Histologic Healing Following Tooth Extraction With Ridge Preservation Using Mineralized Versus Combined Mineralized-Demineralized Freeze-Dried Bone Allograft: A Randomized Controlled Clinical Trial

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Background: Mineralized and demineralized freeze-dried bone allografts (FDBAs) are used in alveolar ridge (AR) preservation; however, each material has advantages and disadvantages. Combinations of allografts aimed at capitalizing on the advantages each offers are available. To date, there is no evidence to indicate if a combination allograft is superior in this application. The primary objective of this study is to histologically evaluate and compare healing of non-molar extraction sites grafted with either mineralized FDBA or a 70:30 mineralized:demineralized FDBA combination allograft in AR preservation. The secondary objective is to compare dimensional changes in ridge height and width after grafting with these two materials.

Methods: Forty-two patients randomized into two equal groups received ridge preservation with either 100% mineralized FDBA (active control group) or the combination 70% mineralized: 30% demineralized allograft (test group). Sites were allowed to heal for 18 to 20 weeks, at which time core biopsies were obtained and dental implants were placed. AR dimensions were evaluated at the time of extraction and at implant placement, including change in ridge width and change in buccal and lingual ridge height. Histomorphometric analysis was performed to determine percentage of vital bone, residual graft, and connective tissue/other non-bone components.

Results: There was no significant difference between groups in AR dimensional changes. Combination allograft produced increased vital bone percentage (36.16%) compared to the FDBA group (24.69%; $P = 0.0116$). The combination allograft also had a significantly lower mean percentage of residual graft particles (18.24%) compared to FDBA (27.04%; $P = 0.0350$).

Conclusions: This study provides the first histologic evidence showing greater new bone formation with a combination mineralized/demineralized allograft compared to 100% mineralized FDBA in AR preservation in humans. Combination allograft results in increased vital bone formation while providing similar dimensional stability of the AR compared to FDBA alone in AR preservation. *J Periodontol 2015;86:348-355.*

KEY WORDS

Alveolar bone grafting; alveolar bone loss; bone resorption; bone transplantation; dental implants; tooth extraction.

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Dental implants are an increasingly common treatment option for the replacement of missing teeth.[1] Following tooth extraction, significant dimensional changes occur in the alveolar ridge (AR). These dimensional changes can manifest as a loss of ≥50% of ridge width and height and occur rapidly after tooth extraction, typically within the first 6 months.[2-4] Loss of AR dimension occurs regardless of factors such as buccal plate thickness or tooth type.[5] Loss of the alveolar bone is problematic for both clinicians and patients who desire dental implant therapy because the remaining alveolus may not be suitable for placement of a dental implant in an appropriate restoratively driven position and may require bone augmentation to reconstruct the ridge.

AR preservation is a procedure aimed at preventing or minimizing dimensional changes following tooth extraction to provide an adequate volume and quality of bone for dental implant placement. Extraction sites treated with AR preservation have been shown repeatedly to have less dimensional change as well as increased vital bone formation compared to controls not treated with ridge preservation procedures.[6-8] AR preservation can be accomplished successfully using a variety of materials such as allografts, xenografts, autografts, and alloplasts.[6-9] As a result of the relatively low cost, lack of a secondary donor site, and well-documented history of success, the use of allografts for AR preservation is increasingly common and appealing to both patients and clinicians.

Both freeze-dried bone allograft (FDBA) and demineralized freeze-dried bone allograft (DFDBA) have been used for AR preservation and demonstrate the ability to minimize AR resorption following tooth extraction.[10] A reported benefit of FDBA is the ability of the allograft to function as an osteoconductive scaffold for new bone formation.[11,12] An ideal scaffold should allow osteoprogenitor cells from the host to produce new bone while maintaining space in the site before graft resorption.[13]

