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HUMAN RANDOMIZED CONTROL TRIAL

Wound healing after ridge preservation: A randomized controlled trial on short-term (4 months) versus long-term (12 months) histologic outcomes

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Abstract

Background: The amount of time it takes for bone allograft particles to be replaced with new vital bone during ridge preservation is unclear. The purpose of this article was to compare the wound healing and vital bone formation following ridge preservation using a combination allograft of 70% mineralized and 30% demineralized freeze-dried bone allograft at 4 months (short-term, ST) versus 12 months (long-term, LT).

Methods: Fifty-seven patients were enrolled in the study who required extraction of a single tooth (excluding second and third molars) and were planned for replacement with a dental implant. After tooth extraction, all sites were grafted with a combination allograft procured from a single donor, and patients were randomized into the ST or LT healing groups. Patients returned for implant placement and an 8-mm bone core biopsy was harvested using a trephine drill during initial implant osteotomy preparation. The cores were then analyzed histologically to determine the percentages of vital bone formation, residual graft particles, and connective tissue/other.

Results: There was significantly greater vital bone formation in the LT group (51.38%) compared with the ST group (31.39%) ($p = 0.0025$) and significantly fewer residual graft particles in the LT group (18.04%) compared with the ST group (40.38%).

Conclusions: A longer healing time following ridge preservation results in more vital bone formation and less residual graft particles at the time of implant placement. However, residual allograft material still remains at 12 months after ridge preservation.

KEYWORDS
allografts, alveolar bone grafting, alveolar bone loss, bone transplantation, dental implants, wound healing

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1 | INTRODUCTION

Alveolar ridge preservation is routinely performed to aid in site development for future dental implant placement in an ideal location following tooth extraction. A consequence of tooth extraction is a wound-healing process that leads to ridge resorption and atrophy,[1,2] which has the potential to impede implant placement without requiring significant bone reconstruction. Ridge preservation is generally performed with bone replacement grafts aimed toward maintaining ridge dimension without interfering with the ability of the host bone to fill the extraction socket. Avila-Ortiz et al.[3] in a systematic review showed that regardless of the particulate graft modality (xenograft, allograft, autogenous graft), ridge preservation decreased horizontal resorption by an average of 1.99 mm and vertical resorption by 1.72 mm compared with extraction alone.

The outcome of ridge preservation is generally evaluated by the quantitative horizontal and vertical bone dimensions at the healed site; however, the quality of bone in the former socket is also an important wound-healing parameter. Bone quality can be evaluated histologically by determining the amount of vital bone formation, residual graft material, and connective tissue present at the previously grafted site. A systematic review by Chan et al.[4] reported the mean vital bone percentage after ridge preservation procedures using various graft materials ranged from 24.4% to 58.8%, while the vital bone percentage in non-grafted control sites was 38.5%. In grafted sites, the residual graft percentages ranged from 0% to 36.6%, with xenografts having the highest amount of residual graft material.

The authors' study group has evaluated the histological wound healing following ridge preservation in multiple publications, mainly using allograft obtained from a single donor for each study. There was no significant difference in vital bone formation at 3- and 6-month time points when a solvent-dehydrated bone allograft was used for ridge preservation.[5] When 100% demineralized freeze-dried bone allograft (DFDBA) was used, there was significantly more vital bone formation (38.4%) compared with using 100% mineralized FDBA (24.6%) at 4.5 months after ridge preservation.[6] A combination 70%/30% FDBA/DFDBA allograft also resulted in significantly greater vital bone formation (36%) than FDBA alone (24%) at 4.5 months.[7] Regarding healing at different time points, ridge preservation with 100% DFDBA resulted in an average of 47% vital bone at 18–20 weeks of healing compared with only 32% at 8–10 weeks[8] Furthermore, a combination 70%/30% FDBA/DFDBA allograft resulted in 40% vital bone at 18–20 weeks compared with only 18% vital bone at 8–10 weeks, over twice the amount of vital bone formation with a longer healing time.[9] A different study group also evaluated the time analysis on alveolar ridge preservation and found a significant difference in vital bone formation at 2-, 4-, and 6-month healing times of 28.31%, 40.87%, and 64.11%, respectively.[10] The summary of these studies reveals a clear correlation between healing time and the formation of more vital bone and less residual graft.

While patients and dentists may wish to place a dental implant only a few months after ridge preservation, the timing of ridge preservation and subsequent implant placement can vary due to many factors. Finances, health issues, moving from one location to another, and many other issues may delay implant placement for long periods. There are little published data on wound healing outcomes of ridge preservation procedures longer than 6 months. Therefore, the primary objective of this parallel two-arm, randomized, controlled study was to examine the histologic wound healing in ridge preserved sites over 12 months with outcome measures of percent vital bone, residual graft material, and connective tissue (CT)/other.

