22. exp Bone Substitutes/	22. graft$.ti,ab.
23. exp Biocompatible Materials/	23. bon* substitut*.mp.
24. biomaterial*.mp.	24. exp biomaterial/
	25. biomaterial*.mp.
Search terms related to design	**Search terms related to design**
25. randomized controlled trial.pt.	26. random$.tw.
26. controlled clinical trial.pt.	27. factorial$.tw.
27. randomized.ab.	28. (crossover$ or cross-over$).tw.
28. placebo.ab.	29. placebo$.tw.
29. drug therapy.fs.	30. (doubl$ adj blind$).tw.
30. randomly.ab.	31. (singl$ adj blind$).tw.
31. trial.ab.	32. assign$.tw.
32. groups.ab.	33. allocat$.tw.
	34. volunteer$.tw.
	35. Crossover Procedure.sh.
	36. Double-blind Procedure.sh.
	37. Randomized Controlled Trial.sh.
	38. Single-blind Procedure.sh.
Combining terms	**Combining terms**
33. or/1-8	39. or/1-7
34. or/9-24	40. or/8-25
35. or/27-34	41. or/26-38
36. and/25-26,37	42. and/26-27,45
37. exp animals/ not humans.sh.	43. animal/
38. 36 not 37	44. animal/ and human/
39. limit 38 to yr="1982 -Current"	45. 43 not 44
	46. 42 not 44
	47. limit 46 to yr="1982 -Current"

* MEDLINE and EMBASE searched through the OVID platform on January 8, 2013.

Appendix Table 2. Search Terms for the Cochrane Databases

	Cochrane[a]
Search terms related to periodontitis	
#1	MeSH descriptor: [Periodontitis] explode all trees
#2	MeSH descriptor: [Periodontal Diseases] explode all trees
#3	vertical near/1 defect*:ti,ab,kw (Word variations have been searched)
#4	angular near/1 defect*:ti,ab,kw (Word variations have been searched)
#5	intraosseous:ti,ab,kw (Word variations have been searched)
#6	"intra osseous":ti,ab,kw (Word variations have been searched)
#7	in*ra bon* defect*:ti,ab,kw (Word variations have been searched)
#8	in*ra*bon* defect*:ti,ab,kw (Word variations have been searched)
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
Search terms related to guided tissue regeneration	
#10	MeSH descriptor: [Guided Tissue Regeneration] explode all trees
#11	guided tissue regeneration:ti,ab,kw (Word variations have been searched)
#12	gtr:ti,ab,kw (Word variations have been searched)
#13	barrier* membrane*:ti,ab,kw (Word variations have been searched)
#14	resorbable near/5 membrane*:ti,ab,kw (Word variations have been searched)
#15	periodontal near/5 regeneration:ti,ab,kw (Word variations have been searched)
#16	bioabsorb* near/5 membrane*:ti,ab,kw (Word variations have been searched)
#17	collagen near/1 membrane*:ti,ab,kw (Word variations have been searched)
#18	collagen barrier*:ti,ab,kw (Word variations have been searched)
#19	"graft":ti,ab,kw (Word variations have been searched)
#20	bon* substitut*:ti,ab,kw (Word variations have been searched)
#21	biomaterial*:ti,ab,kw (Word variations have been searched)
#22	MeSH descriptor: [Bone Substitutes] explode all trees
#23	MeSH descriptor: [Biocompatible Materials] explode all trees
#24	MeSH descriptor: [Transplantation, Heterologous] explode all trees
Combining terms	
#25	#10 or #11 or #12 or #13 or #14
#26	#15 or #16 or #17 or #18 or #19 or #20 or #21
#27	#22 or #23 or #24
#28	#25 or #26 or #27
#29	#9 and #28

[a]Searches in all databases embedded in Cochrane, including the Central Register of Controlled Trials, DARE, and Cochrane reviews search, performed on January 9, 2013.