Unlike mineralized FDBA, DFDBA has been shown to have osteoinductive potential as a direct result of bone morphogenetic proteins (BMPs).[14] BMPs have been shown to induce bone formation ectopically in a nude mouse model.[15] BMPs within DFDBA stimulate mesenchymal stem cells to differentiate into osteoblasts. Specifically, BMP-2, -4, and -7 have been found in DFDBA after processing.[16] It has been demonstrated that different lots of DFDBA have varying levels of BMPs and therefore varying levels of osteoinductivity.[15] FDBA does contain the same BMPs within its matrix; however, it has not been shown to have the same osteoinductive capacity. Osteoclast-mediated demineralization of FDBA is required to release BMPs from the FDBA matrix. After this process, osteoinductive BMPs are available when using FDBA, in contrast to the use of DFDBA, in which the BMPs are available at the time of graft placement. Recent literature has shown that DFDBA produces more vital bone compared to FDBA in AR preservation; however, both materials were effective at maintaining AR dimensions following tooth extraction.[10] The use of DFDBA alone has been criticized for not providing enough of an osteoconductive scaffold for new bone formation.[17] In addition, the relative radiolucency of DFDBA makes the determination of AR preservation graft success difficult to assess preoperatively with radiographic examination. It is possible that a combination of FDBA and DFDBA may combat the potential shortcomings of the use of DFDBA alone in AR preservation.

The purpose of the current study is to histologically (primary outcome) and clinically (secondary outcome) evaluate 100% cortical mineralized FDBA in contrast to a combination allograft of 70% cortical mineralized FDBA and 30% cortical DFDBA in AR preservation following extraction of non-molar teeth.

MATERIALS AND METHODS

Participant Enrollment

The Institutional Review Board of the University of Texas Health Science Center at San Antonio (UTHSCSA), San Antonio, Texas, reviewed and approved the protocol for this parallel-arm study. This trial was registered at ClinicalTrials.gov (NCT 01924390). The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000. All participants provided written informed consent before treatment and were given a copy of the signed informed consent documents. Power analysis determined that a sample size of 14 sites per group was sufficient to detect a mean difference in percentage of new bone formation of ≥1 SD by Mann-Whitney *U* test at the 0.05 level with a power of 88.5%. Results from previous studies conducted by the current authors' research group yielded SDs ranging from 13.7% to 22.4% for percentage of new bone formation.[9,10] Anticipating a dropout rate of 30%, with a minimum of 70% of patients expected to be fully compliant under the study protocol, a total of 44 patients who required extraction of a non-molar tooth and desired replacement with a dental implant were enrolled from October 2012 to November 2013 (Fig. 1). The following site inclusion criteria were used: 1) adequate restorative space for a dental implant restoration; 2) minimum of 10-mm vertical bone without impinging on adjacent vital structures; and 3) single-rooted tooth in the same three-dimensional position as the ideal future implant placement so that the core biopsy could be taken from a site completely within

