The Efficacy of Bone Replacement Grafts in the Treatment of Periodontal Osseous Defects. A Systematic Review

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Background: Bone replacement grafts (BRG) are widely used in the treatment of periodontal osseous defects; however, the clinical benefits of this therapeutic practice require further clarification through a systematic review of randomized controlled studies.

Rationale: The purpose of this systematic review is to access the efficacy of bone replacement grafts in proving demonstrable clinical improvements in periodontal osseous defects compared to surgical debridement alone.

Focused Question: What is the effect of bone replacement grafts compared to other interventions on clinical, radiographic, adverse, and patient-centered outcomes in patients with periodontal osseous defects?

Search Protocol: The computerized bibliographical databases MEDLINE and EMBASE were searched from 1966 and 1974, respectively, to October 2002 for randomized controlled studies in which bone replacement grafts were compared to other surgical interventions in the treatment of periodontal osseous defects. The search strategy included screening of review articles and reference lists of retrieved articles as well as hand searches of selected journals.

Inclusion criteria: All searches were limited to human studies in English language publications.

Exclusion criteria: Non-randomized observational studies (e.g., case reports, case series), publications providing summary statistics without variance estimates or data to permit computation, and studies without BRG intervention alone were excluded.

Data Collection and Analysis: The therapeutic endpoints examined included changes in bone level, clinical attachment level, probing depth, gingival recession, and crestal resorbtion. For purposes of meta-analysis, change in bone level (bone fill) was used as the primary outcome measure, measured upon surgical re-entry or transgingival probing (sounding).

Main Results

1. Forty-nine controlled studies met eligibility criteria and provided clinical outcome data on intrabony defects following grafting procedures.
2. Seventeen studies provided clinical outcome data on BRG materials for the treatment of furcation defects.

Reviewers' Conclusions

1. With respect to the treatment of intrabony defects, the results of meta-analysis supported the following conclusions: 1) bone grafts increase bone level, reduce crestal bone loss, increase clinical attachment level, and reduce probing depth compared to open flap debridement (OFD) procedures; 2) No differences in clinical outcome measures emerge between particulate bone allograft and calcium phosphate (hydroxyapatite) ceramic grafts; and 3) bone grafts in combination with barrier membranes increase clinical attachment level and reduce probing depth compared to graft alone.
2. With respect to the treatment of furcation defects, 15 controlled studies provided data on clinical outcomes. Insufficient studies of comparable design were available to submit data to meta-analysis. Nonetheless, outcome data from these studies generally indicated positive clinical benefits with the use of grafts in the treatment of Class II furcations.
3. With respect to histological outcome parameters, 2 randomized controlled studies provide evidence that demineralized freeze-dried bone allograft (DFDBA) supports the formation of a new attachment apparatus in intrabony defects, whereas OFD results in periodontal repair characterized primarily by the formation of a long junctional epithelial attachment. Multiple observational studies provide consistent histological evidence that autogenous and demineralized allogeneic bone grafts support the formation of new attachment. Limited data also suggest that xenogenic bone grafts can support the formation of a new attachment apparatus. In

contrast, essentially all available data indicate that alloplastic grafts support periodontal repair rather than regeneration.

4. The results of this systematic review indicate that bone replacement grafts provide demonstrable clinical improvements in periodontal osseous defects compared to surgical debridement alone.
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KEY WORDS

Clinical trials, controlled; comparison studies; grafts, bone; periodontal disease/surgery; periodontal diseases/therapy; outcomes assessment; review literature; meta-analysis.

BACKGROUND

The complete and predictable restoration of the periodontium following trauma or infection remains a critical objective in periodontics. Bone replacement grafts remain among the most widely used therapeutic strategies for the correction periodontal osseous defects. A wide range of graft materials have been applied and evaluated clinically, including autografts, allografts, xenografts, and synthetic/semi-synthetic materials.[1] Moreover, observational and controlled studies generally document improvements in clinical parameters following placement of graft materials.[2,3] Comprehensive reviews of the literature, however, have yielded different interpretations regarding the clinical benefits of this therapeutic practice.[1-3] Moreover, there is an appreciation that regenerative outcomes remain somewhat inconsistent and are likely dependent on multiple factors.[1]

RATIONALE

The primary objective was to assess the efficacy of bone replacement grafts in the treatment of periodontal osseous defects relative to open flap debridement as well as other surgical therapies.

FOCUSED QUESTION

The purpose of this systematic review, therefore, was to address the following focused question: In patients with periodontal osseous defects, what is the effect of bone replacement grafts compared to other interventions on clinical, radiographic, adverse, and patient-centered outcomes?

SEARCH PROTOCOL

Data Sources and Search Strategies

The bibliographical databases MEDLINE and EMBASE were searched from 1966 and 1974, respectively, to October 2002 for studies in which bone replacement grafts were compared to other surgical interventions in the treatment of periodontal osseous defects. The search was limited to human studies in English language publications using the search strategy and terms summarized below:

Field 1: Bone graft, bone replacement graft, autogenous, autogenous bone graft, bone matrix, allogenic, allogenic bone graft, osseous autograft, osseous graft, osseous composite graft, allograft, bone allograft, osseous allograft, cancellous bone allograft, freeze-dried bone, demineralized freeze-dried bone, bovine bone, Bio-Oss, synthetic graft, polymer, calcium carbonate, ceramic, bioglass, bioactive glass, Perioglass, Biogran, Unigraft, hydroxyapatite, hydroxyapatite, porous HA, HA, durapatite, coralline calcium carbonate, calcium carbonate, polymethylmethacrylate, hydroxyethylmethacrylate, calcium polymer, beta-tricalcium phosphate, tri-calcium phosphate, tricalcium phosphate, TCP graft, HTR polymer, Periograf, periodontal regeneration, PepGen-15.

Field 2: Periodontal defect, intra-bony, intrabony, infrabony, infrabony, intra-osseous, intraosseous, vertical defect, vertical lesion, furcation, furcations, furcation lesion, furcation invasion, complication, surgical complication, postoperative complication, surgical wound infection, gingival recession

All root words were searched with a truncation symbol, permitting identification of all forms, including plurals, etc.

EMBASE was searched using more restrictive thesaurus terms (bone grafts; periodontal) and key root words (intrabony, infrabony, intraosseous, and furcation) for publications not cataloged in MEDLINE.

These searches were supplemented by screening review articles and reference lists of retrieved articles as well as hand searches of the *International Journal of Periodontics and Restorative Dentistry, Journal of Clinical Periodontology, Journal of Periodontology*, and *Journal of Periodontal Research*.

The search strategy attempted to directly identify all recognized BRG materials through the inclusion of keywords (e.g., tricalcium phosphate).

Selection Criteria

Inclusion criteria: All searches were limited to human studies in English language publications.

Exclusion criteria: Exclusion criteria included nonrandomized observational studies (e.g., case reports, case series), publications providing summary statistics without variance estimates or data to permit computation, and studies without a BRG intervention alone. This review did not consider studies in which graft materials were used in combination with biological mediators, such as bone morphogenetic proteins or enamel matrix derivatives. Root surface biomodifica-

tion with citric acid, tetracycline, or ethylenediaminetetraectic acid (EDTA) was not an exclusion criterion. In addition, this review considered systematic reviews of randomized clinical trials, cohort studies, and case-control studies as well as critical reviews of the literature examining BRGs in the treatment of periodontal osseous defects.

Data Collection and Analysis

Citations were independently reviewed by two investigators (MAR; MEA-R), and publications identified as potentially relevant were retrieved for review. The retrieved articles were reviewed with respect to methodology and inclusion by 3 investigators (MAR, MEA-R, and GB-M).

Two investigators (MEA-R and GB-M) independently abstracted data pertaining to study design, methodology, analysis, and results. Issues of interpretation and discrepancies in data sets were resolved through discussion. Data abstraction forms were reviewed for accuracy (MEA-R, GB-M, and MAR) prior to entry into an electronic data base for analysis. Assessment of study quality included documentation of the following investigational and design parameters: experimental protocol, randomization, masking, and standardization of outcome measures.

Quality Assessment

All studies submitted for meta-analysis were identified as randomized controlled trials. Methodological quality was reviewed primarily with respect to randomization, examiner masking, and description of withdrawals. Problematic for most reports was an absence of sufficient detail regarding method of randomization, examiner masking, and subject withdrawal. Additionally, reports often failed to provide adequate information related to examiner calibration and standardization of outcome assessments.

Outcomes: With respect to clinical outcome parameters, study selection was restricted to randomized controlled clinical studies in which a bone replacement graft was compared to open flap debridement (OFD), a different BRG, or other surgical modality (e.g., guided tissue regeneration) for the correction of intraosseous and furcation defects in patients with periodontitis. With respect to histological outcome parameters, only studies providing data based on excisional biopsy specimens that included the region of the periodontal osseous defect and adjacent tooth were included in the review.

Clinical outcome measures were categorized as short-term (≤12 months) or long-term (≥3 years). The therapeutic endpoints examined in the systematic review included changes in bone level, clinical attachment level, probing depth, gingival recession, and crestal resorption. Other potential secondary outcome measures were sought in the review, such as change in level of oral hygiene efficacy/compliance (based on indices of gingival inflammation and/or bleeding), incidence of disease recurrence, and incidence of tooth loss.

For purposes of the meta-analysis, change in bone level (bone fill) was used as the primary outcome measure. Direct clinical measurements via surgical exposure or transgingival sounding[4-7] were considered for the assessment of intrabony defect level. Secondary outcome measures included crestal resorption (measured at surgical re-entry), clinical attachment level, probing depth, and gingival recession.

Data analysis: The synthesis of data for outcome measures was based on the experimental design. Mean scores and variance estimates for outcome measures were obtained directly from summary statistics or calculated from data tables. Studies were weighted in the analysis according to the number of subjects contributing defect sites in each intervention arm or group. Studies with multiple interventions could contribute more than one treatment group or arm to the analysis. Multiple defect sites from the same subject were averaged to provide a "pooled" estimate of the true outcome value for the individual. Thus, the subject rather than site was used as the unit of measure for purposes of weighting estimates of treatment effect.

The mean and variance estimates for changes in outcome measures were extracted from the full manuscripts or, when not reported, calculated from raw data where possible. The effect size for each study was calculated as the mean difference between treatment and control groups divided by the pooled standard deviation. The data were analyzed using a standardized difference as described by Fleiss.[8] Data were submitted to both random- and fixed-effects models, which yielded consistent results. Heterogeneity was examined using both Cohens' d (unadjusted)[9] and Hedges's g (adjusted) statistics.[10] A lack of heterogeneity was accepted only when both tests yielded nonsignificant statistics. The data were analyzed using a method that was first described by Mantel and Haenszel[11] and subsequently adapted for meta-analysis.[12,13] The results were confirmed by Peto's method for combining odds ratios.[14] Data were analyzed using a statistical software program.

Prior to statistical analysis, graft materials were categorized on an *a priori* basis into one of the following cateogories: autogenous, allogenic, xenogenic, calcium phosphate ceramic (porous/nonporous hydroxyapatite; HA), bioactive glass (silicates), and other (coralline calcium carbonate, polylactic acid, polymethylmethacrylate, polyhydroxylethylmethacrylate, and calcium hydroxide polymer).

MAIN RESULTS

Study Characteristics

The computerized search strategies located 1,299 citations, of which 134 were screened for potentially meet-

Table 1.

Studies Excluded from Meta-Analysis

Reference	Rationale for Exclusion*
Chodroff & Ammons[15] 1984	Inclusion of zero wall defects
Galgut et al.[16] 1990 Nery et al.[17] 1990	Outcome measures evaluated by radiographic data
Toback et al.[18] 1999	Radiographic comparison to previously reported re-entry results
Strub et al.[19] 1979 Froum et al.[20] 1975	Variance estimates not provided
Sanders et al.[21] 1983 Hiatt et al.[22] 1986 Quintero et al.[23] 1982 Costa et al.[24] 1994 Schallhorn et al.[25] 1970 Mellonig et al.[26] 1976 Yukna and Sepe[27] 1982 Yukna[28] 1989	Non-randomized study/or case series
Sepe et al.[29] 1978	Categorical outcome measures
Nielson et al.[30] 1981	Comparable osseous data not included
Bowers et al.[31] 1989	No clinical evaluations provided
Yukna et al.[32] 1984 Yukna et al.[33] 2002 Yukna et al.[34] 1989	Longitudinal follow-up

* More than one exclusion criterion may apply.

ing inclusion criteria. Eighty-four articles were abstracted, and 20[15-34] (Table 1) were excluded during the selection process. A review of publication references revealed 2 master's theses[35,36] that met eligibility criteria. Sixty-six randomized controlled trials were retained for review and possible submission to meta-analysis. Forty-nine randomized controlled studies met eligibility criteria and provided clinical outcome data on BRG materials in the treatment of intrabony defects.[6,37-84] Similarly, 17 studies provided clinical outcome data on BRG materials for the treatment of furcation defects.[35,36,45,48,58,85-96]

BRG Versus OFD

Initial and subgroup analysis. Table 2 summarizes the available studies that provide an OFD intervention arm or group for comparison with a BRG material. The BRG materials examined in these studies were as follows: autogenous bone,[47,70] allogenic bone,[6,37,39,40,42,58-60,62,63,75,82] calcium phosphate (hydroxyapatite) ceramic (porous/nonporous HA),[53,56,61,69,79] bioactive glass,[48,65,67,72] coralline calcium carbonate,[55,63,81] polylactic acid,[60] polymethylmethacrylate, polyhydroxylethyl-methacrylate, and calcium hydroxide polymer,[80] hydroxyapatite cement,[42] and HA-glycosaminoglycan.[54]

In the initial meta-analysis, studies were categorized on an *a priori* basis into one of the following cateogories: autogenous bone,[47,70] allogenic bone,[6,37,39,40,42,58-60,62,63,75,82] calcium phosphate ceramic (CER),[53,56,61,69,79] bioactive glass,[48,65,67,72] and other. The latter classification was heterogeneous

Table 2.

Characteristics of RCT Studies Comparing Bone Replacement Grafts with Open Flap Debridement in the Treatment of Intrabony Defects

Reference	Study Description	Population Age	Assessment Interval	Hard Tissue Assessment
Altiere et al.[37] 1979	Randomized, paired defects	Mean: 37 years	12 months	Re-entry
Blumenthal & Steinberg[39] 1990	Randomized, within subject (by site)	34-57 years	12 months	Re-entry
Borghetti et al.[40] 1993	Randomized, paired defects	Mean: 47 years	12 months	Re-entry
Brown et al.[42] 1998	Split-mouth, paired defects	20-40 years; mean: 40.4 years	12 months	Re-entry
Carraro et al.[44] 1976	Randomized, between subjects	22-67 years; mean: 45 years	12 months	None

by definition and included studies examining coralline calcium carbonate;[55,63,81] polylactic acid;[60] polymethylmethacrylate, polyhydroxylethyl-methacrylate, and calcium hydroxide (PMMA/PHEMA/$CaOH_2$) polymer;[80] hydroxyapatite cement;[42] and HA-glycosaminoglycan.[54]

Treatment effects and heterogeneity within BRG classifications were first examined with respect to the primary outcome measure, change in bone level. The initial analysis revealed significant and consistent treatment effects within the autogenous, allogenic, and calcium phosphate ceramic groups (Fig. 1; page 236). These positive treatment effects indicate that grafting with autogenous bone, allogenic bone, and calcium phosphate ceramic (HA) results in a significantly greater change (increase) in bone level than OFD procedures.

A non-significant effect was obtained in the bioactive glass group ($P \leq 0.10$), although significant heterogeneity was found across studies ($P \leq 0.006$). The inconsistency in effect was attributable to one study,[65] which reported a more favorable change in bone fill following an OFD procedure. The other studies have documented relatively greater increases in bone level following grafting with bioactive glass than with OFD alone.[48,72]

The BRG group designated "Other" (OTH) yielded a significant treatment effect; however, this effect was inconsistent ($P \leq 0.003$) across studies. With the exception of 2 studies,[42,60] changes in bone level were found to be more favorable following grafting than OFD procedures. Comparatively poorer resultant bone levels were reported following grafting with polylactic acid[60] and HA cement[42] relative to an OFD procedure.

Graft materials within the allogenic category were subgrouped *a priori* because of differences in bone procurement and processing as well as potential differences relative to the primary outcome measure; namely, change in bone level. Three subgroups were compared in the analysis—fresh frozen, freeze-dried bone allograft (FDBA), and demineralized freeze-dried bone allograft (DFDBA) (Fig. 2; page 237). Tests of heterogeneity were not significant either within subgroups or collapsing across subgroups. Significantly greater bone level improvements were found for both DFDBA and fresh frozen allografts compared to OFD procedures. However, FDBA was not associated with significant improvements in bone level. Collectively, these data support the efficacy of both DFDBA and fresh frozen allografts with respect to improvements in bone fill in intrabony defects. Noteworthy is the fact that there were only 2 studies with a combined sample size of 34 observations examining FDBA to an OFD procedure. Finally, since the tests of heterogeneity were not significant for allografts, the studies were retained for analysis of the remaining clinical outcome variables.