Appendix Table 3. List of Excluded Reports

Report	Reason for Exclusion
Aimetti *et al.* (2005)	Intervention does not fit
Batista *et al.* (1999)	Intervention does not fit
Bratthall *et al.* (1996)	No full text available
Camargo *et al.* (2001)	No full text available
Camargo *et al.* (2009)	Intervention does not fit
Christgau *et al.* (1996)	No full text available
Christgau *et al.* (1997)	No full text available
Christgau *et al.* (2003)	Intervention does not fit
Cortellini *et al.* (1996a)	Study design does not fit
Cortellini *et al.* (1996b)	Intervention does not fit
Cortellini *et al.* (1998)	Intervention does not fit
Joly *et al.* (2000)	No full text available
Joly *et al.* (2002)	Intervention does not fit
Keles *et al.* (2006)	Intervention does not fit
Kim *et al.* (1996)	Intervention does not fit
Kuru *et al.* (2004)	Intervention does not fit
Lekovic *et al.* (2000)	No full text available
Loos *et al.* (2002)	Intervention does not fit
Proestakis *et al.* (1992)	Intervention does not fit
Sculean *et al.* (2001)	Intervention does not fit
Sculean *et al.* (2004)	Intervention does not fit
Sculean *et al.* (2008)	Intervention does not fit
Stavropoulos *et al.* (2003)	Intervention does not fit
Tonetti *et al.* (1996)	Intervention does not fit
Tonetti *et al.* (1998)	Intervention does not fit

Appendix Table 3. References to Reports Excluded in This Review

Aimetti M, Romano F, Pigella E, Pranzini F, Debernardi C (2005). Treatment of wide, shallow, and predominantly 1-wall intrabony defects with a bioabsorbable membrane: a randomized controlled clinical trial. *J Periodontol* 76:1354-1361.

Batista EL Jr, Novaes AB Jr, Simonpietri JJ, Batista FC (1999). Use of bovine-derived anorganic bone associated with guided tissue regeneration in intrabony defects. Six-month evaluation at re-entry. *J Periodontol* 70:1000-1007.

Camargo PM, Lekovic V, Weinlaender M, Divnic-Resnik T, Pavlovic M, Kenney EB (2009). A surgical reentry study on the influence of platelet-rich plasma in enhancing the regenerative effects of bovine porous bone mineral and guided tissue regeneration in the treatment of intrabony defects in humans. *J Periodontol* 80:915-923.

Christgau M, Aslanidis C, Felden A, Hiller KA, Schmitz G, Schmalz G (2003). Influence of interleukin-1 gene polymorphism on periodontal regeneration in intrabony defects. *J Periodontal Res* 38:20-27.

Cortellini P, Paolo G, Prato P, Tonetti MS (1996a). Long-term stability of clinical attachment following guided tissue regeneration and conventional therapy. *J Clin Periodontol* 23:106-111.

Cortellini P, Pini Prato G, Tonetti MS (1996b). Periodontal regeneration of human intrabony defects with bioresorbable membranes. A controlled clinical trial. *J Periodontol* 67:217-223.

Cortellini P, Carnevale G, Sanz M, Tonetti MS (1998). Treatment of deep and shallow intrabony defects. A multicenter randomized controlled clinical trial. *J Clin Periodontol* 25:981-987.

Joly JC, Palioto DB, de Lima AF, Mota LF, Caffesse R (2002). Clinical and radiographic evaluation of periodontal intrabony defects treated with guided tissue regeneration. A pilot study. *J Periodontol* 73:353-359.

Keles GC, Cetinkaya BO, Isildak I, Koprulu H, Acikgoz G (2006). Levels of platelet activating factor in gingival crevice fluid following periodontal surgical therapy. *J Periodontal Res* 41:513-518.

Kim CK, Choi EJ, Cho KS, Chai JK, Wikesjo UM (1996). Periodontal repair in intrabony defects treated with a calcium carbonate implant and guided tissue regeneration. *J Periodontol* 67:1301-1306.

Kuru L, Griffiths GS, Petrie A, Olsen I (2004). Changes in transforming growth factor-beta1 in gingival crevicular fluid following periodontal surgery. *J Clin Periodontol* 31:527-533.