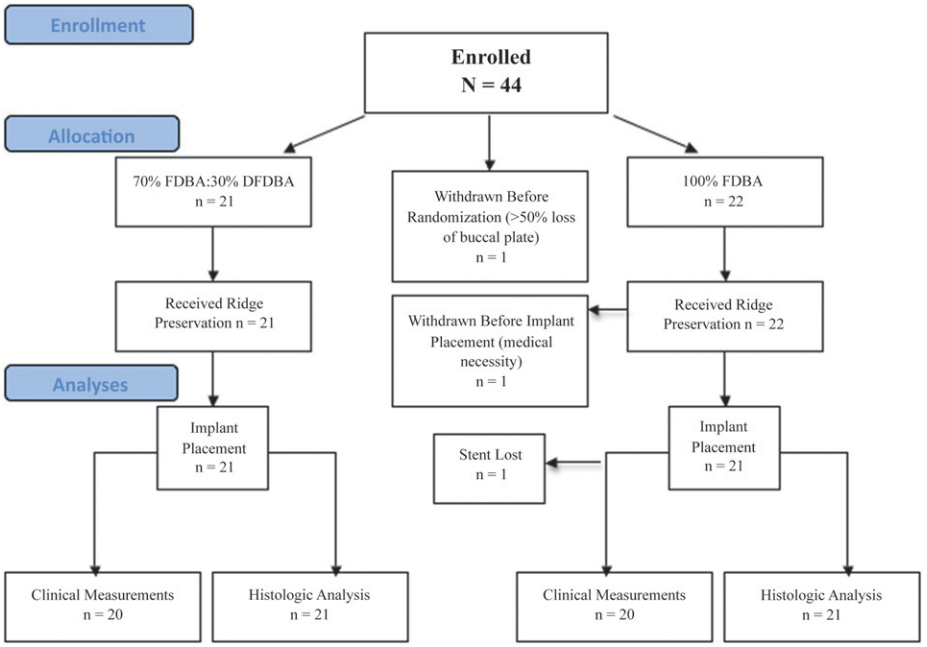

Figure 1.
Consolidated Standards of Reporting Trials (CONSORT) study flowchart.

the previous tooth socket without including adjacent native alveolar bone. The following exclusion criteria were used: 1) did not meet all inclusion criteria; 2) was pregnant; 3) had active systemic or localized infection (not including periodontitis); or 4) had a history of any condition that contraindicated or weighed against dental implant placement such as history of bisphosphonate drug use, chemotherapeutic or immunosuppressive agents, autoimmune disease, or poorly controlled diabetes. Any patient of childbearing age who had not undergone tubal ligation, hysterectomy, or menopause was required to take a pregnancy test to determine pregnancy status before any surgery. In addition, patients who had >50% dehiscence of the AR after tooth extraction were excluded from the study. Forty-four patients were enrolled (16 males and 28 females, aged 20 to 89 years; mean age: 52 years).

To strengthen the comparison between the materials, all allografts used were sourced from a single 64-year-old male donor and had particle size of 250 to 1,000 μm. The lot of DFDBA used in the test group was tested by both in vitro BMP assay and in vivo athymic mouse gluteal-muscle-pouch implantation model to ensure osteoinductivity.† The in vitro BMP-2 assay yielded a result of 7,521 pg/g. The in vivo implantation model was scored on a grade of 0 to 4 based on the percentage of the examined field, defined as the entire implant area, showing evidence of new bone formation. The lot used in this study scored 3 of 4, which corresponds to 51% to 75% of the field showing evidence of new bone formation.

Surgical Protocol

After enrollment, alginate impressions and study models were made and a customized thermoplastic acrylic stent‡ was fabricated on the cast for the purpose of obtaining clinical measurements. Intravenous conscious sedation was administered at the discretion of the surgeon. After local anesthesia, a mucoperiosteal flap was elevated 2 to 3 mm beyond the alveolar crest on both the buccal and lingual surfaces around the tooth scheduled for extraction to allow for visualization of the tooth root and placement of the barrier membrane. Reflection was not extended beyond 3 mm from the bony margin. The tooth was extracted using minimally traumatic techniques. After extraction, the socket was thoroughly debrided and rinsed with sterile saline. If the site in question met the inclusion criteria after tooth extraction, the patient was then randomized into either the test or control group by selecting a sealed envelope from a batch of envelopes prepared at the onset of the study that contained a piece of paper designating the treatment group. Clinical measurements were taken according to the technique described previously.[9] In brief, the customized acrylic stent was used to measure: 1) total ridge width 3 mm apical to the alveolar crest using calipers;§ 2) depth of the socket on both the buccal and lingual aspects using a periodontal probe;‖ 3) vertical AR height from a hole placed in the occlusal portion of the stent directly over the buccal and lingual alveolar crest with a periodontal probe; and 4) buccal plate thickness using a gauge.¶ All guide holes placed in the acrylic stent were made after extraction to ensure accurate measurement. All measurements were measured to the nearest half-millimeter with the exception of the buccal plate thickness, which was measured to the nearest tenth-millimeter.

† WuXi AppTec, St. Paul, MN.
‡ Clear Split Biocryl 0.75/125 mm Round, Great Lakes Orthodontic Laboratories, Tonawanda, NY.
§ Castroviejo, Salvin Dental Specialties, Charlotte, NC.
‖ UNC-15, G. Hartzell & Son, Concord, CA.
¶ Iwanson, Salvin Dental Specialties.