2 | MATERIALS AND METHODS

2.1 | Participant enrollment

Under the Helsinki Declaration of 1975, revised in 2013, the Institutional Review Board of UT Health San Antonio (UTHSA) approved this study. The study began in October 2018 and all patients were completed by June 2021. Inclusion criteria consisted of (1) a single tooth (excluding second or third molars) identified for tooth extraction and planned for replacement by a dental implant, (2) adequate restorative space for a restoration, (3) at least 10 mm of alveolar bone height without interference from vital structures, and (4) nonsmokers, former smokers, or current smokers only if they smoked ≤10 cigarettes per day. Exclusion criteria consisted of (1) non-compliant patients with the surgical protocol, (2) women who were pregnant or intending to become pregnant during the study timeline, (3) smokers who smoked ≥10 cigarettes per day, (4) tooth/root malposition such as dilaceration or inclination of the root that would prevent a future implant from being placed entirely in grafted bone in the same position as the previous tooth root, (5) systemic comorbidities including patients with poorly controlled diabetes, patients taking chemotherapeutic and immunosuppressive agents, autoimmune disease, history of bisphosphonate use or chronic steroids, or history of endocarditis following dental surgery. In addition, if a dehiscence was present after extraction and extended more than half the depth of the socket, the patient was exited from the study.

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2.2 | Surgical protocol

Patients were treated by 11 calibrated periodontal residents with board-certified attending faculty periodontists. Calibration for each surgeon was performed by a single faculty member (B.L.M.). After written consent was obtained, full-thickness flaps were reflected ≈ 3 mm beyond the buccal and palatal/lingual bony crest. A minimally traumatic extraction was performed, and a final study enrollment determination based on the integrity of the buccal bone plate at the extraction site was made (buccal plate dehiscence ≤50%). For molar teeth, the interradicular bone, if present, was removed to a level of at least 8 mm apical to the bony crest to prevent future implant placement solely in native nongrafted interradicular bone. The socket was debrided and irrigated, 70%/30% mineralized/demineralized FDBA[*] was hydrated, and the allograft was placed with gentle condensation in the socket to restore the ridge to the original contour. All bone graft material was procured from a single donor, a 58-year-old male with an osteoinductivity grade of 1 on a scale from 0 to 4, and a residual calcium percentage of 1.70. Bone particle size was 0.25 to 1.0 mm. A nonresorbable dense polytetrafluorethylene (d-PTFE) membrane[†] was then placed over the socket orifice extending 3 mm beyond the bony crest and a minimum distance of 2 mm from adjacent teeth. Polytetrafluorethylene sutures[‡] were then used to reapproximate buccal and lingual flaps, with no attempt to close primarily over the socket orifice. After ridge preservation was completed, the patient was then randomized using sealed envelopes into the short-term (ST = 4 months) or long-term (LT = 12 months) healing groups.

Postoperative instructions included the use of amoxicillin, 500 mg orally three times a day for 7 days, and rinsing with chlorhexidine gluconate 0.12% rinse twice daily. Patients returned for evaluation at 2 and 4 weeks to ensure normal healing events. The d-polytetrafluorethylene membrane[†] was removed at the 4-week appointment. A cone-beam computed tomography scan was performed 1 month before planned implant placement with a radiographic stent to evaluate dimensions for bone core harvesting and implant site placement and to ensure the implant would be placed in the same position as the previous tooth root.

Patients returned depending on their group assignment at either 4 or 12 months for implant placement. A surgical guide was used to ensure that the core biopsy was taken at the center of the former extraction site. During initial implant bed preparation after flap reflection, an 8-mm deep bone core biopsy was harvested in each site using a hollow trephine drill[§] which measured 2 mm internally and stored in a 10% formalin solution. Dental implant diameter ranged from 3.3 to 4.8 mm depending on the anatomy of the site. The patient's participation in the study was complete after the bone core was obtained and the dental implant was placed. Standard care postoperative visits were provided to ensure normal healing after implant placement and implants were restored by the referring dentist 3 to 4 months later.

2.3 | Histomorphometric analysis

The process of examining the bone cores histologically has been established by guidelines from previous studies from the author's study group.[5,7–9,11–14] The bone cores were removed from the trephine drill and stored in formalin for a minimum of 72 h and then decalcified with hydrochloric acid for 1 h. The cores were then dehydrated using a tissue processor[¶] in sequential ethanol baths with concentrations of 75%, 90%, and 100%, respectively, and then embedded in paraffin wax. The specimens were placed on glass slides after being sectioned to a thickness of 4 microns and were stained with Harris hematoxylin and combinations of eosin-Y, orange-G, and acid fuchsin as counterstains.[#]

A masked examiner (J.Z.) completed the histological analysis. Each bone core had 7 to 9 slices that were examined under a light microscope at 1X to identify the best quality slice nearest the center of the bone core. The specimens were then evaluated at 4X magnification and overlapping photos were taken of the core and stored as JPEG images. The number of images taken ranged from six to 15 depending on the size of the harvested core. The images were uploaded into a photo editing software[||] and stitched together using a "photomerge" feature, thus making a single image that was representative of the entire bone core. The photos were taken at 4X to allow magnification of the photomerged core with minimal distortion, while also limiting the number of screenshots necessary. The images were analyzed in detail at 20X and 40X magnification to help differentiate the three different tissue types: vital bone, residual graft, and connective tissue (CT)/other.