The initial meta-analysis yielded an overall significant ($P \leq 0.001$) but inconsistent ($P \leq 0.003$) treatment effect, when collapsing across BRG categories. The next step in the analysis was to explore the sources of heterogeneity, particularly with respect to the category of "Other" BRG materials. The "Other" classification was broadly defined to permit inclusion and comparison of studies not included in the remaining BRG categories. Studies of coralline calcium carbonate within

Table 2. (continued)

Characteristics of RCT Studies Comparing Bone Replacement Grafts with Open Flap Debridement in the Treatment of Intrabony Defects

Examiner Masking	Interventions	Outcome Assessments					Location/Funding
		PD	CAL	REC	CR	VDD	
Yes, re-entry	Allograft (FDBA) OFD	Yes	Yes	No	No	Yes	University/NS
No	Allograft (AAA bone) Allograft (AAA bone)/collagen membrane OFD	Yes	Yes	Yes	Yes	Yes	University/NS
NS	Allograft (cryopreserved cancellous) OFD	Yes	Yes	Yes	Yes	Yes	University/NS
Yes, single examiner	Allograft (DFDBA) OFD	Yes	Yes	Yes	Yes	Yes	Military/industry
NS	Autogenous (cancellous bone) (included 2-wall data only) OFD	No	Yes	N	No	No	Hospital/NS

(continued)

Table 2. (continued)

Characteristics of RCT Studies Comparing Bone Replacement Grafts with Open Flap Debridement in the Treatment of Intrabony Defects

Reference	Study Description	Population Age	Assessment Interval	Hard Tissue Assessment
Flemmig et al.[6] 1998	Randomized, paired defects	Mean: 47.3 ± 4.1 years	6 months	Sounding
Froum et al.[47] 1976	Randomized, between subjects	23-64 years	7-13 weeks	Re-entry
Froum et al.[48] 1998	Randomized, paired defects	Mean age: 43 years	12 months	Re-entry
Galgut et al.[50] 1992	Randomized, paired defects (selected data from sites >6 mm)	33-59 years; mean: 42.5 years	12 months	None
Kenney et al.[53] 1985	Randomized, paired defects	Mean: 38.30 ± 9.87 years	6 months	Re-entry
Kiliç et al.[54] 1997	Randomized, paired defects	35-60 years	6 months	Radiographic, sounding
Kim et al.[55] 1996	Randomized, between subjects	23 to 60 years; mean: 39.3	6 months	Sounding
Krejci et al.[56] 1987	Randomized, paired defects	22-63 years	6 months	Re-entry
Mabry et al.[58] 1985	Randomized, paired defects and parallel arms between subjects	13-26 years; mean: 18.7 ± 13.8 years	12 months	Re-entry
Masters et al.[59] 1996	Randomized, paired defects	35-61 years	12 months	Re-entry
Meadows et al.[60] 1993	Randomized, paired defects	28-58 years; mean: 42	6 months	Re-entry
Meffert et al.[61] 1985	Randomized, paired defects	32-60 years	9 months	Re-entry
Mellonig et al.[62] 1984	Randomized, paired defects	19-25 years; mean: 28 years	6-13 months	Re-entry
Mora & Ouhayoun[63] 1995	Randomized, paired defects	28-62 years; mean: 42.7 years	12 months	Re-entry
Movin & Borring-Møller[64] 1982	Randomized and parallel groups between subjects	21-48 years	12 months	Radiographic
Ong et al.[65] 1998	Randomized, paired defects	35-67 years; mean: 49.1	9-13 months	Re-entry

Table 2. (continued)

Characteristics of RCT Studies Comparing Bone Replacement Grafts with Open Flap Debridement in the Treatment of Intrabony Defects

Examiner Masking	Interventions	Outcome Assessments					Location/Funding
		PD	CAL	REC	CR	VDD	
Yes, single examiner	Allograft (AAA bone)/covered with fibrinogen OFD	Yes	3 months only	No	No	Yes	University/NS
NS	Autogenous (osseous coagulum) OFD	No	No	No	No	Yes	VA/NS
NS, single examiner	Bioactive glass OFD	Yes	Yes	Yes	Yes	Yes	University/ industry
NS, single examiner	HA (particulate) OFD	Yes	Yes	Yes	No	No	University/ industry
No	HA (porous, block) OFD	Yes	Yes	No	Yes	Yes	NS/industry
Clinical: single examiner, NS; radiographic: 4 examiners, yes	HA-collagen/barrier (ePTFE) Membrane (ePTFE) HA collagen (HA-glycosaminoglycan) OFD	Yes	Yes	Yes	No	Yes	University/NS
Yes	Membrane (ePTFE) Coralline calcium carbonate Coralline calcium carbonate /ePTFE barrier OFD	Yes	Yes	Yes	No	Yes	University/ industry
NS	HA (porous particulate) HA (nonporous, nonresorbable, particulate) OFD	Yes	No	No	Yes	Yes	University/NS
NS; single examiner per patient	1. Allograft (FDBA) 2. FDBA/TET (local and systemic) 3. OFD/TET (systemic) 4. OFD	Yes	Yes	Yes	Yes	Yes	University/NIH
NS	DFDBA/TET DFDBA OFD	Yes	Yes	Yes	Yes	Yes	University/ foundation
NS; same examiner all measures	DFDBA PLA OFD	Yes	No	Yes	Yes	No	Navy/navy
NS	HA (porous particulate) OFD	No	No	No	Yes	Yes	University/NS
No	DFDBA OFD	Yes	Yes	Yes	Yes	Yes	Navy/navy
NS; single examiner	HA (porous) Coralline calcium carbonate OFD	Yes	Yes	Yea	Yes	Yes	University/NS
NS	Autogenous cancellous bone Allogenic demineralized dentin OFD	No	Yes	No	No	No	University/NS
Yes; single examiner	Bioactive glass OFD	Yes	Yes	Yes	Yes	Yes	University/ industry

continued

Table 2. (continued)

Characteristics of RCT Studies Comparing Bone Replacement Grafts with Open Flap Debridement in the Treatment of Intrabony Defects

Reference	Study Description	Population Age	Assessment Interval	Hard Tissue Assessment
Park et al.[67] 2001	Randomized, between subjects	28-67 years; mean: 43.9 ± 9.0 years	6 months	Sounding
Pearson et al.[68] 1981	Randomized, between subjects and paired defects	18-47 years	6-13 months	Radiographic, selected re-entry
Rabalais et al.[69] 1981	Randomized, split-mouth or alternating defect design	32-65 years	6 months	Re-entry
Renvert et al.[70] 1985	Within patient comparison of multiple defects; 3 operators with variable technique	26-66 years	12 months	Sounding
Rosenberg et al.[72] 2000	Randomized, paired defects	Mean: 41	6 months	Re-entry
Schrad & Tussing[75] 1986	Randomized, within subjects by quadrants	31-56 years; mean: 41 years	12 months	Re-entry
Schulz et al.[76] 2000	Randomized, parallel arms between subjects	NS	11 months	None
Shahmiri et al.[78] 1992	Randomized, paired defects	18-65 years	12 months	None
Yukna et al.[81] 1994	Randomized, within subjects by alternating defects	32-71 years; mean: 47.2 ± 11.2 years	6-12 months; mean: 6.9 months	Re-entry
Yukna et al.[80] 1990	Randomized, within subject (multiple paired defects)	29-69 years; mean: 40.6 years	6 months	Re-entry
Yukna et al.[79] 1985	Randomized, paired defects	31-65 years; mean: 43.5 years	12 months	Re-entry
Yukna et al.[82] 1998	Randomized, paired defects, and multi-centered	35 to 65 years	6-7 months	Re-entry
Zamet et al.[84] 1997	Randomized, paired defects	23 to 55 years	12 months	None

Abbreviations: AAA = autolyzed, antigen-extracted, allogenic; CAL = clinical attachment level; CR = crestal resorption; DFDBA = demineralized freeze-dried bone allograft; ePTFE = expanded polytetrafluoroethylene; FDBA = freeze-dried bone allograft; HA = hydroxyapatite; OFD = open flap debridement; NS = not stated; P-15: peptide-15; PLA = polylactic acid; PMMA/PHEMA, $CaOH_2$ = polymethyl-methacrylate + polyhydroxyl-ethylmethacrylate + calcium hydroxide; REC = gingival recession; TET = tetracycline; VDD = vertical defect depth.

this category were identified *a priori* for subgroup analysis.

Figure 3 (page 237) summarizes the results for the subgroup analysis of changes in bone level for studies in the category. The overall analysis yielded a modestly significant ($P \leq 0.05$), but heterogeneous ($P \leq 0.001$) treatment effect. The analysis suggests that coralline calcium carbonate (subgroup 2) represents the only consistent treatment effect in this category, which was significant ($P \leq 0.001$) and consistent (P = NS). Of the 3 other graft materials, only PMMA/PHEMA/$CaOH_2$ polymer[80] was found to improve bone levels relative to

Table 2. (continued)

Characteristics of RCT Studies Comparing Bone Replacement Grafts with Open Flap Debridement in the Treatment of Intrabony Defects

Examiner Masking	Interventions	Outcome Assessments					Location/Funding
		PD	CAL	REC	CR	VDD	
Yes	Bioactive glass OFD	Yes	Yes	Yes	No	Yes	University/NS
NS	DFDBA OFD	No	Yes	No	No	Yes	University/NS
NS	HA (particulate) OFD	Yes	Yes	Yes	Yes	Yes	University/ industry
NS	Autogenous cancellous OFD	Yes	Yes	No	No	Yes	University/NS
NS	Bioactive glass OFD	No	Yes	Yes	No	Yes	University/ industry
NS	Allogenic (iliac bone and marrow) OFD	No	Yes	Yes	Yes	Yes	University/NS
NS	OFD Coralline calcium carbonate	Yes	Yes	No	No	No	University/ industry
NS	OFD PMMA/PHEMA/$CaOH_2$ polymer	Yes	Yes	Yes	No	No	University/ industry
NS	Coralline calcium carbonate OFD	Yes	Yes	Yes	Yes	Yes	Private practice & university/ industry
NS	PMMA/PHEMA/$CaOH_2$ polymer OFD	Yes	Yes	Yes	Yes	Yes	Private practice & university/ industry
NS	HA, ceramic particulate OFD	Yes	Yes	Yes	Yes	Yes	University/ industry
Yes	HA-P-15 (bovine) DFDBA OFD	Yes	Yes	Yes	Yes	Yes	University & private practice/ industry
Yes	Bioactive glass OFD	Yes	Yes	No	No	No	University/ industry

OFD.[42,60] Moreover, there was no more than one study contributing outcome data for each graft material. Consequently, these studies were dropped in the final analysis.[42,54,60,80]

Final analysis. Tables 3 and 4 (page 238) summarize the weighted and unweighted mean differences for outcome measures in the final meta-analysis comparing grafts with open flap debridement procedures.

Bone level: The final meta-analysis revealed significant effects for changes in bone level in all BRG categories, except bioactive glass, with significant heterogeneity ($P \leq 0.001$) for the combined groups (Fig. 4; page 239). Although the treatment effect for autogenous bone grafts was intermediate in size relative to the other BRG categories, only 2 studies contributed data for autografts in this analysis ($P \leq 0.58$). Significant heterogeneity was found in the calcium phosphate ceramic group ($P \leq 0.04$), autogenous bone group ($P \leq 0.004$), and the bioactive glass group ($P \leq 0.006$). With the exception of the bioactive glass group, heterogeneity

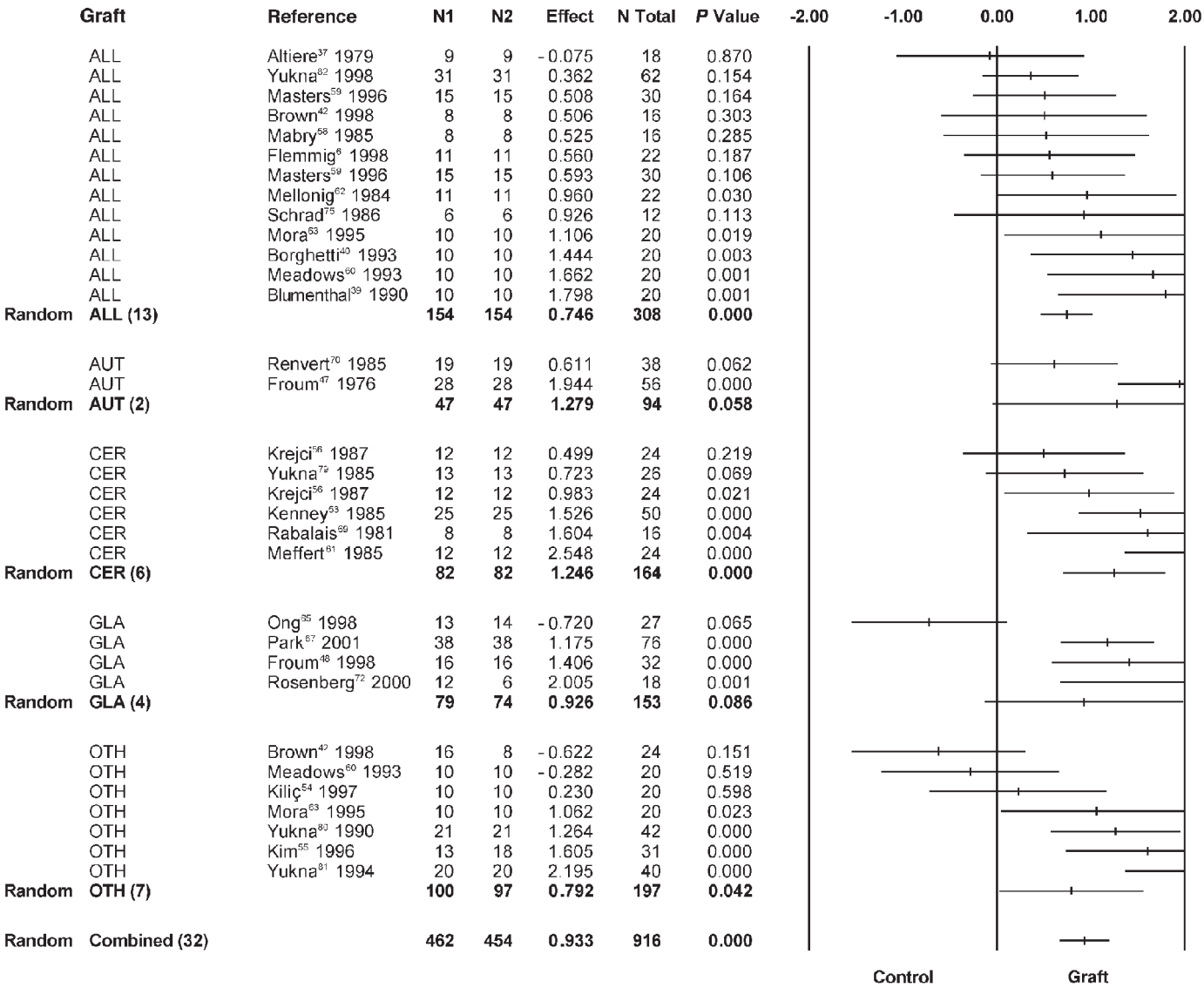

Figure 1.
Initial meta-analysis of change in bone level (defect fill) in randomized controlled clinical studies comparing BRG to OFD in the treatment of intrabony defects. Abbreviations: ALL = allograft; AUT = autograft; CER = calcium phosphate (hydroxyapatite) ceramic; GLA = bioactive glass; and OTH = other.

in subgroups was generally associated with positive treatment effects across studies. Within the bioactive glass group, only one study[65] reported a negative result for graft compared to an OFD procedure. This final analysis supports significant and consistent effects for all subgroups except for the bioactive glass group. Also, when the bioactive glass group was eliminated from the combined analysis, the combined analysis was significant and consistent.

Crestal bone loss (CBL): A significant treatment effect was obtained for CBL in the overall analysis, indicating that OFD was associated with greater crestal resorption than after graft placement (Fig. 5; page 240). The results of the overall analysis support the hypothesis that BRG grafts significantly reduce CBL when compared to OFD procedures. Although crestal bone loss was generally less in each BRG category, the treatment effect was only significant for the bone allograft and coralline calcium carbonate groups. Similar but non-significant effects were observed in the bioactive glass and autogenous bone groups, presumably failing to reach statistical significance most likely due to small sample sizes. Significant heterogeneity was again found in the bioactive glass group ($P \leq 0.05$). In summary, this analysis supports the hypothesis that grafting materials reduce the amount of CBL.