Loos BG, Louwerse PH, Van Winkelhoff AJ, Burger W, Gilijamse M, Hart AA, *et al.* (2002). Use of barrier membranes and systemic antibiotics in the treatment of intraosseous defects. *J Clin Periodontol* 29:910-921.

Proestakis G, Bratthall G, Söderholm G, Kullendorff B, Grondahl K, Rohlin M, *et al.* (1992). Guided tissue regeneration in the treatment of infrabony defects on maxillary premolars. A pilot study. *J Clin Periodontol* 19:766-773.

Sculean A, Windisch P, Chiantella GC, Donos N, Brecx M, Reich E (2001). Treatment of intrabony defects with enamel matrix proteins and guided tissue regeneration. A prospective controlled clinical study. *J Clin Periodontol* 28:397-403.

Sculean A, Donos N, Schwarz F, Becker J, Brecx M, Arweiler NB (2004). Five-year results following treatment of intrabony defects with enamel matrix proteins and guided tissue regeneration. *J Clin Periodontol* 31:545-549.

Sculean A, Kiss A, Miliauskaite A, Schwarz F, Arweiler NB, Hannig M (2008). Ten-year results following treatment of intra-bony defects with enamel matrix proteins and guided tissue regeneration. *J Clin Periodontol* 35:817-824.

Stavropoulos A, Karring ES, Kostopoulos L, Karring T (2003). Deproteinized bovine bone and gentamicin as an adjunct to GTR in the treatment of intrabony defects: a randomized controlled clinical study. *J Clin Periodontol* 30:486-495.

Tonetti MS, Prato GP, Cortellini P (1996). Factors affecting the healing response of intrabony defects following guided tissue regeneration and access flap surgery. *J Clin Periodontol* 23:548-556.

Tonetti MS, Cortellini P, Suvan JE, Adriaens P, Baldi C, Dubravec D, *et al.* (1998). 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* 69:1183-1192.

Appendix Table 4. Trial Descriptions

Trial	Design	No. of Trial Arms	No. of Study Centers	No. of Patients Randomized	No. of Teeth Involved	Follow-up Duration	Fraction of Females (%)	Mean Age (yrs)	Fraction of Smokers (%)	Type of Periodontitis	Morphology (walls)				Outcomes Included
											3	2	1	Combination	
al-Arrayed *et al.*, 1995	split-mouth	2	1	14	nr	6	7/14 (50%)	44	nr	Other	18/38	16/38	4/38	n/a	CAL; PPD