After all clinical measurements were obtained, the patient underwent AR preservation using the control material[#] (100% cortical mineralized FDBA) or the test material[**] (70% cortical mineralized FDBA and 30% cortical DFDBA). The allograft allocated for the patient was hydrated in sterile saline for a period of 10 minutes. Graft material was placed incrementally into the site. No attempt was made to place allograft material coronal to the existing alveolar crest. A dense polytetrafluoroethylene (d-PTFE) membrane[††] with pore size <0.3 μm was trimmed to allow for placement 3 mm beyond the buccal and lingual alveolar crests and was positioned such that it was not in contact with adjacent teeth. If the extraction socket had a dehiscence <50% of the total apical-coronal dimension of the socket, the membrane was trimmed to extend 3 mm beyond the apical component of the defect. Mucoperiosteal flap release was not performed, since primary closure was not a goal. A horizontal mattress suture was placed over the d-PTFE membrane to reapproximate the papillae using a 4-0 d-PTFE suture.[‡‡] The membrane was left exposed at the location of the socket orifice.

At the conclusion of the procedure, patients were placed on an antibiotic regimen consisting of doxycycline 100 mg twice a day for 10 days. If the patient had an allergy to tetracyclines, amoxicillin 500 mg three times a day for 10 days was substituted. Patients were given pain medication at the discretion of the surgeon, which included the use of non-steroidal anti-inflammatory drugs as well as narcotic analgesics. Patients were instructed to abstain from normal oral hygiene measures in the surgical site and to use a prescription oral rinse of 0.12% chlorhexidine for 30 seconds twice a day for 4 weeks. Patients were required to return for postoperative evaluation at 2 weeks for suture removal, and then again at 4 weeks for removal of the membrane. Membrane removal was accomplished without incident and without the use of local or topical anesthetic in all patients.

After a healing period of 17 to 21 weeks (average 19 weeks), the patients were recalled for dental implant placement. Mucoperiosteal flaps were elevated to expose the alveolus, and clinical measurements were obtained using the same customized acrylic stent and measuring techniques used during the extraction procedure. The initial osteotomy was prepared using a trephine drill with a 2-mm internal and 3-mm external diameter[§§] to obtain a core biopsy of ≥8 mm in length. The core biopsy was placed into 10% neutral-buffered formalin.

Histologic Processing

Core biopsies were decalcified, embedded in paraffin, and sliced to a 4-μm thickness. A minimum of nine sections were sliced for each specimen. All the sections were examined at 1× magnification to determine which cut yielded the best sample for analysis. A single section per individual was selected for histologic evaluation in its entirety from its most apical end to its most coronal end. When multiple representative sections were available for possible analysis, preference was given to the innermost aspect of the original core biopsy. If the innermost section was not available for analysis due to artifact, the section nearest was examined. Adjacent sections were located 4 to 20 μm from the innermost section. Hematoxylin and treosin counterstain[||||] was used in preparation for light microscopy. Treosin is a slightly acidified combination of eosin Y and orange G, with the addition of acid fuchsin. Histomorphometric analysis was completed by one examiner (TB) who was masked to the treatment group during examination of all cores. Each section was examined at a minimum of 20× magnification. To identify the different tissue components, images were taken of each section.[¶¶] Each section was subsequently traced into three component layers (vital bone, residual graft, and non-mineralized connective tissue) using imaging software.[##] These component layers were then converted to binary images, which allowed for analysis of the total area of each layer based on the number of pixels in each image.[***] This method of analysis was originally developed by Beck and Mealey.[9]

Statistical Analyses

For all treatment group comparisons of bone core percentages and ridge dimensional data, two sample Student *t*-tests were performed. To assess whether parametric statistical tests were appropriate, box plots were constructed, and if pronounced departures from symmetry or extreme outliers were visible, then non-parametric Mann-Whitney *U*-tests were also performed to verify the findings for Student *t*-tests. Treatment group comparisons were also performed for categorical parameters (arch, tooth-bound space, dehiscence) using Fisher exact tests. For all tests, $P < 0.05$ was considered significant. Pearson and Spearman rank correlations among histologic parameters and clinical parameters were also analyzed.