Clinical attachment level (CAL): A significant treatment effect was obtained for CAL in the overall analysis and in each BRG category, indicating that grafts were associated with greater attachment level gains than OFD

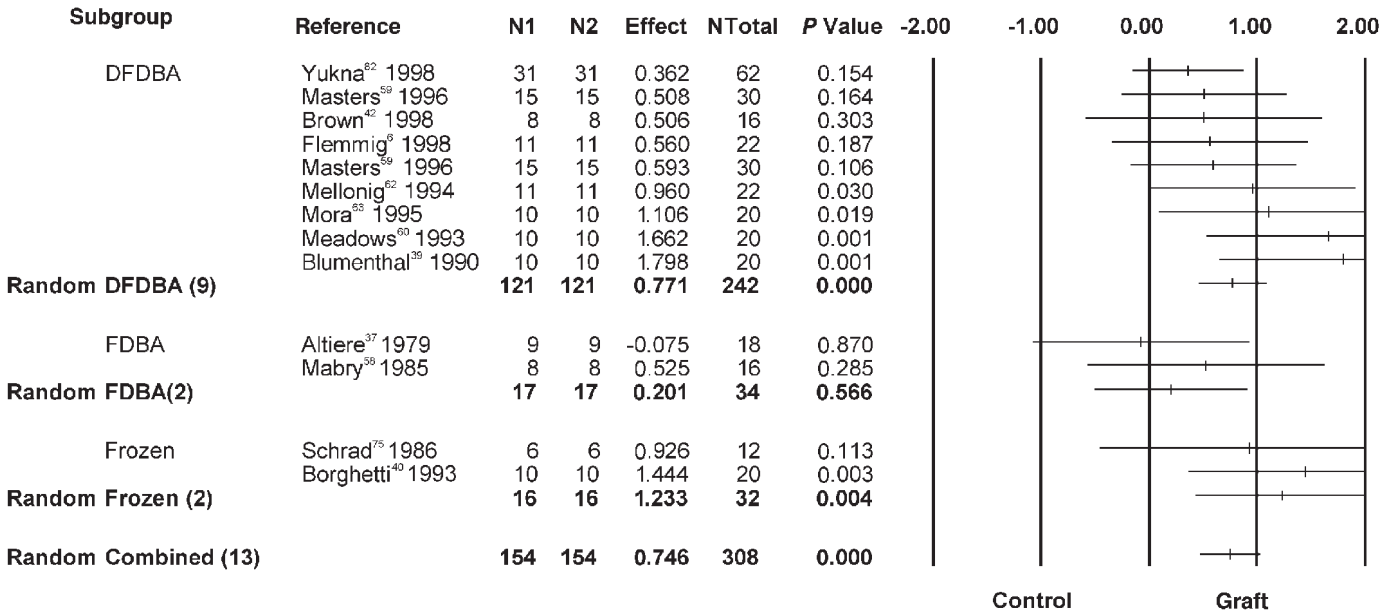

Figure 2.
Subgroup meta-analysis of change in bone level (defect fill) randomized controlled clinical studies comparing allograft (Graft) to OFD (Control) in the treatment of intrabony defects. Abbreviations: DFDBA = demineralized freeze-dried bone allograft; FDBA = freeze-dried bone allograft.

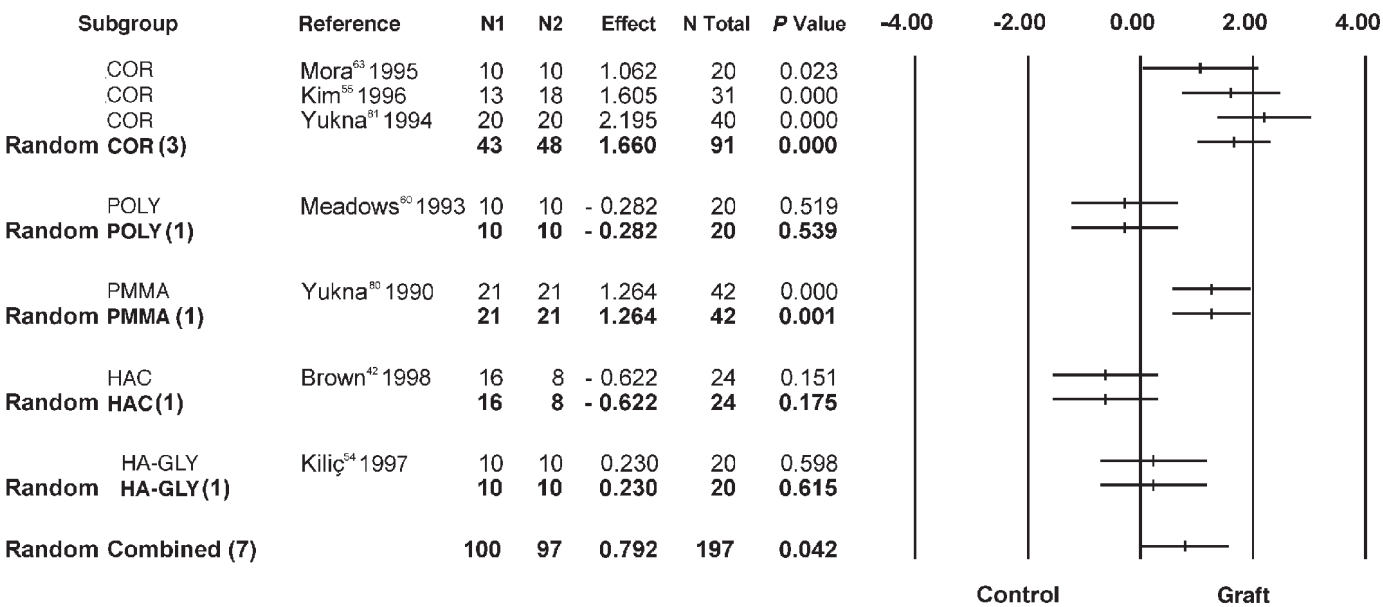

Figure 3.
Subgroup meta-analysis of change in bone level (defect fill) in randomized controlled clinical studies comparing materials classified as other (Graft) to OFD (Control) in the treatment of intrabony defects. Abbreviations: COR = coralline calcium carbonate; HAC = hydroxyapatite cement; HA-GLY = hydroxyapatite-glycosaminoglycan, PMMA = PMMA/PHEMA/$CaOH_2$ polymer; and POLY = polylactic acid.

procedures (Fig. 6; page 241). The results of the analysis support the hypothesis that BRG grafts significantly enhance gains in CAL compared to OFD alone. The treatment effects were consistent both across and within groups, with nonsignificant tests for heterogeneity in all cases.

Probing depth (PD): A significant treatment effect was obtained for PD in the combined analysis, reflecting an overall larger, consistent (heterogeneity, NS) reduction in PD that was consistent, when collapsing across BRG groups (Fig. 7; page 242). Significant and consistent effects also were shown for the allograft, cal-

Table 3.

Unweighted Mean Differences in Outcome Measures Comparing BRG and OFD Procedures in Meta-Analysis

	Clinical Attachment Level		Probing Depth		Recession		Crestal Resorption		Bone Fill	
BRG	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
ALL	12	0.50 ± 2.03	10	0.46 ± 2.26	7	–0.08 ± 1.56	11	–0.45 ± 1.35	13	1.14 ± 1.94
AUT	3	0.81 ± 1.57	1	0.60 ± 1.35	–	–	1	–0.32 ± 1.38	2	1.46 ± 1.50
CER	6	0.90 ± 2.14	7	0.60 ± 2.03	2	–0.11 ± 1.25	5	–0.20 ± 0.96	6	1.37 ± 1.64
COR	4	0.98 ± 1.76	4	0.08 ± 2.05	3	–0.17 ± 1.33	2	–0.25 ± 0.50	3	2.07 ± 1.79
GLA	4	1.06 ± 1.87	4	0.71 ± 2.24	3	–0.17 ± 1.54	2	–0.10 ± 0.93	4	1.62 ± 1.30

Abbreviations: ALL = allograft; AUT = autograft; CER = calcium phosphate ceramics; COR = coralline calcium carbonate; GLA = bioactive glass, N = number of study groups/arms.

Table 4.

Weighted Mean Differences in Outcome Measures Comparing Bone Replacement Graft and Open Flap Debridement Procedures in Meta-Analysis

	Clinical Attachment Level		Probing Depth		Recession		Crestal Resorption		Bone Fill	
BRG	WT	Mean ± SD	WT	Mean ± SD	WT	Mean ± SD	WT	Mean ± SD	WT	Mean ± SD
ALL	136	0.44 ± 2.25	127	0.43 ± 2.25	84	–0.01 ± 1.65	134	–0.43 ± 1.38	154	1.06 ± 1.97
AUT	51	0.72 ± 1.82	19	0.60 ± 1.35			28	–0.32 ± 1.38	47	1.62 ± 1.53
CER	58	1.20 ± 2.22	90	0.74 ± 2.12	46	–0.16 ± 1.34	74	–0.19 ± 0.98	82	1.58 ± 1.77
COR	60	0.91 ± 1.94	60	0.09 ± 2.16	48	–0.25 ± 1.34	30	–0.30 ± 0.62	48	2.21 ± 1.82
GLA	78	1.05 ± 1.89	88	0.71 ± 2.22	68	–0.28 ± 1.81	30	–0.13 ± 0.94	74	1.61 ± 1.47

Abbreviations: ALL = allograft; AUT = autograft; COR = coralline calcium carbonate; GLA = bioactive glass; WT: weight (denotes the total number of subjects across studies who contributed observations toward each outcome measure).

cium phosphate ceramic, and bioactive glass groups (heterogeneity, NS). Evaluation of PD in the autogenous group was not possible, with only one study contributing data for this outcome measure. The coralline calcium carbonate grafts were the only BRG category that exhibited a non-homogeneous group of studies ($P \leq 0.001$), with a nonsignificant treatment effect. The heterogeneity in this group was largely attributable to one study.[76] In summary, the overall findings of this analysis support a larger reduction in probing depth associated with grafting than OFD procedures. This conclusion was further supported by significant and consistently greater reductions in probing depth in the allograft, calcium phosphate ceramic, and bioactive glass groups.

Gingival recession: Comparison of graft and OFD procedures yielded no significant effect for gingival recession in the overall analysis, indicating comparable clinical outcomes with regard to this measure (Fig. 8). Variability in treatment outcomes across studies was not heterogeneous ($P \geq 0.05$).

Bone Allograft Versus Calcium Phosphate (Hydroxyapatite) Ceramic

Four clinical trials[38,41,45,66] provided comparisons of calcium phosphate ceramic (CER) with bone allograft (Table 5). Comparison of CER and bone allografts yielded no significant effects for bone level, crestal resorption, clinical attachment level, probing depth, or gingival recession, indicating comparable clinical out-

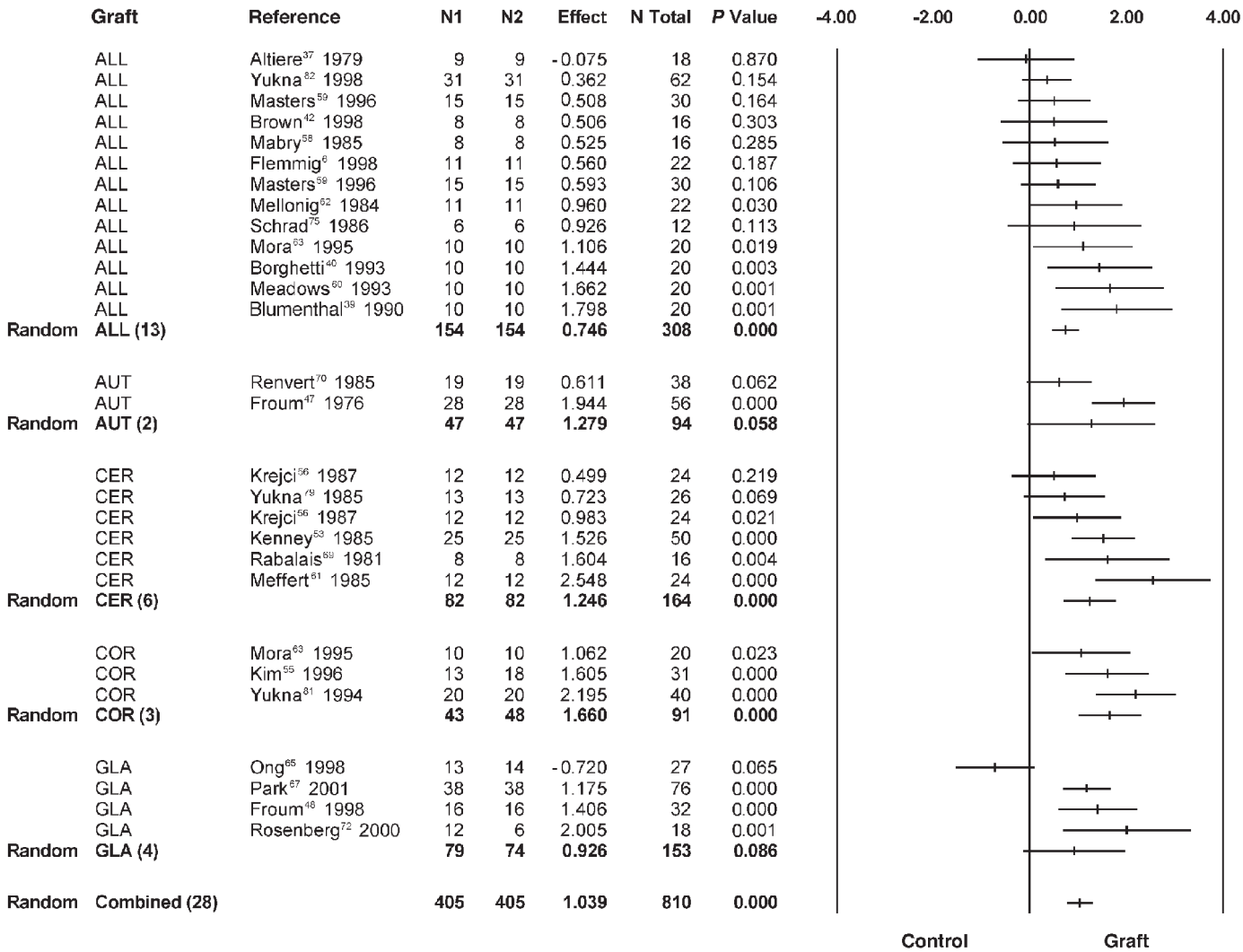

Figure 4.

Final meta-analysis of change in bone level (defect fill) in randomized controlled clinical studies comparing BRG to OFD in the treatment of intrabony defects. Abbreviations: ALL = allograft; AUT = autograft; CER = calcium phosphate (hydroxyapatite) ceramic; COR = coralline calcium carbonate; GLA = bioactive glass.

comes with regard to these measures. (Figs. 9 through 13; pages 243-244) Tests for heterogeneity were nonsignificant for all outcome measures. Richardson and coworkers[71] similarly reported comparable improvements in clinical outcome measures (bone fill, CAL, and PD) following treatment of intrabony defects with DFDBA and bovine-derived bone mineral matrix.

Graft Versus Combination Graft with Barrier

Four clinical trials provided comparisons of treatment with graft alone versus a combination of graft and barrier[39,51,54,55] (Figs. 14 through17; page 246). These studies provide clinical outcome data for different graft-barrier combinations: coralline calcium carbonate expanded polytetrafluoroethylene (ePTFE) barrier,[55] demineralized bone allograft-ePTFE barrier,[51] demineralized bone allograft-collagen barrier,[39] and HA-glycosaminoglycan-ePTFE barrier[54] (Table 6; page 248). With respect to bone level, a modest but nonsignificant trend ($P \leq 0.11$) towards more favorable improvement was found for combination graft-barrier membrane compared to graft alone (Fig. 14). Although all studies reported more favorable changes in bone level associated with combination therapy, there was significant heterogeneity among the studies ($P \leq 0.05$). Significant and consistent treatment effects were obtained for both clinical attachment level and probing depth (heterogeneity, NS), indicating more favorable gains in attachment level and reductions in probing depth following combination therapy compared to graft alone (Figs. 15 and 16). Finally, no significant effect was found in relation to gingival recession (heterogeneity, NS).

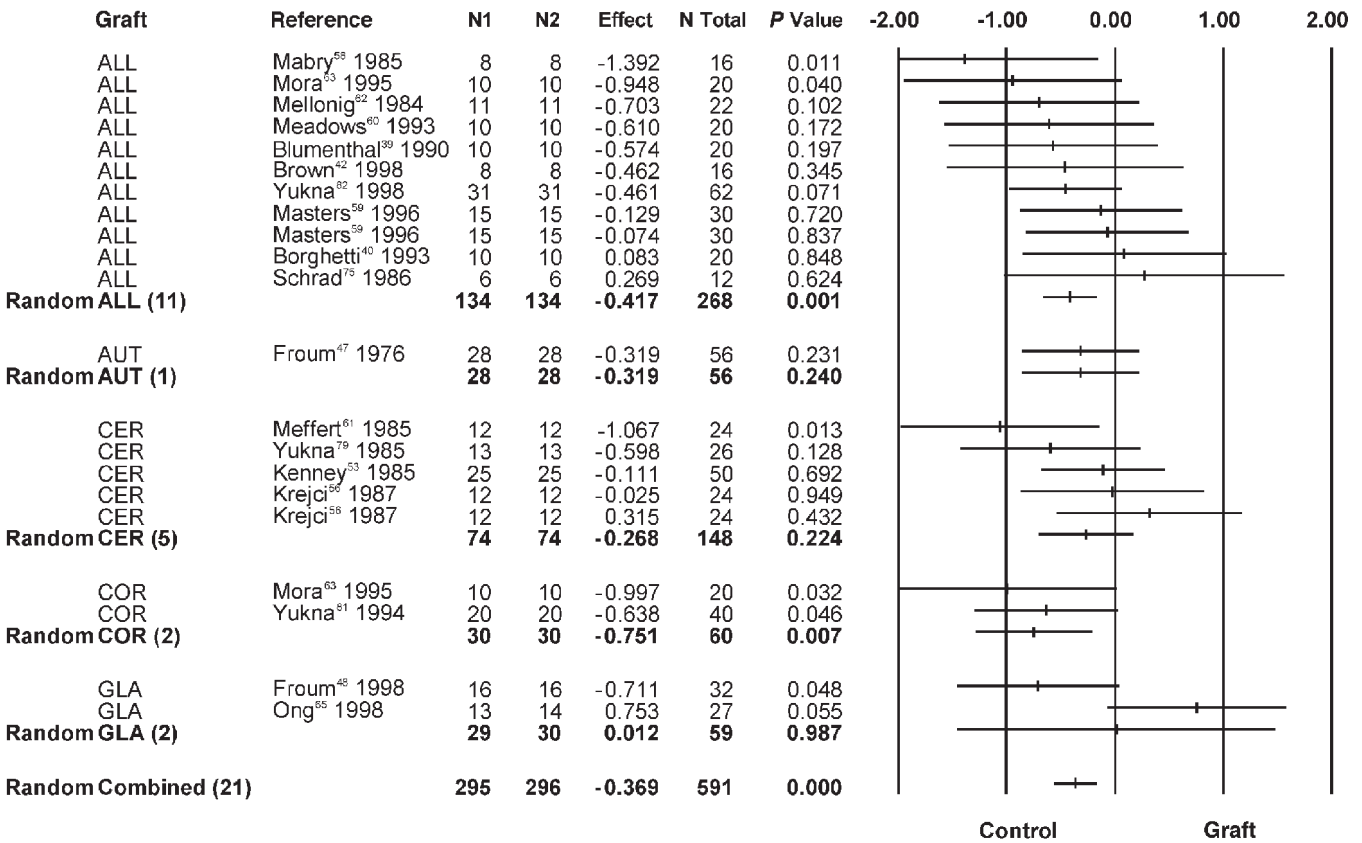

Figure 5.
Final meta-analysis of crestal resorption in randomized controlled clinical studies comparing BRG to OFD in the treatment of intrabony defects. Abbreviations: ALL = allograft; AUT = autograft; CER = calcium phosphate (hydroxyapatite) ceramic; COR = coralline calcium carbonate; GLA = bioactive glass.