Blumenthal and Steinberg, 1990	split-mouth	5	1	10	71	12	4/10 (40%)	nr	nr	Other	19/71	25/71	3/71	24/71	CAL; PPD; REC; HTF clin; Membrane exp; Infection
Boynuegri *et al.*, 2009	parallel	4	1	20	nr	6	9/20 (45%)	nr	0/20 (0%)	Chronic	nr	nr	nr	nr	CAL; PPD; HTF Rx
Camargo *et al.*, 2000	split-mouth	2	nr	22	44	6	nr	43	14/22 (64%)	nr	11/44	33/44	0/44	n/a	CAL; PPD; REC; HTF clin; Membrane exp; Infection
Camargo *et al.*, 2005	split-mouth	2	1	28	56	6	12/28 (43%)	41	12/28 (43%)	Other	21/56	35/56	0/56	n/a	CAL; PPD; REC; HTF clin ; Infection
Chung *et al.*, 1990	split-mouth	2	1	15	30	12	8/15 (53%)	nr	nr	nr	nr	nr	nr	nr	CAL; PPD; HTF clin
Lekovic *et al.*, 2001	split-mouth	2	1	18	36	6	8/18 (44%)	42	12/18 (67%)	Other	11/36	25/36	0/36	n/a	CAL; PPD; REC; HTF clin; Membrane exp; Infection
Paolantonio *et al.*, 2008	parallel	3	1	51	51	12	29/51 (57%)	46	0/51 (0%)	Chronic	nr	nr	nr	nr	CAL; PPD; REC; HTF clin; Membrane exp; Infection
Paolantonio *et al.*, 2010	parallel	3	1	42	42	12	22/42 (52%)	48	0/42 (0%)	Chronic	nr	nr	nr	nr	CAL; PPD; REC; HTF clin; Membrane exp; Infection
Quteish and Dolby, 1992	split-mouth	2	1	19	52	6	nr	nr	nr	Other	nr	nr	nr	nr	CAL; PPD; Infection
Sculean *et al.*, 2005	parallel	2	1	32	32	12	17/32 (53%)	nr	0/32 (0%)	nr	5/32	18/32	9/32	n/a	CAL; PPD; REC; HTF clin; Membrane exp; Infection
Sculean *et al.*, 2007	parallel	2	1	28	28	60	15/28 (54%)	nr	5/28 (18%)	Chronic	4/28	15/28	9/28	n/a	CAL; PPD; REC; HTF clin; Membrane exp; Infection
Singh *et al.*, 2012a	parallel	2	1	16	20	6	7/16 (44%)	nr	0/16 (0%)	nr	0/18	12/18	0/18	6/18	CAL; PPD; REC; HTF Rx; Membrane exp; Infection
Sowmya *et al.*, 2010	split-mouth	2	1	10	20	9	7/10 (70%)	46	0/10 (0%)	nr	20/20	0/20	0/20	0/20	CAL; PPD; REC; HTF clin; HTF Rx; Membrane exp; Infection
Tonetti *et al.*, 2004	parallel	2	10	124	124	12	nr/124 (62%)	50	nr	Chronic	nr	nr	nr	n/a	CAL; PPD; REC; HTF clin
Trombelli *et al.*, 2010	parallel	2	1	24	24	6	7/24 (29%)	51	2/24 (8%)	nr	6/24	11/24	7/24	n/a	CAL; PPD; REC; Membrane exp; Infection
Vouros *et al.*, 2004	parallel	3	1	34	40	12	23/34 (68)	nr	0/34 (0%)	Chronic	nr	nr	nr	n/a	CAL; PPD; HTF clin; HTF Rx; Membrane exp