RESULTS

Forty-two (15 males and 27 females, aged 20 to 89 years; mean age: 52 years) of the 44 enrolled patients

Osteogenics Biomedical, Lubbock, TX.
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†† Osteogenics Biomedical.
‡‡ Osteogenics Biomedical.
§§ Salvin Dental Specialties.
|||| Harris Hematoxylin and Treosin, Statlab Medical Products, Lewisville, TX.
¶¶ CellSens, v.1.4, Olympus America, Center Valley, PA.
Photoshop, v.CS5.1, Adobe, San Jose, CA.
*** ImageJ, National Institutes of Health, Bethesda, MD.

Table 1.

AR Dimensional Changes (mean ± SD)

Group	Change in Ridge Width (%)	Change in Ridge Width (mm)	Change in Ridge Height, Buccal (mm)	Change in Ridge Height, Lingual (mm)
Test (combination)	–12.63 ± 14.55	–1.19 ± 1.36	0.26 ± 2.08	–0.80 ± 1.27
Control (FDBA)	–17.93 ± 13.44	–1.63 ± 1.18	–0.25 ± 1.85	–0.62 ± 1.78

No significant difference between groups for any measurements ($P > 0.05$).

completed the study. None of the patients enrolled in the study reported a history of current or past tobacco use. One patient in the control group did not have clinical measurements made at the time of reentry due to loss of the customized measurement stent at the second surgical appointment; however, a core biopsy of the healed extraction site was obtained. One patient was withdrawn at the time of extraction due to buccal plate dehiscence >50%, and one patient was withdrawn before implant placement due to medical treatment that prevented dental surgery within the specified study time frame. In total, 42 core biopsies were obtained, 21 from each group, and 41 patients provided clinical measurements, 21 from the combination allograft group and 20 from the FDBA group. None of the patients presented with evidence of infection after either ridge preservation or implant placement, and no site was determined to have partial or total graft loss during healing. All 42 patients who completed the study had adequate bone volume and quality to allow for the placement of a dental implant in the ideal restoratively driven position.

There was no significant difference in healing time between the groups. The combination allograft group had an average healing time of 18.6 ± 0.80 weeks, and the FDBA group had an average healing time of 19.0 ± 0.83 weeks. A majority of sites were in the maxilla, 15 in the test group and 17 in the control group. There was no significant difference between groups when evaluating buccal plate thickness at the time of tooth extraction. The combination allograft group had a mean buccal plate thickness of 0.77 ± 0.51 mm, and the FDBA group had a mean buccal plate thickness of 0.77 ± 0.42 mm. There was also no significant difference when evaluating initial ridge width at the time of tooth extraction. The combination allograft group had a mean AR width at extraction of 9.07 ± 2.10 mm, and the FDBA group had a mean AR width at extraction of 9.02 ± 1.57 mm.

Dimensional Changes

In both groups, there was no significant difference in AR dimensions at the time of implant placement. Regardless of material used, the changes following tooth extraction were very similar (Table 1). Both groups lost 1.19 to 1.63 mm of ridge width and <1 mm of ridge height, on average. The dimensional stability after AR preservation with these two materials was not clinically different. There was no significant correlation between initial buccal plate thickness and subsequent changes in ridge dimension.