Furcation Defects

Only 15 randomized controlled clinical trials compared grafts to another surgical procedure in the treatment of furcation defects and met the eligibility criteria.[35,36,45,48,58,85-88,90-96] Graft materials examined in these studies included alloplasts (PMMA/PHEMA/$CaOH_2$, HA, bioactive glass, β-TCP/$CaSO_4$),[45,48,85,90,92-96] allogenic bone,[35,36,45,58,87-89] and autogenous bone.[91,94] One published report provided a longitudinal evaluation of a previously reported clinical trial.[95] Table 7 (page 248) is a compilation of the clinical trials with a bone replacement graft treatment group and provides a summary of the characteristics and clinical outcome measures examined in these furcation studies. Seven of the available randomized controlled trials compared bone replacement grafts to open flap debridement.[48,58,86,87,90,92,93] The remaining 8 compared different graft materials, graft to barrier, or graft to barrier with graft. The frequency and distribution of grafts and interventions, as well as furcation defect types across studies, prevented the meaningful application of meta-analysis. No meaningful clustering or grouping of studies for comparison of grafts or comparison of grafts with another intervention was possible.

The efficacy of bone replacement grafts compared to open flap debridement is summarized below. Of the available 7 studies with debridement controls, 3 reported on the treatment of mandibular Class III defects[86,92,93] and 3 studies on mandibular Class II defects.[87,90,92] The seventh study reported furcation closure but no soft or hard tissue measures; nor was clarification of the furcation classification provided.[58] These data were part of an intrabony defect trial. In addition, another intrabony defect trial reported soft tissue measure changes but did not define the furcation types or report hard tissue measures.[48] Therefore, there were no consistent comparisons possible for contrasting the regenerative outcome attained following bone grafting alone when compared to open flap debridement.

The mean soft and hard tissue changes in furcations for all controlled clinical trials of bone replacement grafts are found in Table 8 (page 252). When compared to open flap debridement, the most dramatic changes are reported in a clinical trial by Froum et al.,[48] comparing bioactive glass (N = 5) to debridement alone (N = 4). The debridement arm in this study had greater mean soft tissue and hard tissue changes than other

	Graft	Reference	N1	N2	Effect	N Total	*P* Value
	ALL	Masters[59] 1996	15	15	-0.316	30	0.382
	ALL	Brown[42] 1998	8	8	-0.279	16	0.565
	ALL	Yukna[62] 1998	31	31	0.184	62	0.465
	ALL	Borghetti[40] 1993	10	10	0.272	20	0.533
	ALL	Masters[59] 1996	15	15	0.293	30	0.417
	ALL	Mabry[63] 1995	8	8	0.292	16	0.546
	ALL	Schrad[75] 1986	6	6	0.347	12	0.530
	ALL	Altiere[37] 1979	9	9	0.362	18	0.432
	ALL	Mellonig[62] 1984	11	11	0.813	22	0.061
	ALL	Movin[64] 1982	22	6	1.023	28	0.031
	ALL	Blumenthal[39] 1990	10	10	1.056	20	0.024
	ALL	Pearson[68] 1981	7	7	1.479	14	0.012
Random	**ALL (12)**		**152**	**136**	**0.376**	**288**	**0.008**
	AUT	Renvert[70] 1985	19	19	0.277	38	0.390
	AUT	Carraro[44] 1976	39	26	0.562	65	0.028
	AUT	Movin[64] 1982	6	6	1.644	12	0.012
Random	**AUT (3)**		**64**	**51**	**0.584**	**115**	**0.030**
	CER	Yukna[79] 1985	13	13	0.205	26	0.595
	CER	Galgut[53] 1992	10	10	0.584	20	0.190
	CER	Mora[63] 1995	10	10	0.917	20	0.046
	CER	Kenney[53] 1985	25	25	1.279	50	0.000
Random	**CER (4)**		**58**	**58**	**0.783**	**116**	**0.003**
	COR	Yukna[61] 1994	20	20	0.299	40	0.342
	COR	Kim[55] 1996	13	18	0.464	31	0.201
	COR	Schulz[76] 2000	11	12	1.233	23	0.006
	COR	Mora[63] 1995	10	10	1.226	20	0.010
Random	**COR (4)**		**54**	**60**	**0.705**	**114**	**0.004**
	GLA	Zamet[84] 1997	20	20	0.111	40	0.722
	GLA	Ong[65] 1998	13	14	0.254	27	0.503
	GLA	Park[37] 2001	38	38	0.902	76	0.000
	GLA	Rosenberg[72] 2000	12	6	1.264	18	0.017
Random	**GLA (4)**		**83**	**78**	**0.585**	**161**	**0.022**
Random	**Combined (27)**		**411**	**383**	**0.553**	**794**	**0.000**

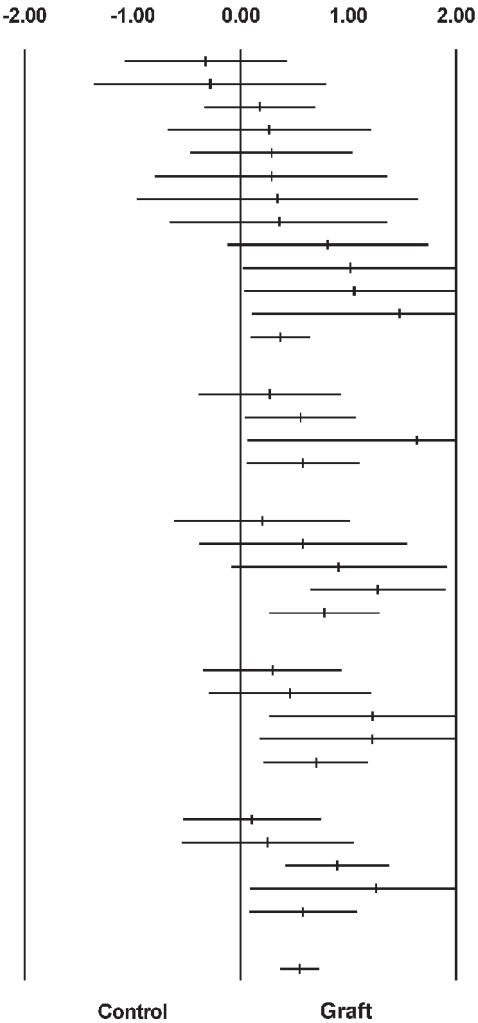

Figure 6.
Final meta-analysis of clinical attachment level in randomized controlled clinical studies comparing BRG to OFD in the treatment of intrabony defects. Abbreviations: ALL = allograft; AUT = autograft; CER = calcium phosphate (hydroxyapatite) ceramic; COR = coralline calcium carbonate; GLA = bioactive glass.

reports.[86,87,90,92,93] Initial PD and defect depths were similar to the other reports in the group.

Overall, probing depth reduction for the Class II defects ranged from 1.9 mm to 2.31 mm for bone replacement grafts when compared to their controls (debridement alone) which attained a PD reduction of 0 mm to 1.8 mm.[87,90,92] For Class III defects, grafts produced a change of 0. 7 mm to 2.43 mm, as opposed to the controls, that attained a PD change of –1.0 to 2.6 mm.[86,92,93] Clinical attachment level changes were similar for mandibular Class II and III defects. The graft treatment groups ranged from a mean change of 1.6 mm to 1.9 mm for the Class II defects and 2.2 mm to 2.6 mm for the Class III defects. Their debridement control groups attained mean clinical attachment level reductions of –0.04 mm to 1.5 mm and 0.43 mm to 1.5 mm, respectively.

There appeared to be no more dramatic difference between postsurgical recession in the graft treatment group for Class II defects than that obtained following debridement alone when compared to the treatment of Class III defects, although there were only 2 studies where possible comparison could be made. The range for mean recession change of the graft treatment groups was 0.2 mm to 1.7 mm and the range for the debridement controls 0.7 mm to 1.7 mm for both Class II and III furcation defects. Again crestal resorption varied little between treatment groups or defect types with only 2 studies each for comparison. Crestal resorption was minimal and ranged from 0.4 mm to 1.7 mm for bone replacement grafts and 0.3 mm to 1.4 mm for the controls. Differences between the graft treatment arm and the debridement controls were most apparent when comparing horizontal defect fill. The horizontal defect

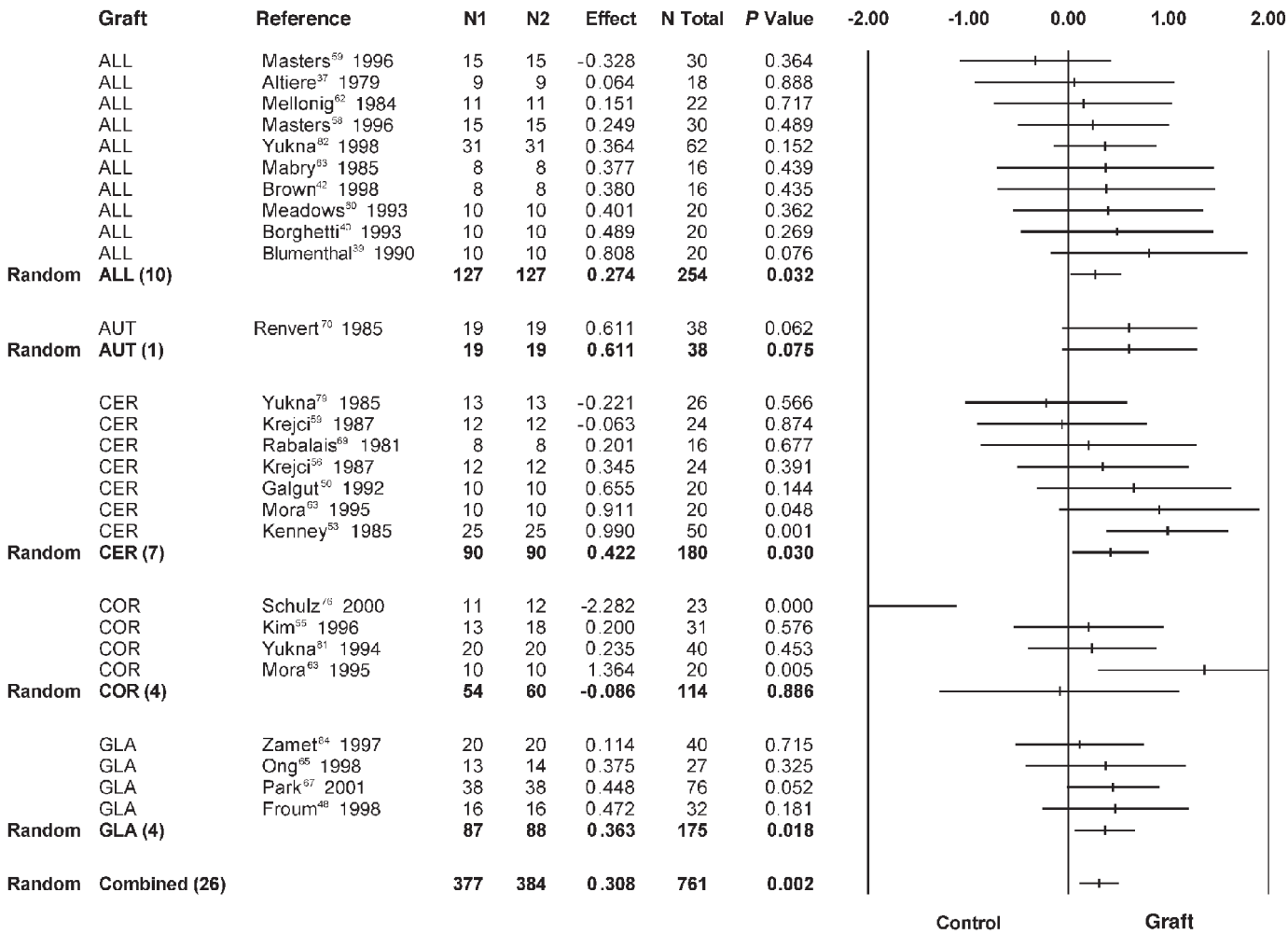

Figure 7.
Final meta-analysis of probing depth in randomized controlled clinical studies comparing BRG to OFD in the treatment of intrabony defects. Abbreviations: ALL = allograft; AUT = autograft; CER = calcium phosphate (hydroxyapatite) ceramic; COR = coralline calcium carbonate; GLA = bioactive glass.

fill for the graft treatment groups in Class II defects was 1.6 mm to 3.4 mm and that for the controls was –0.3 mm to 1.24 mm. There was only one Class III defect study that reported horizontal defect fill and this report yielded a change of 3.33 mm and –0.16 mm for the graft and control treatment groups, respectively.

There are 4 studies that compare bone graft alone to bone graft with an ePTFE barrier[35,36,85,89] for the treatment of mandibular furcation defects. One of which was non-randomized with the control treatment arm completed prior to the experimental treatment arm.[89] When compared to graft alone, Garrett et al.[89] in mandibular Class III defects and Calogne et al.[85] in mandibular Class II defects actually reported slightly lower mean PD reductions, CAL changes, and vertical defect fill for the combined treatment group when compared to the graft alone treatment arm. Overall among the 4 studies, comparisons for the mean horizontal defect fill and vertical defect fill produced similar results for combined therapy with the ePTFE barrier and bone replacement grafts. However, the largest gains in mean horizontal furcation fill were associated with combination therapy. Mean horizontal furcation defect fill ranged from 1.1 mm to 3.3 mm for combination therapy, whereas the corresponding gains ranged only from 1.0 mm to 1.8 mm for grafting alone. Improvements in mean vertical defect fill for combined therapy (0.1 mm to 2.9 mm) more closely paralleled those observed following grafting alone (0.4 mm to 2.8 mm).

The impact of combining grafts with barriers may be most apparent for furcation closure, especially the Class III defects reported by Garrett et al.,[89] where partial bony closure was greater for the defects treated with DFDBA and ePTFE and was 21.4% as opposed to 8% for OFD. In mandibular Class II defects, com-

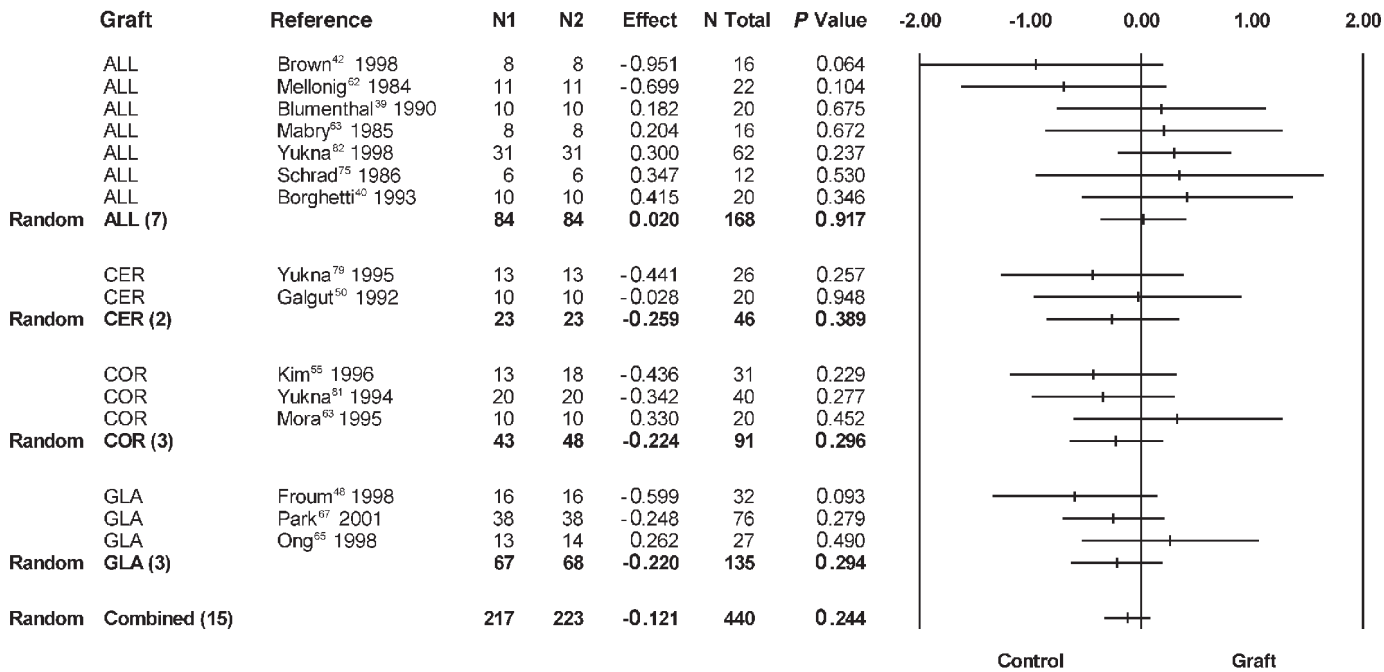

Figure 8.
Final meta-analysis of gingival recession in randomized controlled clinical studies comparing BRG to OFD in the treatment of intrabony defects. Abbreviations: ALL = allograft; CER = calcium phosphate (hydroxyapatite) ceramic; COR = coralline calcium carbonate; GLA = bioactive glass.