nr = not reported; n/a = not applicable; CAL = clinical attachment level; PPD = probing pocket depth; REC = gingival recession; HTF clin = hard-tissue fill, clinical; HTF Rx = hard-tissue fill, radiographic; Membrane exp = membrane exposure

Appendix Table 5. Description of Trial Arms and Interventions

Trial	Included Trial Arms	Flap Design	Collagen Membrane (CM)	Bone Graft	Cross-linked Membrane	Protocol-mandated Antibiotic Use	Post-surgical Care Provided	Supportive Periodontal Therapy Provided	Ascertainment of Defect
al-Arrayed *et al.*, 1995	OFD *vs.* GTR CM	Sulcular incisions	Freeze-dried cross-linked human type I CM	n/a	yes	no	yes	yes	Unclear if measurements of the 6 sites were averaged, or if the deepest defect was used
Blumenthal and Steinberg, 1990	OFD *vs.* GTR CM *vs.* GTR CM + bone	Sulcular incisions	CM (source / brand not reported)	autolyzed antigen-extracted allogeneic freeze-dried bone - collagen gel implant	nr	yes	yes	yes	≥ 1 tooth *per* quadrant *per* patient was included in the analyses for each treatment modality; results were averaged
Boynuegri *et al.*, 2009	OFD *vs.* GTR CM	Sulcular incisions	CM (source / brand not reported) soaked in chitosan gel 1%	n/a	nr	yes	nr	nr	No report on number of teeth included *per* patient, or if measurements were averaged, or if only the deepest defects at baseline were considered
Camargo *et al.*, 2000	OFD *vs.* GTR CM + bone	Sulcular incisions	Porcine CM (Bio-Gide)	Cancellous bovine porous bone mineral (BPBM) granules (0.25-1.0 mm) (Bio-Oss)	no	yes	yes	yes	Adequate
Camargo *et al.*, 2005	OFD *vs.* GTR CM + bone	Sulcular incisions	Porcine CM (Bio-Gide)	Cancellous BPBM granules (0.25-1.00 mm) (Bio-Oss) and coagulated platelet-rich plasma	no	yes	yes	yes	Adequate
Chung *et al.*, 1990	OFD *vs.* GTR CM	Sulcular incisions	Bovine cross-linked CM (Perio-Barrier)	n/a	yes	no	yes	yes	Outcomes were measured at 6 probing sites *per* tooth; whole-tooth means were used for analysis
Lekovic *et al.*, 2001	OFD *vs.* GTR CM + bone	Sulcular incisions	Bovine collagen/PLA membrane (Bio-Gide Composite)	BPBM granules (Bio-Oss) and enamel matrix proteins (Emdogain)	no	yes	yes	yes	Adequate
Paolantonio *et al.*, 2008	OFD *vs.* GTR CM	Sulcular incisions	Lyophilized human pericardium CM (Tutoplast Pericardium)	n/a	no	yes	yes	yes	Unclear if measurements of the 6 sites were averaged, or if the deepest defect was used
Paolantonio *et al.*, 2010	OFD *vs.* GTR CM	Papilla preservation	Lyophilized human pericardium CM (Tutoplast Pericardium)	n/a	no	yes	yes	yes	Unclear if measurements of the 6 sites were averaged, or if the deepest defect was used
Quteish and Dolby, 1992	OFD *vs.* GTR CM	Sulcular incisions	Irradiated, glutaraldehyde-crosslinked human placenta CM (type I)	n/a	yes	no	nr	nr	Adequate
Sculean *et al.*, 2005	OFD *vs.* GTR CM + bone	Sulcular incisions	Porcine CM (Bio-Gide Perio)	Bovine-derived xenograft (Bio-Oss Collagen)	no	no	yes	yes	Adequate
Sculean *et al.*, 2007	OFD *vs.* GTR CM + bone	Sulcular incisions	Porcine CM (BioGide Perio)	BPBM granules (0.25-1.0 mm) (Bio-Oss)	no	yes	yes	yes	Adequate
Singh *et al.*, 2012a	OFD *vs.* GTR CM + bone	nr	Fish CM (PerioCol)	Nano-crystalline Hydroxyapatite (HA) bone replacement graft (Sybograf)	no	yes	yes	yes	Adequate
Sowmya *et al.*, 2010	OFD *vs.* GTR CM + bone	Sulcular incisions	Xenogen CM (Healiguide)	Xenogen DMBM type I collagen (Osseograft)	no	yes	no	no	Unclear if measurements of the 6 sites were averaged, or if the deepest defect was used
Tonetti *et al.*, 2004	OFD *vs.* GTR CM + bone	Papilla preservation	Porcine CM (Bio-Gide).	BPBM granules (Bio-Oss)	no	yes	yes	yes	Adequate
Trombelli *et al.*, 2010	OFD *vs.* GTR CM + bone	Papilla preservation	Equine cross-linked CM (Paroguide)	HA-based biomaterial (Biostite)	yes	no	yes	yes	Adequate
Vouros *et al.*, 2004	OFD *vs.* GTR CM + bone	Sulcular incisions	Porcine CM (BioGide)	BPBM granules (Bio-Oss spongiosa)	no	yes	yes	yes	Adequate

OFD = open flap debridement; GTR = guided tissue regeneration; CM = collagen membrane; bone = bone substitute; nr = not reported; n/a = not applicable.