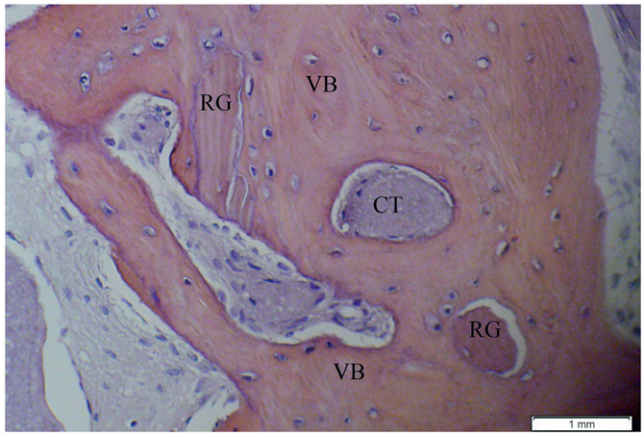

Figure 2.
Combined allograft group. (Hematoxylin and a slightly acidified combination of eosin Y and orange G, with addition of acid fuchsin; original magnification ×10.) VB = vital bone, RG = residual graft, CT = non-mineralized connective tissue/other material.

Histologic Observations

Each specimen was examined at 10×, then further under 20× or 40× magnification for identification of vital bone, residual graft, and connective tissue (CT)/other fractions (Fig. 2). Residual graft particles were located and defined by regions of lamellar bone with the absence of osteocytes in lacunae. Vital bone was identified by the presence of osteocytes in lacunae. It was common to observe vital bone in direct contact with residual graft material in both groups. The third category observed was CT/other. This fraction included loose fibrous connective tissue, vasculature, and inflammatory cells.

There was no significant difference in the CT/other fraction between treatment groups (Table 2). The test

Table 2.

Histologic Analysis (mean ± SD)

Group	Vital Bone (%)	Residual Graft (%)	CT/Other (%)
Test (combination)	36.16 ± 11.91*	18.24 ± 12.47†	45.38 ± 11.09
Control (FDBA)	24.69 ± 15.92*	27.04 ± 13.62†	48.27 ± 14.16

* $P = 0.0116$ for test group versus control.
† $P = 0.0350$ for test group versus control.

group presented with significantly more vital bone, (36.16%) compared to the control group (24.69%; $P = 0.0116$). The test group also had significantly less residual graft (18.24%) compared to the control group (27.04%; $P = 0.0350$). The bone tissue components alone were then evaluated between groups, excluding the CT/other component. The test group yielded 54.40% total bone area and the control group 51.72%. When evaluating only this bone fraction of the cores as the denominator, in the test group vital bone comprised 67.48% and residual graft 32.52% of the bone tissue. In the control group, vital bone comprised 46.17% and residual graft 53.83% of the bone tissue. The difference between the two groups related to these findings was statistically significant ($P = 0.003$).

DISCUSSION

The primary objective of the study is to histologically compare new bone formation using 100% cortical mineralized FDBA to a combination allograft of 70% cortical mineralized FDBA and 30% cortical DFDBA in AR preservation after extraction of non-molar teeth. All patients showed vital new bone formation, but the combination allograft yielded significantly greater mean vital bone formation and less residual graft material at 18 to 20 weeks after AR preservation.

The rationale for the use of DFDBA as an osteoinductive material has been described numerous times in the literature.[14-17] The osteoinductive character of the material relies on the presence of BMPs within the sample.[16] Evidence illustrates that not all commercially procured lots of DFDBA are osteoinductive, and that the nature of their osteoinductive capacity relies on the age of the donor as well as BMP within the sample after processing.[15] To confirm the osteoinductive capacity of a given sample, it must undergo adequate testing before implantation. DFDBA alone has been shown to be superior to natural healing when evaluating ability to form vital bone in AR preservation.[8] In contrast, the use of FDBA as an osteoconductive scaffold for new bone formation allows for both space maintenance and clot stability during healing.[17]

The current study is designed to eliminate as many variables as possible to objectively compare these two graft materials. The use of a single donor for both groups, as well as the use of both in vitro and in vivo testing of the osteoinductive nature of the DFDBA lot, eliminated possible factors that could alter results. The DFDBA used in this study was shown to be osteoinductive through both in vitro assay and in vivo testing. In addition, the particle size of both groups was identical. The use of only non-molar teeth, strict exclusion criteria, and specific surgical technique and timing eliminated yet another possible source of variation. Specifically, the use of extraction sites with a minimum of 10 mm of bone oriented in the position of ideal implant placement helped to ensure that the core biopsy did not include native bone from the socket wall. The resultant groups also showed no differences in regard to initial ridge width or buccal plate thickness at the time of extraction, and the healing time was nearly identical between groups.