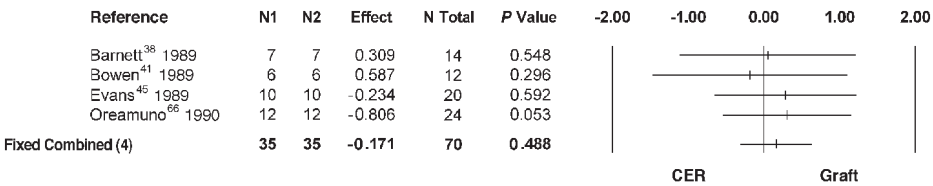

Figure 9.
Meta-analysis of change in bone level (defect fill) in randomized controlled clinical studies comparing bone allograft (DFDBA or FDBA) and calcium phosphate (hydroxyapatite) ceramic (CER) in the treatment of intrabony defects.

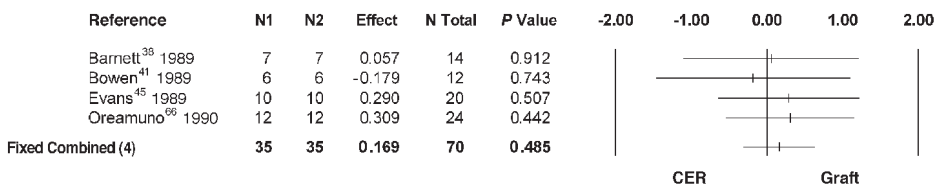

Figure 10.
Meta-analysis of crestal bone resorption in randomized controlled clinical studies comparing bone allograft (DFDBA or FDBA) and calcium phosphate (hydroxyapatite) ceramic (CER) in the treatment of intrabony defects.

paring treatment with PMMA/PHEMA/$CaOH_2$ polymer to treatment with polymer and an ePTFE barrier, partial bony closure was slightly better with the combined regenerative treatment.[85] Fifty percent (50%) of the defects treated with polymer alone and 62.5% of those treated with both polymer and guided tissue regeneration (GTR) were converted to Class I furcations, as documented upon re-entry.

Additionally, there were 2 randomized controlled trials, using comparable flap designs, that compared BRG to barrier alone and reported furcation closure.[85,96] A third compared DFDBA to duramater but the defects treated with duramater had either a replaced flap or apical positioned flaps while the DFDBA sites were treated with a coronally positioned flap.[88] Excluding the third, where the DFDBA sites performed better with respect to defect volumetric change, these studies reported no significant differences between the treatment groups with the graft and ePTFE barrier performing similarly.[85,96] The limited number of studies and the number of defects treated make conclusions difficult.

Studies not submitted to meta-analysis are summarized in Table 9 (page 254).

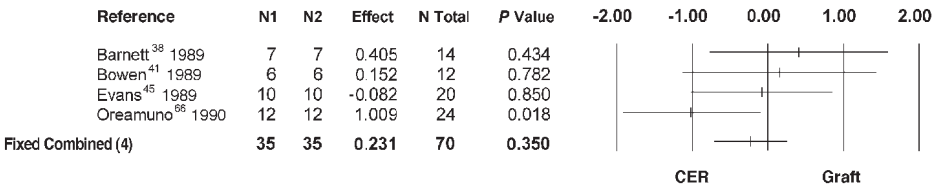

Figure 11.
Meta-analysis of clinical attachment level in randomized controlled clinical studies comparing bone allograft (DFDBA or FDBA) and calcium phosphate (hydroxyapatite) ceramic (CER) in the treatment of intrabony defects.

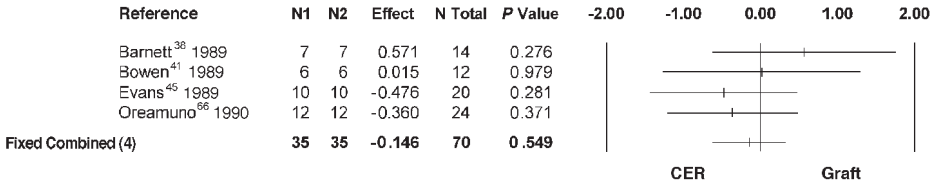

Figure 12.
Meta-analysis of probing depth in randomized controlled clinical studies comparing bone allograft (DFDBA or FDBA) and calcium phosphate (hydroxyapatite) ceramic (CER) in the treatment of intrabony defects.

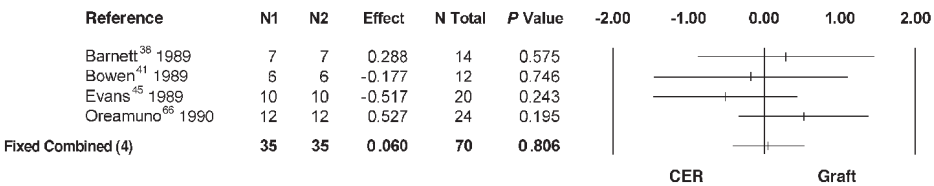

Figure 13.
Meta-analysis of gingival recession in randomized controlled clinical studies comparing bone allograft (DFDBA or FDBA) and calcium phosphate (hydroxyapatite) ceramic (CER) in the treatment of intrabony defects.

Radiographic, Adverse, and Patient-Centered Outcomes

Insufficient data are available to permit meta-analytic comparisons among surgical therapies related to radiographic outcomes. Radiographic examinations using standardized clinical and evaluation techniques,[54,56,68] including computer assisted densitiometric image analysis (CADIA),[42,46,59,84,97] were included in studies of intrabony defects. Radiographic measures generally parallel assessments of clinical outcome. However, Toback et al.[18] recently reported that linear radiographic measurements of postsurgery bone fill significantly underestimate this outcome. Moreover, although linear-CADIA estimates correlated significantly with measures of post-treatment bone fill, the magnitude of these associations was modest, accounting for approximately 50% of the variance in the clinical assessment. Therefore, linear-CADIA appears to provide valuable but less accurate information regarding changes in bone fill following graft procedures.

The majority of studies included in the review report no adverse outcomes associated with osseous defects treated with grafts,[35,39-41,45,46,50,53,55-61,63,85-93]

Table 5.

Characteristics of Clinical Trials Comparing Calcium Phosphate (Hydroxyapatite) Ceramic to Allograft (DFDBA or FDBA) in the Treatment of Intrabony Defects

Reference	Study Description	Population Age	Assessment Interval	Hard Tissue Assessment
Barnett et al.[38] 1989	Randomized, paired defects	37-63 years; mean: 48.7	6 months	Re-entry
Bowen et al.[41] 1989	Randomized, paired defects	28-52 years; mean: 42.6	6 months	Re-entry
Evans et al.[45] 1989	Randomized, split-mouth, and bilateral posterior defects	16-26 years; mean: 21.1	7-11 months	Re-entry
Oreamuno et al.[66] 1990	Randomized, paired defects	Mean: 41.4 ± 11.5 years	6 months	Re-entry

Abbreviations: β-TCP = β-tricalcium phosphate; CAL = clinical attachment level; CR = crestal resorption; DFDBA = demineralized freeze-dried bone allograft; FDBA = freeze-dried bone allograft; HA = hydroxyapatite; NS = not stated; PD = probing depth REC = gingival recession; TET = tetracycline; VDD = vertical defect depth.

although not all studies provided information relative to incidence of adverse events.[6,37,44,47,48,51,52,54,62,76,97] The most common untoward event reported was partial loss (exfoliation) of graft particles postoperatively;[42,50,56,57,69,79,80,93] however, with one exception,[42] occurrence was limited to a few patients. One report described poor clinical response to calcium HA cement in the treatment of Class III furcations.[93]

Insufficient data were available to permit analytic comparisons among surgical therapies related to patient-centered outcomes, such as changes in esthetics, incidence of residual probing depth, incidence of disease recurrence, incidence of tooth loss, and ease of receiving supportive periodontal maintenance. Of the clinical trials that provided pre- and postsurgical indices of plaque and gingival inflammation, the majority revealed stability or improvement in mean scores relative to pretreatment following treatment of intrabony[6,42,48,53,54,54,56,65,66,82,83] and furcation defects.[35,36,48,92,93] Several publications specified the absence of patient-related differences in frequency of complaints, level of comfort, or need for analgesia.[80,82,83]

Longitudinal Stability of Clinical Outcomes

Longitudinal reports are limited for the retention of treatment outcomes of bone replacement grafts for the treatment of intrabony defects and furcations. The literature search identified 5 publications providing longitudinal evaluations from 3 clinical trials of intrabony defects and 1 trial for furcation defects.[32-34,95,98] Longitudinal data were available from only 1 clinical trial[32,34] providing soft tissue evaluations of hydroxyapatite graft and OFD procedure. Forty percent of the OFD sites lost attachment over the 5-year period, whereas two-thirds of the hydroxyapatite sites gained attachment over the same interval.[34] Flemmig and coworkers[6] reported significantly greater bone fill and gains in CAL intrabony sites grafted with demineralized bone allograft (AAA bone) compared to control defects treated by modified Widman flap surgery at 36-months post-treatment. Improvements in clinical measures found at 36 months were comparable to those initially documented at 6 months. The remaining studies provide longitudinal data on stability of grafted sites, but do not permit comparative evaluations with another intervention (e.g., OFD). These studies generally report positive maintenance of the clinical response obtained postsurgically.

Histologic Evidence

Table 10 (page 254) summarizes studies reporting histological outcome following the placement of bone grafts in the treatment of periodontal osseous defects. One case report on a contiguous bone graft technique was excluded from the review.[99] Studies based on biopsy specimens of grafted defects without the bordering tooth were excluded in the summary.[38,60,100] Only 2 randomized controlled series of studies[31,101] provide comparative histological data. Bowers and colleagues provide compelling histological documentation that DFDBA supports the formation of a new attachment apparatus, including new bone, cementum, and periodontal ligament, when used as a graft in intrabony defects.[31,101] OFD alone was found to result in periodontal repair characterized primarily by the formation of a long junctional epithelial attachment.[31,101,102] A review of other histological data also provides compelling evidence that autogenous and demineralized allogeneic bone grafts support the for-

Table 5. (continued)

Characteristics of Clinical Trials Comparing Calcium Phosphate (Hydroxyapatite) Ceramic to Allograft (DFBA or FDBA) in the Treatment of Intrabony Defects

Examiner Masking	Interventions	Outcome Assessments					Location/Funding
		PD	CAL	REC	CR	VDD	
NS	HA (porous, particulate) Allograft (FDBA)	Yes	Yes	Yes	Yes	Yes	Navy/navy
No	Allograft (DFDBA) HA (porous, particulate)	Yes	Yes	Yes	Yes	Yes	Navy/NS
NS	Allograft (FDBA)/TET HA (sintered particulate)/TET β-TCP/TET	Yes	Yes	Yes	Yes	Yes	University/NS
NS	Porous HA, particulate DFDBA	Yes	Yes	Yes	Yes	Yes	University/NS

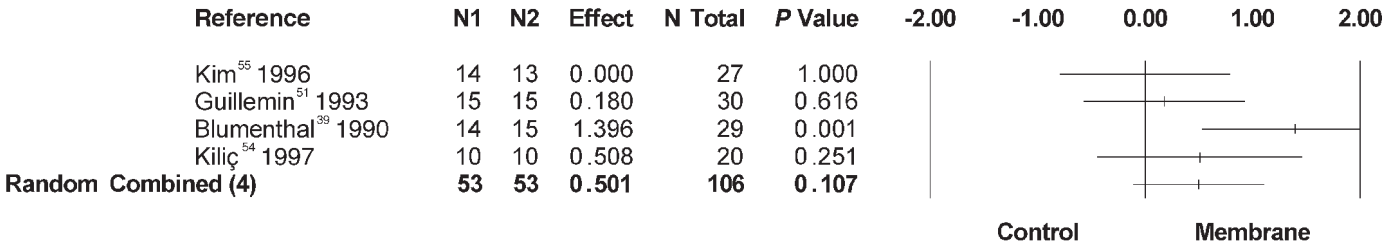

Figure 14.
Meta-analysis of change in bone level (defect fill) in randomized controlled clinical studies comparing BRG versus combination BRG/barrier membrane in the treatment of intrabony defects. BRG/BRG-barrier membrane combinations included calcium carbonate/expanded polytetrafluoroethylene (ePTFE),[55] demineralized freeze-dried bone allograft/ePTFE,[51] AAA (autolyzed, antigen-extracted, allogenic) bone/collagen,[39] and hydroxyapatite-glycosaminoglycan/ePTFE.[54]

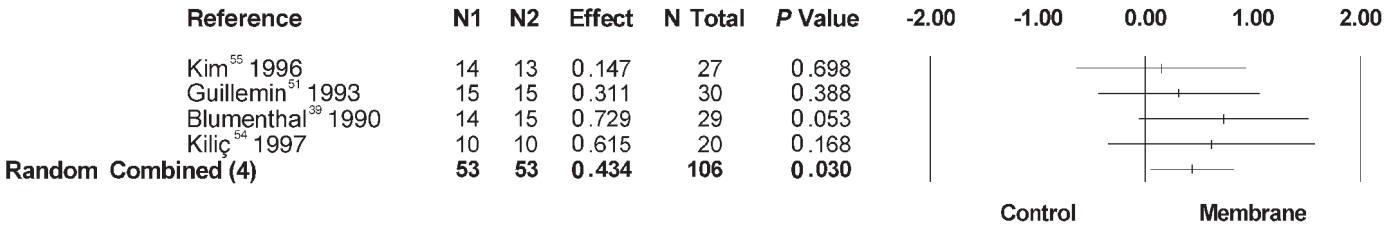

Figure 15.
Meta-analysis of clinical attachment level in randomized controlled clinical studies comparing BRG versus combination BRG/barrier membrane in the treatment of intrabony defects. BRG/BRG-barrier membrane combinations included calcium carbonate/expanded polytetrafluoroethylene (ePTFE),[55] demineralized freeze-dried bone allograft/ePTFE,[51] AAA (autolyzed, antigen-extracted, allogenic) bone/collagen,[39] and hydroxyapatite-glycosaminoglycan/ePTFE.[54]

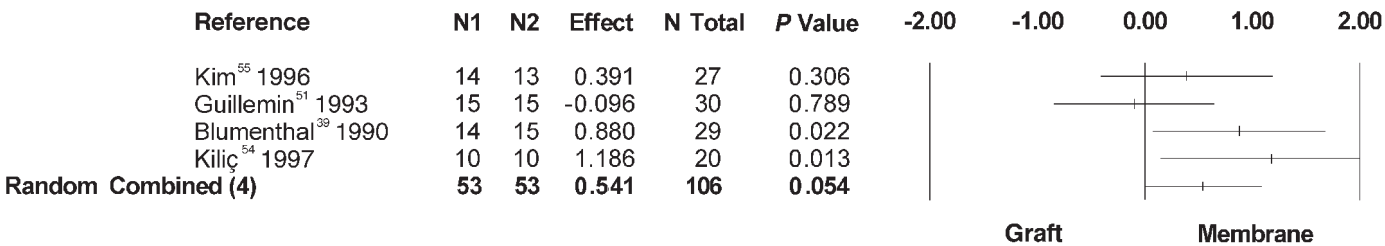

Figure 16.
Meta-analysis of probing depth in randomized controlled clinical studies comparing BRG versus combination BRG/barrier membrane in the treatment of intrabony defects. BRG/BRG-barrier membrane combinations included calcium carbonate/expanded polytetrafluoroethylene (ePTFE),[55] demineralized freeze-dried bone allograft/ePTFE,[51] AAA (autolyzed, antigen-extracted, allogenic) bone/collagen,[39] and hydroxyapatite-glycosaminoglycan/ePTFE.[54]

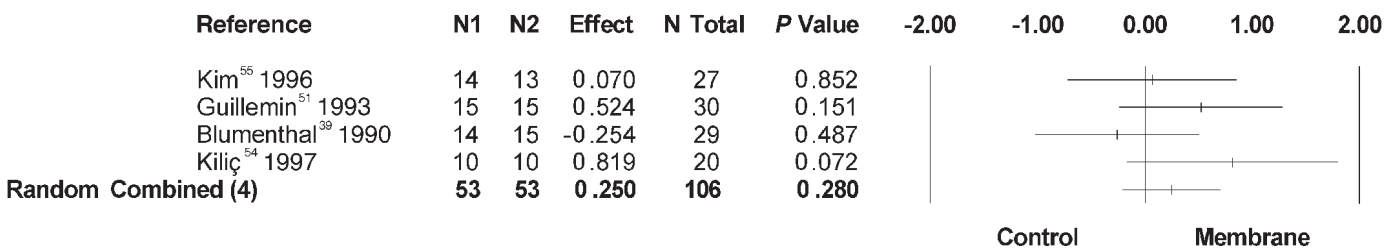

Figure 17.
Meta-analysis of gingival recession in randomized controlled clinical studies comparing BRG versus combination BRG/barrier membrane in the treatment of intrabony defects. BRG/BRG-barrier membrane combinations included calcium carbonate/expanded polytetrafluoroethylene (ePTFE),[55] demineralized freeze-dried bone allograft/ePTFE,[51] AAA (autolyzed, antigen-extracted, allogenic) bone/collagen,[39] and hydroxyapatite-glycosaminoglycan/ePTFE.[54]

mation of new attachment apparatus. Two case series provide data that xenogeneic bone can also support regeneration.[103,104] In contrast, essentially all available data indicate that alloplastic grafts support periodontal repair rather than regeneration.