Appendix Table 6. Methodological Characteristics of Trials

Author/ Year	Generation of Allocation Sequence	Description of Allocation Generation	Concealment of Allocation Method	Description of Concealment	Blinding of the Surgeon	Blinding of Outcome Assessors	Control Group ITT: numbers analyzed / numbers randomized	Experimental Group ITT: numbers analyzed / numbers randomized
al-Arrayed *et al.*, 1995	unclear	Allocation of matched bilateral lesions was "decided by random design and when appropriate". Randomization method not reported.	unclear	nr	The surgeon was blinded until after debridement at the first defect. At the second defect, the surgeon was not blinded (split-mouth design).	Assessor was not the surgeon and was blind to the sites.	19 / nr analyzed	19 / nr analyzed
Blumenthal and Steinberg, 1990	unclear	Randomization seemed *per* quadrant, allocating each of the 4 quadrants to 1 of the 4 experimental groups. Allocation of the control teeth remained unclear.	unclear	nr	nr	nr	15 /15 analyzed	CM: 15 / 15 analyzed; CM + bone: 15 / 15 analyzed
Boynuegri *et al.*, 2009	unclear	Not mentioned if a randomization method was used.	unclear	nr	nr	nr	5 / 5 analyzed	5 / 5 analyzed
Camargo *et al.*, 2000	coin-tossing	Two interproximal sites were randomly assigned to the experimental or control groups.	unclear	nr	nr	Assessors were not the surgeons and were blind to the sites.	22 / 22 analyzed	22 / 22 analyzed
Camargo *et al.*, 2005	coin-tossing	Two interproximal sites were randomly assigned to the experimental or control groups.	unclear	nr	nr	Assessor was not the surgeon and was blind to the sites.	28 / 28 analyzed	28 / 28 analyzed
Chung *et al.*, 1990	unclear	Experimental sites were randomly selected for test treatment; matching contralateral site served as a control within the same patient.	unclear	nr	nr	nr	10 / 15 analyzed	10 / 15 analyzed
Lekovic *et al.*, 2001	coin-tossing	Two interproximal sites were randomly assigned to the experimental or control groups.	unclear	nr	nr	Assessor was not the surgeon and was blind to the sites.	18 / 18 analyzed	18 / 18 analyzed
Paolantonio *et al.*, 2008	computer-generated	"computer-generated table"	unclear	nr	nr	Assessor was blind to the sites.	17 / 17 analyzed	17 / 17 analyzed
Paolantonio *et al.*, 2010	computer-generated	"computer-generated table"	unclear	nr	nr	Assessor was blind to the sites.	14 / 14 analyzed	14 / 14 analyzed
Quteish and Dolby, 1992	unclear	Randomization method not reported.	unclear	nr	nr	nr	26 / 26 analyzed	26 / 26 analyzed
Sculean *et al.*, 2005	unclear	Defects were randomly assigned before surgery to the two treatment groups with the randomized block approach.	unclear	nr	nr	Assessor was not aware of surgical procedure to be performed (blinded at baseline). Unclear blinding at follow-up assessment.	16 / 16 analyzed	16 / 16 analyzed
Sculean *et al.*, 2007	unclear	Defects were randomly assigned before surgery to the two treatment groups with the randomized block approach.	unclear	nr	nr	Assessor was not the surgeon. Blinding unclear.	9 / 14 analyzed	10 / 14 analyzed
Singh *et al.*, 2012a	coin-tossing	"coin flip" method	unclear	nr	nr	nr	9 / 10 analyzed	9 / 10 analyzed
Sowmya *et al.*, 2010	unclear	Randomization method not reported. "The sites were divided randomly."	unclear	nr	nr	nr	10 / 10 analyzed	10 / 10 analyzed
Tonetti *et al.*, 2004	computer-generated	Assignment was performed by a central study registrar using a custom-made program based on balanced random permuted blocks	envelopes	Use of a central registrar and sealed envelopes, not reported if latter were opaque or consecutively numbered.	The surgeon was blinded until after debridement	Assessor and surgeon were identical. No blinding.	59 / 62 analyzed	61 / 62 analyzed
Trombelli *et al.*, 2010	computer-generated	"computer-generated randomization list"	unclear	nr	The surgeon was blinded until after debridement.	Assessor was blind to the sites.	12 / 12 analyzed	12 / 12 analyzed
Vouros *et al.*, 2004	computer-generated	Computer randomization program. Randomization seems to be at the tooth level.	envelopes	Sealed envelopes, not reported if these were opaque or consecutively numbered.	The surgeon was blinded until after debridement	Assessor was not the surgeon and was blind to the sites.	12 / 12 analyzed	14 / 14 analyzed

ITT = intention-to-treat; nr = not reported.