DFDBA alone in this application has been shown to be superior to FDBA alone when evaluating vital bone formation;[10] however, to the best of the authors' knowledge, the use of a combination 70% FDBA and 30% DFDBA allograft compared to 100% FDBA to evaluate new bone formation has not been described before. It is interesting to note that these results are very similar both histologically and clinically to results previously reported[10] comparing 100% DFDBA to 100% FDBA in this identical application. In the study by Wood and Mealey,[10] the percentage of vital bone formation was 24.63% in the mineralized FDBA group compared to 24.68% in the 100% mineralized FDBA group in the current study. Furthermore, Wood and Mealey found 38.42% vital bone formation using 100% DFDBA[10] compared to 36.16% vital bone formation in the combination 70:30 mineralized: demineralized FDBA group in the current study. This confirms the advantage of the use of osteoinductive DFDBA in ridge preservation procedures. From a clinical convenience standpoint, the use of this combination allograft material results in a radiopaque appearance of the site because of the inclusion of the 70% mineralized fraction. This allows for simplified radiographic analysis through the use

of either traditional dental radiographs or computed tomography at the point of dental implant case planning compared to DFDBA alone, since 100% DFDBA is often associated with a radiolucent appearance long after its implantation.

The secondary objective of this study is to evaluate AR dimensional changes. Both allograft groups produced favorable clinical results that were superior to recent studies evaluating tooth extraction without AR preservation.[4,5] Based on the results of this study, there is no difference in AR changes when ridge preservation procedures are performed with mineralized FDBA alone compared to a combination of mineralized and DFDBA. Interestingly, there was no correlation between initial buccal plate thickness and ridge width changes during the 18- to 20-week postextraction healing period. This finding questions the recommendation of clinicians who propose that AR preservation is indicated only in sites with thin buccal plates. The results, along with those of other authors,[5] suggest that AR preservation should be considered in all sites where the placement of a dental implant is a potential future treatment option irrespective of the buccal plate thickness.

One unique aspect of this study in comparison to others is the use of a d-PTFE membrane in contrast to a collagen orifice barrier. It is interesting to note that although the dimensional changes are only slightly superior to those reported with the collagen orifice barrier technique, all participants in this study had adequate bone volume and quality to allow for dental implant placement at the time of reentry. Previously reported research using protocols identical to this study, but that used a collagen orifice barrier rather than a d-PTFE membrane, did not yield such favorable results.[9,10] Clinically, the use of this barrier membrane for ridge preservation adds a minimal amount of time and cost to the procedure and may result in more predictable outcomes. The role of the d-PTFE barrier membrane in both graft retention and dimensional AR maintenance after tooth extraction warrants additional investigation.

The use of DFDBA, either alone or in a combination allograft, has been shown to be superior to the use of FDBA alone when evaluating vital bone formation following tooth extraction and ridge preservation;[10] however, the role or potential benefit of this increased vital bone in dental implant therapy remains unclear. Perhaps this increased vital bone formation leads to increased bone-to-implant contact around dental implants or results in superior clinical bone quality at the time of reentry, which may increase primary stability and lead to the potential for immediate loading. Whether this trend remains when these materials are evaluated at different time points is unclear. Both materials have been shown to provide adequate ridge dimensions for implant placement when evaluated at 18 to 20 weeks of healing. The long-term dimensional stability of AR preservation beyond this time point has not been investigated in a controlled study. Specifically, in reference to combination allografts, the ratio of demineralized to mineralized component has not been thoroughly investigated in a controlled fashion.

CONCLUSIONS

The present study is the first to histologically and clinically compare 100% cortical mineralized FDBA to a combination allograft of 70% cortical mineralized FDBA and 30% cortical DFDBA in AR preservation after extraction of non-molar teeth. The results of this study indicate that this combination allograft results in increased vital bone formation while providing similar dimensional stability of the AR compared to FDBA alone.

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