DISCUSSION

The goal of this systematic review was to compare the clinical, radiographic, adverse, and patient-centered outcomes following treatment with bone replacement grafts and other surgical interventions in patients with periodontal osseous defects. Toward this end, 72 randomized controlled studies evaluating BRG materials in the treatment of osseous defects (intrabony and/or furcation) were identified in English language publications. Study populations included patients with a clinical diagnosis of chronic and aggressive periodontitis. For purposes of meta-analysis, the primary clinical outcome measure was bone fill; secondary outcome measures included crestal bone height, clinical attachment level, probing depth, and gingival recession.

The first objective of the systematic review was to determine the clinical efficacy of BRGs relative to OFD in the treatment of periodontal osseous defects. The majority of controlled studies examining the treatment of intrabony defects included an OFD comparison group or arm.[6,37,39,40,42,44,47,48,50,53-56,58-65,67-70,72,75,76,78-82,84] With respect to the primary outcome measure, bone fill, the final meta-analysis revealed significant improvements for all BRG materials, except bioactive glass; however, significant heterogeneity was observed among the combined groups. The combined analysis was significant and consistent when the bioactive glass subgroup was removed from the combined analysis. Noteworthy, however, was that in all but one study,[65] bioactive glass demonstrated enhanced bone fill relative to OFD alone. The overall analysis also indicated that significantly less crestal bone resorption was associated with BRGs than OFD alone, which was attributable largely to bone allograft and coralline subgroups. Moreover, each BRG subgroup was found to yield significantly greater gains in CAL compared to OFD. Although a significant overall treatment effect was found with respect to greater reductions in PD following treatment with BRGs than OFD, differences in PD were significant only for the bone allograft, calcium phosphate ceramic, and bioactive glass subgroups. No differences were observed in the degree of gingival recession following treatment with BRGs and OFD procedures. Collectively, the results of these controlled studies provide strong evidence that BRGs provide superior clinical outcomes than OFD procedures in the treatment of intrabony defects.

The most extensively evaluated graft material for the treatment of intrabony defects remains demineralized bone allograft, as reflected in this review. With respect to bone fill, the meta-analysis revealed significant, consistently superior gains in bone fill with demineralized bone allograft compared to OFD procedures.[6,39,42,59,60,62,63,82] These results are particularly informative, given clinical concerns arising from apparent inconsistencies in osteoinductive capacity of DFDBA related to processing and donor age.[105-108] Commercially-prepared DFDBA has been shown to retain active bone matrix proteins, such as bone morphogenetic proteins-2, -4, and -7, although some biological activity appears to be lost as a result of tissue processing compared to fresh allograft.[109] Within the context of evidence on clinical outcome, the data strongly indicate that DFDBA results in consistently superior improvements relative to OFD in the treatment of intrabony defects. Osteoinductive capacity, therefore, may be important to the histological rather than clinical outcome following grafting with demineralized bone matrix.

Freeze-dried bone allograft also has been shown in observational and controlled studies to improve clinical outcomes in intrabony defects.[21,26,37,38,58,73] However, only 2 controlled studies were identified that examined the clinical benefits of FDBA relative to OFD.[37,58] With respect to bone fill, the subgroup analysis failed to show a significant benefit of FDBA compared to OFD.[58] Although these studies do not support the use of FDBA in the treatment of intrabony defects, insufficient data are available to conclude that the material lacks clinical efficacy with regard to changes in bone fill. That positive clinical outcomes have been reported with FDBA in other studies is consistent with this interpretation.[38,66,110] Furthermore, the clinical characteristics of FDBA, such as containment and space maintenance, contribute to the interest in this graft matrix as a scaffold-based carrier for biologically active molecules.[111] Moreover, there is human evidence to suggest that the osteoconductive properties of FDBA may be superior to those of DFDBA.[112] DFDBA has been shown to function clinically as a carrier for biologically active proteins,[101,113,114] and a case series documents the use of FDBA as a carrier for enamel matrix derivative with successful clinical outcomes in advanced osseous defects.[111] In vitro studies indicate that biological mediators can significantly modify the cellular effects of FDBA and DFDBA matrices.[115-117] Future studies are required to determine the potential therapeutic role of allografts as scaffold-based carriers of biologically active molecules, such as growth and differentiation factors.

The relative clinical benefits of different BRGs in the treatment of intrabony defects have been examined in multiple studies. However, sufficient comparative studies were available only to permit meaningful comparisons of clinical outcomes between bone allograft

Table 6.

Characteristics of Clinical Trials Comparing Bone Replacement Grafts and Barriers in the Treatment of Intrabony Defects

Reference	Study Description	Population Age	Assessment Interval	Hard Tissue Assessment
Blumenthal & Steinberg[39] 1990	Randomized, within subject (by site)	34-57 years	12 months	Re-entry
Kiliç et al.[54] 1997	Randomized, paired defects	35-60 years	6 months	Radiographic & sounding
Kim et al.[55] 1996	Randomized, between subjects	23-60 years; mean: 39.3	6 months	Sounding
Guillemin[51] 1993	Randomized, paired defects	Mean: 43.4 years	6 months	Re-entry

Abbreviations: AAA = autolyzed, antigen-extracted, allogenic; CAL = clinical attachment level; CR = crestal resorption; DFDBA = demineralized freeze-dried bone allograft; ePTFE = expanded polytetrafluoroethylene; HA = hydroxyapatite; OFD = open flap debridement; NS = not stated; REC = gingival recession; VDD = vertical defect depth.

Table 7.

Characteristics of Clinical Trials Examining BRG in the Treatment of Class II and Class III Furcation Defects

Reference	Study Description	Population Age	Assessment Interval	Hard Tissue Assessment
Calogne et al.[85] 2001	Randomized, paired mandible Class II defects	48-63 years; mean: 54 years	6 months	Re-entry
Evans et al.[45] 1989	Randomized, split-mouth, and bilateral posterior defects	16-26 years; mean: 21.1	7-11 months; mean: 9 months	Re-entry
Gantès et al.[86] 1991	Randomized, between subjects, mandibular Class III defects	NS	6 months	None (re-entry 1 of 27 subjects)
Gantès et al.[87] 1988	Randomized within and between subjects; comparison of mandibular Class II buccal furcation defects	NS	12 months	Re-entry and sounding
Garrett et al.[88] 1990	Randomized between subjects, mandibular Class II furcation defects	NS	12 months	Re-entry

Table 6. (continued)

Characteristics of Clinical Trials Comparing Bone Replacement Grafts and Barriers in the Treatment of Intrabony Defects

Examiner Masking	Interventions	Outcome Assessments					Location/Funding
		PD	CAL	REC	CR	VDD	
No	Allograft (AAA bone) Allograft (AAA bone)/collagen membrane OFD	Yes	Yes	Yes	Yes	Yes	University/NS
Clinical: single examiner, NS; radiographic: 4 examiners, Yes	HA-collagen/barrier (ePTFE) Membrane (ePTFE) HA collagen (HA-glycosaminoglycan) OFD	Yes	Yes	Yes	No	Yes	University/NS
Yes	Membrane (ePTFE) Coralline calcium carbonate Coralline calcium carbonate/ePTFE barrier OFD	Yes	Yes	Yes	No	Yes	University/industry
NS	Allograft (DFDBA) Allograft (DFDBA)/membrane (ePTFE)	Yes	Yes	Yes	Yes	Yes	University/foundation

Table 7. (continued)

Characteristics of Clinical Trials Examining BRG in the Treatment of Class II and Class III Furcation Defects

Examiner Masking	Interventions	Outcome Assessments								Location/Funding
		PD	CAL	REC	CR	VDF	HP	HDF	FC	
Yes; 2 calibrated examiners	PMMA/PHEMA/$CaOH_2$ ePTFE PMMA/PHEMA/$CaOH_2$/ePTFE	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	University industry
NS	Allograft (FDBA)/TET HA (sintered particulate)/TET β-TCP/TET	No	No	No	No	No	No	No	No	University/NS
NS; single examiner for osseous measures; 3 for soft tissue measures	CPF/CA, CPF/CA, DFDBA,	Yes	Yes	No	No	No	No	No	Yes	University/NIH
NS	DFDBA, CPF/CA CPF/CA	Yes	Yes	No	No	Yes	No	Yes	Yes	University/NIDR
Yes; 2 examiners	DFDBA, CPF, Duramater, replaced or apically positioned flap (at level of the alveolar crest)	Yes	No	No	Yes	Yes	No	Yes	Yes	University/NIDR

(continued)

Table 7. (continued)

Characteristics of Clinical Trials Examining BRG in the Treatment of Class II and Class III Furcation Defects

Reference	Study Description	Population Age	Assessment Interval	Hard Tissue Assessment
Garrett et al.[89] 1994	Non-randomized, between subjects comparison, Class III furcation defects	40-65 years; mean: 59 years	12-15 months	Re-entry
Froum[48] 1998	Randomized, paired intrabony or furcation defects	Mean: 43 years	12 months	Re-entry
Kenney et al.[90] 1988	Randomized, paired Class II mandible furcations	Mean: 43.2 ± 8.4 years	6 months	Re-entry
Mabry et al.[58] 1985	Randomized, paired intraosseous defects (associated with Class I, II, and III furcation defects) and parallel arms between subjects	13-26 years; mean: 18.7 ± 3.8 years	12 months	Re-entry
Peltzman[91] 1989	Randomized, paired mandibular Class II defects	NS	6 months	Re-entry
Pepelassi et al.[92] 1991	Randomized, within patient comparison of either Class II or Class III furcation defects	32-64 years	6 months	Re-entry
Rosen[35] 1989	Randomized, paired mandibular Class II defects	30-60 years	24-28 weeks	Re-entry
Rupprecht et al.[93] 2001	Randomized, Class III defects	Mean: 58.7 ± 7.65 years	9 months	Re-entry and sounding
Tetzner[36] 1997	Randomized, paired Class II mandibular defects	29-63 years	7-9 months	Re-entry
Yukna[94] 1994	Randomized, paired mandible Class II defects	38-64 years; mean: 50.9 years	6-12 months	Re-entry
Yukna et al.[95] 1997	Six year follow-up of subgroup from reference 94	NS	6+ years	None
Yukna et al.[96] 2001	Randomized paired mandible Class II defects	39-72 years; mean: 54 years	6 months	Re-entry

Abbreviations: β-TCP = β-tricalcium phosphate; CA = citric acid; CAL = clinical attachment level; CPF = coronally positioned flap; CR = crestal resorption; DFDBA = demineralized freeze-dried bone allograft; ePTFE = expanded polytetrafluoroethylene; FC = furcation closure; FDBA = freeze-dried bone allograft; HA = hydroxyapatite; HDF = horizontal defect fill; HP = horizontal probing depth; OFD = open flap debridement; NS = not stated; PD = probing depth; PMMA/PHEMA, $CaOH_2$ = polymethyl-methacrylate + polyhydroxylethyl-methacrylate; REC = gingival recession; TET = tetracycline; VDF = vertical defect fill.

(DFDBA and FDBA) and HA,[38,41,45,66] which yielded no significant differences with respect to changes in bone level, crestal resorption, clinical attachment level, probing depth, and gingival recession. The results of the meta-analysis, therefore, suggest comparable clinical outcomes following the application of particulate bone allograft and HA. Tests for heterogeneity were not significant for the outcome measures. In addition, similar clinical outcomes have been reported for DFDBA and FDBA in the treatment of intrabony defects.[73] Future controlled studies are necessary to determine the relative efficacy of different BRG materials in the treatment of periodontal osseous defects.

Case reports document the combined use of BRGs and barrier membranes in the successful treatment of intrabony defects.[118-122] Clinical improvements with graft-barrier combinations often have been in association with larger, non-space maintaining defects,[121] despite limited controlled studies to support clinical benefits of combined approaches beyond those attain-

Table 7. (continued)

Characteristics of Clinical Trials Examining BRG in the Treatment of Class II and Class III Furcation Defects

Examiner Masking	Interventions	Outcome Assessments								Location/Funding
		PD	CAL	REC	CR	VDF	HP	HDF	FC	
No	DFDBA, CPF/CA DFDBA/ePTFE, CPF/CA	Yes	Yes	No	No	Yes	No	No	Yes	University/NIH
NS; single examiner	Bioactive glass OFD	Yes	Yes	Yes	Yes	Yes	No	No	No	University/ industry
NS	Porous HA OFD	Yes	Yes	Yes	No	Yes	No	Yes	No	University/NS
NS; single examiner per patient	1. Allograft (FDBA) 2. FDBA/TET (local and systemic) 3. OFD/TET (systemic) 4. OFD	No	No	No	No	No	No	No	Yes	University/NIH
NS	Autograft/fibronectin autograft	Yes	Yes	No	No	No	No	No	No	University/NS
NS	β-TCP, plaster of Paris and doxycycline, CPF CPF	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	University/NS
Yes	DFDBA/ePTFE, CPF DFDBA, CPF	No	Yes	Yes	Yes	Yes	No	Yes	No	University/none
NS	CPF/CA HA cement, CPF/CA	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Navy/industry
No	DFDBA, CPF DFDBA/ePTFE, CPF	No	Yes	Yes	Yes	Yes	No	Yes	No	University/none
NS	PMMA/PHEMA/$CaOH_2$, CPF Osseous coagulum, CPF	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Private practice and university/ industry
NS	PMMA/PHEMA/$CaOH_2$, CPF	Yes	Yes	Yes	No	No	No	No	Yes	Private practice/ industry
Yes	Bioactive glass, CPF ePTFE, CPF	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	University/ industry

able with grafting alone.[123] This review identified several controlled studies that compared treatment outcomes following use of grafts in combination with barrier membranes to grafting alone.[39,51,54,55] Although comparing different graft-barrier combinations, the studies nonetheless permit a general comparison of clinical outcomes following a combined approach (BRG-barrier membrane) relative to BRG alone. With respect to bone fill, a modest but nonsignificant trend was found towards more favorable improvement for combination therapy compared to graft alone. Moreover, significant and consistently greater gains in CAL and reductions in PD were found following combination therapy compared to graft alone. Interestingly, in a systematic review by Needleman and coworkers,[124] the combination of a BRG and GTR was found to result in a greater gain in hard tissue probing than GTR alone, when comparing each to OFD. Collectively, these results suggest that combination therapy using BRG and GTR may offer therapeutic advantages beyond those of either approach alone in the management of more challenging osseous defects.

In contrast to intrabony defects, substantially fewer controlled clinical trials have compared BRGs to OFD

Table 8.

Mean Change in Clinical Outcome Measures in Studies Examining Bone Replacement Grafts in the Treatment of Class II and III Furcation Defects

Reference	Interventions	N	PD	CAL	REC	CR	VDF	HDF	FC
Calogne et al.[85] 2001	1. PMMA/PHEMA/ $CaOH_2$, CPF	8	1.6 ± 0.9	1.4 ± 1.1	0.3 ± 1.6	1.0 ± 1.3	0.4 ± 1.2	1.8 ± 1.0	Complete bone closure 1. 1/8 (13%)
	2. ePTFE, CPF	8	0.9 ± 0.9	0.8 ± 1.5	0.4 ± 1.1	1.3 ± 0.6	−0.4 ± 1.4	0.7 ± 1.2	2. 0
	3. PMMA/PHEMA/ $CaOH_2$/ ePTFE, CPF	8	1.3 ± 1.3	1.3 ± 1.3	0.6 ± 1.4	1.1 ± 1.4	0.1 ± 1.4	1.1 ± 0.9	3. 0 Partial bone closure 1. 4/8 (50%) [II → I] 2. 5/8 (62.5%)[II → I] 3. 5/8 (62.5%)[II → I]
Evans et al.[45] 1989	1. Allograft FDBA/TET	9							Complete bone closure 1. 2/9 (22.2%) [II → 0]
	2. HA (sintered particulate)/TET	6							2. 2/6 (33.3%) [II → 0]
	3. β-TCP/TET	10	NA	NA	NA	NA	NA	NA	3. 0/10 (0%) Partial bone closure 1. 4/9 (44.4%) [II → I] 2. 4/6 (66.7%) [II → I] 3. 5/10 (50%) [II → I]
Gantès et al.[86] 1991	1. CPF/CA,	14	2.6 ± 1.5	2.2 ± 1.1					Soft tissue closure 1. 1/14 (7.1%)
	2. CPF/CA, DFDBA,	13	1.9 ± 2.1	1.5 ± 2.4	NA	NA	NA	NA	2. 3/13 (23.1%)
Gantès et al.[87] 1988	1. DFDBA, CPF/CA	16	1.9 ± 1.2	1.6 ± 1.2			2.4 ± 1.4	2.6 ± 1.4	Complete bone closure
	2. CPF/CA	14	1.8 ± 1.7	1.5 ± 1.9	NA	NA	2.4 ± 1.9	3.0 ± 1.9	1. 6/14 (43%) 2. 7/16 (44%)
Garrett et al.[88] 1990	1. DFDBA, CPF,	16	2.7 ± 1.4			0.3 ± 0.4	2.3 ± 1.2	2.6 ± 1.1	Bone closure
	2. Duramater, RF, or APF	15	2.3 ± 1.1	NA	NA	0.1 ± 0.5	2.3 ± 1.2	2.3 ± 1.2	1. 9/16 (56%) 2. 3/15 (20%)
Garrett et al.[89] 1994	1. DFDBA, CPF/CA	12	2.9 ± 1.1	2.0 ± 1.1			2.8 ± 3.4		Partial bone closure
	2. DFDBA/ePTFE, CPF/CA	14	1.6 ± 1.2	1.0 ± 1.2	NA	NA	1.6 ± 1.6	NA	1. 1/12 (8%) [III → II] 2. 3/14 (21%) [III → II] Soft Tissue Change 1. 4/12 (33%) 2. 4/14 (29%)
Froum et al.[48] 1998	1. Bioactive glass	5	3.7 ± 0.9 (SE)	2.9 ± 0.9	0.7 ± 0.5	0.6 ± 0.4	3.5 ± 0.6		
	2. OFD	4	2.9 ± 1.0 (SE)	1.9 ± 1.0	1.0 ± 0.6	1.4 ± 0.5	2.6 ± 0.7	NA	NA
Kenney et al.[90] 1988	1. Porous HA	23	1. 21 mm	1.8 ± 0.7	0.2 ± 0.4		2.0 ± 0.5	1.6 ± 0.9	
	2. OFD	23	2. NS	−0.04 ± 0.9	0.7 ± 0.7	NA	−0.3 ± 0.7	−0.3 ± 0.7	NA
Mabry et al.[58] 1985	1. Allograft (FDBA)	4							Complete bone closure 1. 0/2 (0%) [II → 0]
	2. FDBA/TET (local and systemic)	8							2. 3/4 (75%) [II → 0]
	3. OFD/TET (systemic)	7							3. 0/7 (0%)
	4. OFD	3	NA	NA	NA	NA	NA	NA	4. 0/3 (0%) Partial bone closure 1. 1/2 (50%) [II → I] 2. 1/4 (25%) [II → I] 3. 5/7 (71.4%) [II → I] 4. 1/1 (100%) [II → I]

Table 8. (continued)

Mean Change in Clinical Outcome Measures in Studies Examining Bone Replacement Grafts in the Treatment of Class II and III Furcation Defects

Reference	Interventions	N	PD	CAL	REC	CR	VDF	HDF	FC
Peltzman[91] 1989	Autogenous/ fibronectin	4	2.8 ± 1.17	0.40 ± 1.52			0 (no bone fill)		
	Autogenous	4	1.6 ± 1.62	0.00 ± 1.87	NA	NA	0 (no bone fill)	NA	NA
Pepelassi et al.[92] 1992	Class II defects								
	1. β-TCP, plaster of Paris & doxycycline, CPF	13	2.31 ± 1.77	1.88 ± 1.66	0.23 ± 0.39	0.28 ± 0.12	2.33 ± 1.33	3.41 ± 0.91	
	2. CPF	13	1.5 ± 1.56	0.57 ± 0.95	0.85 ± 0.69	0.60 ± 0.10	0.52 ± 0.74	1.24 ± 0.99	NA
Pepelassi et al.[92] 1991	Class III defects (buccal)								
	1. β-TCP phosphate, plaster of Paris & doxycycline, CPF	7	2.43 ± 0.73	2.64 ± 0.69	0.26 ± 0.38	0.36 ± 0.11	2.43 ± 0.41	3.33 ± 1.40	
	2. CPF	7	0.5 ± 1.04	0.43 ± 1.09	0.86 ± 0.69	0.66 ± 0.19	0.56 ± 0.45	–0.16 ± 0.15	NA
Rosen[35] 1989	DFDBA/ ePTFE, CPF	6	0.57 ± 1.17	0.75 ± 1.16	0.87 ± 0.99	–0.25 ± 0.71	1.0 ± 1.07	1.63 ± 1.41	
	DFDBA, CPF	6	0.63 ± 0.74	0.62 ± 0.74	0.63 ± 0.52	0.13 ± 0.64	0.63 ± 0.5	1.00 ± 0.53	NA
Rupprecht et al.[93] 2001	(Buccal data only)								Complete bone closure
	1. CPF/CA with Hydroxylapatite cement,	6	0.7 ± 1.8	2.3 ± 2.2	1.7 ± 1.8	1.7 ± 2.0	2.0 ± 2.3		0
	2. CPF/CA	3	–1.0 ± 1.0	0.7 ± 2.1	1.7 ± 1.2	0.3 ± 0.6	0.7 ± 1.2	NA	0
Tetzner[36] 1997	DFDBA/ePTFE, CPF	5	1.16 ± 1.27	1.7 ± 0.9	1.0 ± 0.6	0.7 ± 0.6	2.9 ± 1.2	3.3 ± 1.0	
	DFDBA, CPF	5	1.18 ± 1.50	1.2 ± 1.3	0.7 ± 0.4	0.0 ± 0.9	2.7 ± 1.3	1.6 ± 0.7	NA
Yukna[94] 1994	1. PMMA/PHEMA/ $CaOH_2$, CPF	15	2.1 ± 1.2	0.8 ± 1.4	1.3 ± 1.1	0.6 ± 1.4	1.6 ± 1.4	1.9 ± 1.2	Complete bone closure
	2. Autogenous osseous coagulum, CPF	15	1.9 ± 1.1	1.0 ± 1.2	0.8 ± 1.6	0.4 ± 0.9	1.7 ± 0.7	0.8 ± 0.6	1. 1/15 (6.7%) [II → 0] 2. 0/15 (0%) [II → 0] Partial bone closure 1. 11/15 (73.3%) [II → I] 2. 6/15 (40%) [II → I]
Yukna et al.[95] 1997	1. (PMMA/PHEMA, $CaOH_2$), CPF (6-year follow-up of subgroup from reference 94)	26	NSD to Yukna[94]	NSD to Yukna[94]	NSD to Yukna[94]	NA	NA	NA	Complete bone closure 1. 3/10 (30%) Partial bone closure 1. 5/10 (50%) [II → I] Response over time 1. 8/10 improved from re-entry; 2/10 remained the same or worsened
Yukna et al.[96] 2001	Bioactive glass, CPF	27	1.4 ± 1.2	0.4 ± 1.0	0.8 ± 1.2	0.3 ± 1.1	2.54 ± 1.03	1.4 ± 1.4	Complete bone closure
	ePTFE, CPF	27	1.1 ± 1.1	0.3 ± 0.9	0.8 ± 1.1	0.7 ± 0.7	0.78 ± 1.17	1.3 ± 1.1	1. 0/27 (0%) [II → I] 2. 0/27(0%) [II → I]

Abbreviations: APF = apically positioned flap; β-TCP = β-tricalicum phosphate; CA = citric acid; CAL = clinical attachment level; CPF = coronallly positioned flap; CR = crestal resorption; DFDBA = demineralized freeze-dried bone allograft; ePTFE = expanded polytetrafluoroethylene; FC = furcation closure; FDBA = freeze-dried bone allograft; HA = hydroxyapatite; HDF = horizontal defect fill; HP = horizontal probing depth; OFD = open flap debridement; NA = not available; NS = not stated; PD = probing depth; REC = gingival recession; RF = repositioned flap; TET = tetracycline; VDF = vertical defect fill.

Table 9.

Characteristics of RCT Bone Replacement Graft Studies Not Submitted to Meta-Analysis

Reference	Study Description	Population Age	Assessment Interval	Hard Tissue Assessment
Richardson et al.[71] 1999	Randomized, paired within subjects and some unpaired intrabony defects	34-67 years	6 months	Re-entry
Sculean et al.[77] 2002	Randomized, parallel design	NS	12 months	None
Scheyer et al.[74] 2002	Randomized, paired defects	32-73 years	6 months	Re-entry
Yukna et al.[83] 2000	Randomized, paired defects and multi-centered	33-81 years	6-7 months	Re-entry

Abbreviations: ABM = anorganic bone mineral matrix; CAL = clinical attachment level; CR = crestal resorption; DFDBA = demineralized freeze-dried bone allograft; EMD = enamel matrix derivative; HA = hydroxyapatite; NS = not stated; OFD = open flap debridement; P-15 = peptide 15; REC = gingival recession; VDD = vertical defect depth.

Table 10.

Histological Outcomes Following Treatment of Periodontal Osseous Defects with Bone Replacement Grafts

Reference/BRG	Intervention	Defect	Histologic Landmark	N (sites)	NAA (mm), NC (mm), NB (mm), CT (mm)	Location
Bone Replacement Graft						
None						
Hiatt et al.[149] 1978	OFD	ID	RP	21	NAA (evidence for 7 of 21)	USA
Listgarten & Rosenberg[150] 1979	OFD	ID	NBD	3	NC (0 mm)	Colombia
Bowers et al.[102] 1989	OFD	ID	CN	22	No evidence of NAA	USA
Bowers et al.[31] 1989	OFD	ID	CN	25	No evidence of NAA	USA
Autograft or Allograft						
Ross and Cohen[151] 1968	AUT	ID		1	NB	
Hiatt et al.[149] 1978	AUT, ALL (frozen)	ID	RP	39	NAA (evidence for 33 of 39)	USA
Moskow et al.[152] 1979	AUT	ID		1	No evidence of NAA	USA
Nabers et al.[153] 1972	AUT	ID		1	No evidence of NAA	USA
Langer et al.[154] 1981		ID	None	1		USA
Dragoo & Sullivan[155] 1973	AUT	ID	NBC	12	0.7, 1.7, 0.7, 1.0	USA
Hawley & Miller[156] 1975	AUT	ID	RP	1	NAA	USA
Hiatt & Schallhorn[157] 1973	AUT	ID	RP	1	NAA, NC, NB (5 mm)	USA
Evans[158] 1981	AUT	ID		1	NAA, NC, NB	USA
Froum et al.[159] 1975	AUT	ID	RP	3	NAA, NC, NB	USA
Froum et al.[160] 1982	AUT + CA	ID	CN	3	NAA, NC, NB (at the base of the defect)	USA
Stahl et al.[161] 1983	AUT	ID	CN	5	Limited coronal regeneration (not quantified)	USA
	AUT + CA	ID	CN	3	Limited coronal regeneration	USA
Listgarten & Rosenberg[150] 1979	AUT + no RP	ID	NBD	3	NC (0.3 mm) + F71 + F26	Colombia
	AUT + RP	ID	NBD	3	NC (1.7 mm)	
Listgarten & Rosenberg[150] 1979	ALL + no RP	ID	NBD	3	NC (0.3 mm)	Colombia
	ALL + RP	ID	NBD	3	NC (2.7 mm)	
Stahl et al.[161] 1983	ALL (DFDBA)	ID	CN	1	Limited coronal regeneration	USA
Dragoo & Kaldahl[162] 1983	ALL (DFDBA)	ID	NBD	NS	No evidence of NAA	USA
Dragoo & Kaldahl[162] 1983	ALL (DFDBA) + CA	ID	NBD	NS	No evidence of NAA	USA

Table 9. (continued)

Characteristics of RCT Bone Replacement Graft Studies Not Submitted to Meta-analysis

Examiner Masking	Interventions	Outcome Assessments					Location/Funding
		PD	CAL	REC	CR	VDD	
Yes; single masked and calibrated examiner	ABM DFDBA	Yes	Yes	No	Yes	Yes	University/ industry
Yes; calibrated examiner	Bioactive glass Bioactive glass + EMD	Yes	Yes	Yes	No	No	University/NS
Yes; single examiner	Bioactive glass Bioactive glass + EMD	Yes	Yes	Yes	Yes	Yes	University/ industry
Yes	HA-P-15 OFD	Yes	Yes	Yes	Yes	Yes	University & private practice/ industry

Table 10. (continued)

Histological Outcomes Following Treatment of Periodontal Osseous Defects with Bone Replacement Grafts

Reference/BRG	Intervention	Defect	Histologic Landmark	N (sites)	NAA (mm), NC (mm), NB (mm), CT (mm)	Location
Bowers et al.[31] 1989	ALL (DFDBA) + FGG	ID	CN	32	1.2, 1.2, 1.8, 1.3	USA
Bowers et al.[101] 1991	ALL (DFDBA)	ID	CN	11	1.7, 1.7, 2.5, 0.02	USA
Dragoo & Kaldahl[162] 1983	ALL (FDBA)	ID	NBD	NS	No evidence of NAA	USA
Froum[163] 1996	ALL (FDBA)	ID	CN	3	No evidence of NAA	USA
Dragoo & Kaldahl[162] 1983	ALL (dentin, demineralized)	ID	NBD	NS	No evidence of NAA	USA
Xenograft						
Nevins et al.[103] 2003	ABM collagen	ID	CN	2	NAA (3.0, 3.1) NB (4.1, 3.1) NC (3.4, 3.7)	USA
Camelo et al.[104] 1998	ABM	ID	NBD	2	NC, NB, CT	USA
Bowers et al.[101] 1991	Collagen	ID	CN	12	0.1, 0.1, 0.1, 0	USA
Alloplast/Ceramic Grafts						
Froum et al.[160] 1982	Durapatite	ID	RP	4	No evidence of NAA	USA
Stahl et al.[161] 1983	Durapatite	ID	CN	1	No evidence of NAA	USA
Moskow & Lubarr[164] 1983	Durapatite/AUT	ID/FUR	none	1	NC, CT, (associated with AUT only)	USA
Sapkos[165] 1986	HA	ID	RP	5	No evidence of NAA	USA
Shepard et al.[166] 1986	HA	ID	RP	1	No evidence of NAA	USA
Loise et al.[167] 1992	Coralline calcium carbonate	ID	RP	4	No evidence of NAA	USA
Carranza et al.[168] 1987	PHA	ID	RP	2	1 specimen limited NC	USA
Stahl & Froum[169] 1987	PHA	ID	CN	12	No evidence of NAA	USA
Baldock et al.[170] 1985	β-TCP	ID	NBD	6	NC (0.5), CT (1.6)	USA
Stahl & Froum[171] 1986	β-TCP	ID	CN	8	No evidence of NAA	USA
Bowers[172] 1986	β-TCP	ID		4	No evidence of NAA	USA
Froum & Stahl[173] 1987	β-TCP	ID	CN	5	No evidence of NAA	USA
Saffar et al.[174]	β-TCP	ID		5	No evidence of NAA	France
Froum[163] 1996	PMMA/PHEMA, $CaOH_2$	ID	CN	3	No evidence of NAA	USA
Stahl et al.[175] 1990	PMMA/PHEMA, $CaOH_2$	ID	CN	11	Limited NAA in 4/11	USA
Nevins et al.[176] 2000	Bioactive glass	ID	NBD	5	No evidence of NAA, limited NB at base	USA

Table 10. (continued)

Histological Outcomes Following Treatment of Periodontal Osseous Defects with Bone Replacement Grafts

Reference/BRG	Intervention	Defect	Histologic Landmark	N (sites)	NAA (mm), NC (mm), NB (mm), CT (mm)	Location
Biologically Modified Graft						
Yukna et al.[177] 2002	ABM + P-15	ID	CN	1	NB, NC, NAA (not quantified)	USA
Bone Replacement Graft + Barrier						
Harris[178] 1999	ALL (DFDBA) + polymer membrane	FUR	CN	3	NAA, NC, NB (2 sites)	USA
Harris[179] 2000	ALL (DFDBA) + TET + polymer membrane	ID	CN	2	No evidence of NAA, NC, CT	USA
Harris[180] 2002	ALL (DFDBA) + PHA + TET + polymer membrane	FUR	CN	3	NAA (1 site) CT NC (2 sites)	USA
Stahl et al.[181] 1991	ALL (DFDBA) + ePTFE	ID	CN	4	NC (0.1.5, 1.7, 1.3; raw data for 4)	USA
Mellonig[182] 2000	ABM + collagen membrane	ID	CN	4	NB, NC, NAA (IN 3/4)	USA
Nevins et al.[103] 2003	ABM + collagen membrane	ID	CN	2	NAA (1.9, 1.7) NB (3.0, 3.1) NC (2.2, 1.9)	USA
Paolantonio et al.[183] 2001	ABM + collagen membrane	ID	None	1	No evidence of NAA	Italy
Camelo, et al.[184] 2001	ABM + AUT + collagen membrane	ID	NBD	4	NAA (4.7) NB (4.7) NC (5.3)	USA
Camelo et al.[104] 1998	ABM + collagen membrane	ID	NBD	2	NC, NB, CT	USA
Stahl & Froum[185] 1991	PHA + ePTFE membrane	ID	CN	7	NC, NB 5 sites; no evidence of NAA	USA
Stahl et al.[185] 1991	PHA + ePTFE membrane	ID	CN	7	NC (2.4, 1.4, 1.0, 0.9, 1,0; raw data for 7)	USA
Nevins et al.[103] 2000	Bioactive glass + ePTFE membrane	ID	NBD	5	No evidence of NAA	USA

Note. Nonsubmerged sites reported for Bowers et al.[31] and Bowers et al.[101]
Abbreviations: ABM = anorganic bone mineral matrix; ALL = allograft; AUT = autograft; CA = citric acid; CN = notch base calculus; CT = connective tissue; DFDBA = demineralized freeze-dried bone allograft; ePTFE = expanded polytetrafluoroethylene; FDBA = freeze-dried bone allograft; FGG = free gingival graft; FUR = class II furcation; HA = hydroxyapatite; NAA = new attachment apparatus; NB = new bone; NBC = notch base crest; NBD = notch base defect; NC = new cementum; NS = not stated; OFD = open flap debridement; PHA = porous hydroxyapatite; PMMA/PHEMA, $CaOH_2$ = polymethacrylate + hydroxyethyl-methacrylate + calcium hydroxide polymer RP = root planing bevel; β-TCP = tricalcium phosphate; TET = tetracycline.

procedures or other surgical approaches in the treatment of furcation defects.[35,36,45,48,58,85-88,90-96] Only 7 randomized controlled studies meeting entry criteria compared BRGs to OFD.[48,58,86,87,90,92,93] However, the frequency and distribution of grafts and interventions, as well as furcation defect types across studies, precluded the application of meta-analysis. Therefore, there was no inherent basis for clustering or grouping of studies to compare treatment outcomes among grafts or between grafts and other interventions.

Overall probing depth reductions for the Class II defects ranged from 1.9 mm to 2.31 mm for BRGs compared to 0 mm to 1.8 mm for OFD alone.[87,90,92] For Class III defects, BRGs produced a change of 0.7 mm to 2.43 mm, as opposed to the controls, which attained a probing depth change of –1.0 to 2.6 mm.[86,92,93] Clinical attachment level changes were similar for mandibular Class II and III defects, ranging from approximately 1.5 mm to 2.5 mm for grafted sites compared to 0 mm to 1.5 mm for OFD controls. The results of these studies suggest that BRGs alone add relatively modest clinical benefits in the treatment of Class II and III furcation defects, if complete furcation closure is the desired endpoint of therapy. Other evidence-based reviews have concluded that combination therapies (BRG-GTR) are superior to either therapy alone in the management of Class II furcation defects.[125,126]

The successful closure of Class II furcation defects remains an attainable but challenging clinical goal.[126] Multiple clinical factors are considered important in achieving a successful regenerative outcome, such as plaque control,[1] smoking,[127-131] and defect/root morphology.[132-134] Regardless of therapeutic approach, multiple patient-, site-, and treatment-related factors influence the predictability of achieving furcation closure.[1,126,132,135-137] Bowers and coworkers recently examined the relationship of multiple factors to the clinical closure of randomly selected mandibular Class II furcations following treatment with DFDBA and a nonabsorbable membrane after 1 year.[134] Complete

clinical closure was achieved in 74% of all sites. The results of this study revealed that increases in vertical bone loss, horizontal bone loss, and root divergence were associated with monotonic decreases in the percentage of sites demonstrating complete clinical closure. The lowest frequency of complete closure was found for defects with vertical or horizontal bone loss of ≥5 mm. These findings provide important prognostic information regarding the influence of patient-, site-, and treatment-related factors on the clinical closure of furcation defects following combination therapy. Further, the results suggest that clinical trials involving furcation defects must include substantially larger sample sizes and/or adjust for group differences in factors impacting on treatment outcome. Future studies are necessary to further characterize the individual and collective contribution of such factors to treatment outcome.

The overall conclusions of this systematic review are consistent with those of an earlier evidence-based review, which examined randomized, controlled clinical trials of at least 6-months duration comparing graft materials to OFD in intraosseous defects.[138] The results of the meta-analysis indicated significantly greater improvements in CAL following grafting with coralline calcium carbonate, bioactive glass, and HA compared to OFD alone. Additionally, significantly greater reductions in PD were found for bone allograft, bioactive glass, and hydroxyapatite than for OFD alone. However, significant heterogeneity was associated with outcome measures across studies. Intraosseous (bone) fill was not submitted to meta-analysis due to the small number of qualifying studies. The results of the present meta-analysis revealed significant improvements in bone fill for each BRG material, except bioactive glass, relative to OFD. Moreover, allografts also were found to result in significant improvements in CAL compared to OFD. Thus, the results of this meta-analysis corroborate and extend those reported by Trombelli et al.[138]

This systematic review differed with respect to inclusion criteria from that of Trombelli and coworkers,[138] which permitted the qualification of a larger number of controlled studies in the current analysis. In the present review, all controlled clinical trials providing mean scores and variance estimates for outcome measures were reviewed for inclusion, regardless of the unit of analysis. In contrast, Trombelli et al. only included qualified controlled studies in which the defect/site, not the patient, was regarded as the unit of measure in the original statistical analysis. Consequently, substantially fewer controlled studies were eligible for inclusion and analysis. To compensate for potential errors in summary statistics (i.e., variance estimates), studies were weighted in this meta-analysis according to the number of participants contributing defects/sites in each intervention arm or group. Each participant, therefore, was considered the unit of measure for purposes of analysis. Multiple defects/sites within a patient were considered to provide a "pooled" estimate of the true outcome value for the individual. This analytical approach permitted a more inclusive, and presumably more balanced, evaluation of available randomized controlled studies.

Although most literature reviews conclude that grafts are clinically beneficial in the treatment of intrabony defects,[1,2,126,139-141] some have questioned the clinical significance of gains relative to other regenerative procedures.[3] Effect-size estimates for each BRG were calculated for clinical outcome measures from studies submitted to meta-analysis in this review. Estimates for each clinical parameter reflect adjustment for corresponding changes in the OFD group/arm. Most bone grafts yielded improvements of 1 to 2 mm on average in bone fill above that obtained with OFD. Gains in clinical attachment level and reductions in probing depth, however, were generally 0.5 to 1 mm superior to those improvements achieved with OFD. Thus, compared to OFD, BRGs appear to support greater improvements in hard tissue (bone fill) than soft tissue parameters (CAL and PD). In the presence of excellent plaque control during wound healing, OFD procedures clearly support substantial gains in CAL and reductions in PD, attributable primarily to repair via a long junctional epithelial attachment.[31,101,102,142]

Literature-based estimates of bone fill range from 2.3 to 3.0 mm or 60% of the defect following grafting of intrabony defects.[2,143] Such effect-size estimates do not adjust for differences obtained in the comparison group (e.g., OFD). Laurell et al.[3] reviewed all observational and controlled studies published during the prior 20 years on the surgical treatment of intrabony defects with OFD, GTR, and bone grafts (DFDBA, FDBA, or autogenous bone). When collapsing across studies, defect fill was found to be positively correlated to initial defect depth following OFD and grafting procedures, as reported by others. Importantly, summary statistics provided in this exhaustive review highlight important differences among regenerative studies with respect to average initial defect depths: OFD (4.3 mm), bone grafts (3.8 mm), and GTR (5.8 mm). Importantly, the magnitude of the differences in mean defect fill parallel initial differences in average pretreatment defect depth: OFD (1.1 mm), bone grafts (2.2 mm), and GTR (3.2 mm). Thus, comparative estimates of treatment effect-size based on literature-based statistics are difficult to compare and vulnerable to confounding.[144]

The goals of regenerative therapy include patient-centered outcomes, such as esthetics, ease of personal and professional care, incidence of disease recurrence, and incidence of tooth loss. In general, the review revealed a paucity of documented information related

to patient-centered outcomes. Insufficient clinical data were available to assess the effects of bone grafts on gingival recession relative to other treatments; however, bone grafts were associated with significantly less crestal bone loss than OFD procedures, consistent with a potentially more favorable esthetic outcome. Documentation regarding adverse outcomes is commonly but incompletely reported. In this review, graft exfoliation was found to be the most common untoward event.

The need for prospective studies on the long-term maintenance of regenerated sites has been identified in earlier evidence-based reviews.[145] Currently, few controlled studies provide comparative data on the long-term retention of clinical outcomes following treatment of periodontal osseous defects with bone replacement grafts.[6,32-34,95,98] Generally, longitudinal evaluations have demonstrated the stability of early clinical improvements beyond 3 years. Longitudinal data from one clinical trial[32,34] provided soft tissue assessments of intrabony sites treated with OFD or bovine-derived hydroxyapatite matrix. Forty percent of the sites treated with OFD lost attachment over the 5-year period, whereas two-thirds of the sites grafted with hydroxyapatite gained attachment over the same interval.[34] Flemmig and coworkers[6] reported significantly greater bone fill and gains in CAL intrabony sites grafted with demineralized bone allograft (AAA bone) compared to control defects treated by modified Widman flap surgery at both 6- and 36-month evaluations. Improvements in clinical measures remained stable over time. Longitudinal studies of osseous graft procedures alone or in combination with GTR generally report positive maintenance of clinical outcome parameters.[131,146] Patient compliance with oral hygiene measures and frequent periodontal maintenance appear critical for optimal wound healing and maintenance of long-term therapeutic success following regenerative therapy.[123,147,148] Smoking appears to increase the risk for periodontal breakdown following regenerative treatments.[131,148] Future studies are necessary to establish the stability of clinical outcomes achieved with grafting relative to other treatment interventions.

The results of this meta-analysis indicate that several classes of BRGs support comparable outcomes with respect to clinical parameters, such as bone fill. However, within the context of regenerative outcomes, interpretation of improvements in clinical parameters is incomplete without consideration of wound healing on a histological level. Numerous case reports provide histological data obtained from excisional biopsy specimens. However, only 2 series of randomized controlled studies were identified that provide histological data.[31,101] Bowers and colleagues reported compelling histological documentation in humans that particulate DFDBA supports the formation of a new attachment apparatus, including new bone, cementum, and periodontal ligament, when placed in intrabony defects.[31,101] In contrast, OFD has been found to result in periodontal repair characterized primarily by the formation of a long junctional epithelial attachment,[31,101,102] consistent with the results of others.[142] A review of other histological data also provides strong evidence that autogenous bone grafts support the formation of new attachment apparatus. Limited but well-substantiated evidence also indicates that xenogenic bone mineral matrix[104] and bovine collagen/mineralized bovine bone matrix[103] possess the capacity to induce regeneration in intrabony defects. In contrast, available data indicate that alloplastic grafts support periodontal repair rather than regeneration.

Current evidence suggests that most postoperative improvements in clinical outcome are maintainable in the presence of compliance with oral hygiene measures and frequent periodontal maintenance. What remains unclear, however, is whether the nature of the healed wound; e.g., a new attachment apparatus versus long junctional epithelial attachment, influences the stability of clinical improvements in the presence of risk factors for periodontal breakdown.

REVIEWERS' CONCLUSIONS

1. Bone replacement grafts generally increase bone level, reduce crestal bone loss, increase clinical attachment level, and reduce probing depth compared to OFD procedures in the treatment of intrabony defects.
2. Hydroxyapatite and bone allograft provide similar improvements in clinical measures in the treatment of intrabony defects.
3. The combination of bone grafts and barrier membranes may provide superior clinical outcomes than grafts alone in the treatment of intrabony defects.
4. Insufficient studies of comparable design are available for meta-analytical comparison of treatment results for furcation defects.
5. Histological evidence indicates that autogenous bone and DFDBA support the formation of a new attachment apparatus.
6. Histological evidence indicates that alloplastic grafts support periodontal repair rather than regeneration.

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APPENDIX A
CONSENSUS REPORT

Members of the Section read and studied the review titled "The Efficacy of Bone Replacement Grafts in the Treatment of Periodontal Osseous Defects," by Mark Reynolds, Mary Elizabeth Aichelmann-Reidy, Grishondra L. Branch-Mays, and John C. Gunsolley. The focused PICO question addressed by this evidence-based systematic review is: "In patients with periodontal osseous defects, what is the effect of bone replacement grafts compared to other interventions on clinical, radiographic, adverse, and patient-centered outcomes?"

INTRODUCTION

The bibliographical databases MEDLINE and EMBASE were searched by a group of reviewers for studies in which bone replacement grafts were compared to other surgical interventions in the treatment of periodontal osseous defects. The search was limited to human studies in English language publications using the search strategy with qualifier terminology. EMBASE was searched using more restrictive thesaurus terms (bone grafts; periodontal) and key words (intrabony, intrabony intraosseous, and furcation) with all affixes and inflectional endings, for publications not catalogued in MEDLINE. These searches were supplemented by screening review articles and reference lists of retrieved articles as well as hand searches of the *International Journal of Periodontics & Restorative Dentistry, Journal of Clinical Periodontology, Journal of Periodontology*, and *Journal of Periodontal Research*. Section members evaluated the manuscript that summarized this information and in open forum evaluated the conclusions brought forth from this review.

1. Does the Section agree that the evidence-based systematic review is complete and accurate?
The Section was in complete agreement that the systematic review was complete and accurate.

2. Has any new information been generated or discovered since the evidence-based search cut-off date?
The Section reviewed the literature since the cut-off date of April 1, 2002 and 1 citation, Trombelli et al.,[1] was identified. This publication included a meta-analysis of randomized controlled clinical trials (RCTs) comparing the adjunctive effect of grafting materials with open flap debridement (OFD) in the treatment of deep intraosseous defects. That review examined only RCTs of at least 6-months duration where the patient, not the defect/site, was regarded as the unit of measure. Meta-analysis showed that clinical attachment level (CAL) change significantly improved after treatment for coralline calcium carbonate (weighted mean difference 0.90 mm; 95% confidence interval [CI]: 0.53 to 1.27), bioactive glass (weighted mean difference 1.04 mm; 95% CI: 0.31 to 1.76), and hydroxyapatite (HA) (weighted mean difference 1.40 mm, 95% CI 0.64 to 2.16). Heterogeneity in results between studies was statistically significant for HA and bioactive glass. The authors concluded that overall, the use of specific biomaterials was more effective than OFD in improving clinical attachment levels in intraosseous defects. With respect to CAL, the results of the meta-analysis are consistent with the conclusions of the present review regarding coralline calcium carbonate, bioactive glass, and HA implants. However, due to differences in inclusion criteria, the present systematic review included a larger number of RCT studies, classification of allografts for analysis, and clinical outcome parameters examined (i.e., bone fill, crestal resorption, and gingival recession); the present review provides important additional results.

3. Does the section agree with the interpretations and conclusions of the reviewers?
The Section agreed with the interpretations and conclusions of the review.

4. What further research needs to be done relative to the focused questions of the evidence-based review?
It was the consensus of the Section that the following research needs should be addressed:

1. Perform prospective long-term (3 years or longer) studies on treatment outcomes (e.g., CAL gains, probing depth reductions, and bone level improvements) to determine their stability.
2. Evaluate the effects of the treatment on patient-centered outcomes (e.g., comfort, esthetics, ease of maintenance, function, tooth retention, and systemic status) to enhance patient acceptance.
3. Investigate morphologic factors that influence treatment outcomes to provide guidelines for the therapist that enhance predictability.
4. Perform more investigations of maxillary furcation defects.
5. Identify the role of systemic, acquired, or environmental risk factors (e.g., smoking, diabetes) that influence treatment outcomes.
6. Perform studies that assess factors that affect clinical predictability (e.g., presurgical management, intramarrow penetration, flap design, root preparation, operator experience, postsurgical management).
7. Randomized controlled trials on combination therapies that include a bone graft.
8. Trials that compare bone grafts with non-surgical therapy in patients with multiple sites of intrabony and/or furcation defects.

The Section further recommends that publications reporting the results of RCTs specify the primary and secondary outcome measures, inclusion/exclusion criteria; randomization procedures; allocation concealment; evaluator masking; calibration; and summary statistics including means, variance estimates, and frequency distributions for outcome measures (including furcation closure). Publications on this topic should also include estimates of treatment magnitudes, treatment predictability, adverse events within the trial (e.g., root resorption, root sensitivity, ankylosis), risk/benefit ratio, and specification of graft bioactivity and source of the graft to assist in interpretation across studies.

5. How can the information from the evidence-based review be applied to patient management?
The consensus of the Section was to reaffirm the criteria for periodontal regeneration that were stated in the Proceedings of the 1996 World Workshop in Periodontics.[2]

A. The evidence supports the use of demineralized freeze-dried bone allograft (DFDBA) as a periodontal regenerative material in patients.

Level of Evidence:[3] Strong.

Rationale: There are well-designed RCTs providing both histological and clinical outcomes which are consistent with this conclusion. There are 2 histologic RCTs and 8 clinical RCTs to support this.

B. The evidence supports the use of bone grafts to increase bone level, reduce crestal bone loss, increase clinical attachment level, and reduce probing depth compared to open flap debridement procedures in the treatment of infrabony defects.

Level of Evidence: Strong.

Rationale: Assignment of a "strong" level of evidence is based on multiple RCTs (32 of 36 studies) providing clinical outcomes that are consistent with this conclusion.

C. There is evidence to support the use of the following bone graft materials for periodontal regeneration: autogenous bone, DFDBA in combination with an absorbable polylactide barrier, anorganic bovine bone, anorganic bovine bone-collagen, and anorganic bovine bone with peptide attachment factor.

Level of Evidence: Limited.

Rationale: Assignment of a "limited" level of evidence is based on a small number of RCTs that provide clinical outcome data and uncontrolled human histologic studies that demonstrate proof of principle.

D. The evidence supports the use of porous hydroxyapatite and bone allograft to achieve similar improvements in clinical measures when treating intrabony defects.

Level of Evidence: Moderate.

Rationale: Assignment of a "moderate" level of evidence is based on 4 RCTs demonstrating nonsignificant differences between groups.

E. There is evidence to support the use of combination therapy (i.e., bone graft and barrier membrane) to provide superior clinical outcomes than bone graft alone in the treatment of intrabony defects.

Level of Evidence: Limited.

Rationale: Assignment of a "limited" level of evidence is based on 4 small RCTs, comparing different graft/membrane combinations that generally found more favorable outcomes with adjunctive use of a barrier.

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