Vital bone was distinguished by observation of viable osteocytes housed within lacunae, primarily consisting of

[*] 70%/30% Combination FDBA/DFDBA, Osteogenics Biomedical, Lubbock, TX.
[†] Cytoplast PTFE TXT-200 singles, Osteogenics Biomedical, Lubbock, TX.
[‡] Cytoplast PTFE 4-0 sutures, Osteogenics Biomedical, Lubbock, TX.
[§] Trephine bur, Salvin Dental Specialties, Charlotte, NC.
[¶] Tissue-Tek VIP 1000, Sakura Finetek USA Inc., Torrance, CA.
[#] Treosin, Statlab Medical Products, Lewisville, TX.
[||] Adobe Photoshop CC, Adobe, San Jose, CA.

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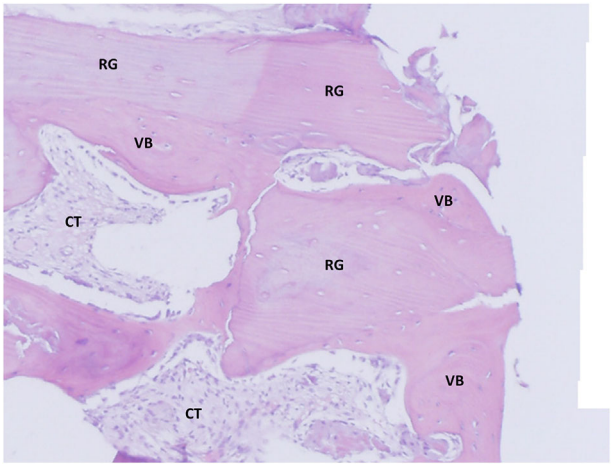

FIGURE 1 Representative sample from the short-term healing group at 4X magnification displaying the three different tissue types. VB, vital bone; RG, residual graft; CT, connective tissue/other; (Harris hematoxylin and combinations of eosin-Y, orange-G, and acid fuchsin as counterstains)

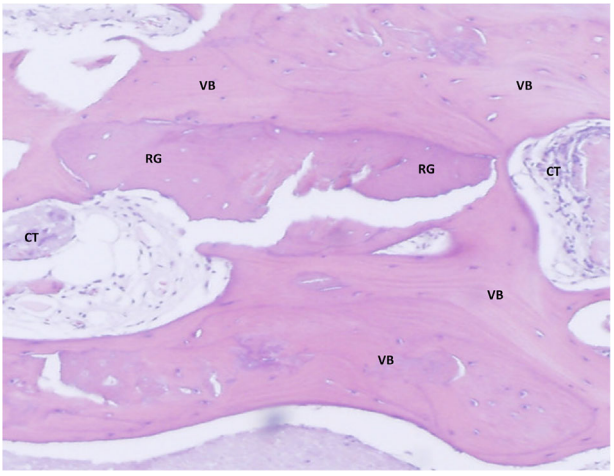

FIGURE 2 Representative sample from the long-term healing group at 4X magnification displaying the three different tissue types. VB, vital bone; RG, residual graft; CT, connective tissue/other; (Harris hematoxylin and combinations of eosin-Y, orange-G, and acid fuchsin as counterstains)

woven bone, while residual graft was identified by the absence of osteocytes in mineralized, primarily lamellar bone particles (Figures 1 and 2). All other remaining tissues consisting of blood vessels, fibrous tissue, and voids within the processed specimen were classified as CT/other. Using image analysis software, the three tissue types were traced and layered, saved as individual JPEG images, and converted to binary images (black and white) using ImageJ.* The total number of pixels in each tissue type was divided by the total number of pixels in all 3 tissue types to identify the total area percentage of vital bone formation, residual graft, and CT/other for each bone core.

2.4 | Statistical analysis

For sample size estimation, standard deviation (SD) range of 11.9% to 22.4% has been demonstrated by other studies within the author's group.[7,8] Therefore, to detect a difference of at least one SD in the percentage of new vital bone formation using a Mann-Whitney *U* test with a power of 90% at a 0.05 level, a minimum sample size of 21 bone cores from each treatment group was required. Due to the extended length of the time interval between ridge preservation and bone core harvest, especially in the LT group, a higher than usual dropout rate was anticipated. Thus, a total of 26 and 31 patients were enrolled in the ST and LT groups, respectively. For data analysis, pairwise comparisons between each group were assessed using Mann-Whitney *U* tests at $\alpha = 0.05$ to determine if the histological parameters of interest (% vital bone, % residual graft, % CT/other) differed between the LT and ST groups. Further, to assess if certain clinical variables of interest (edentulous site location, dehiscence at the time of extraction, maxilla versus mandible, smoking status, diabetes status) affected new bone formation, Mann-Whitney *U* tests were performed in the subgroups of interest using the entire sample size. All analyses were performed using RStudio.[15]

3 | RESULTS

A total of 57 patients were enrolled in the study, 14 of whom were exited from the study before completion (Figure 3). Six patients were exited at the time of the extraction due to the presence of a dehiscence, one patient was lost due to beginning orthodontic treatment during the study period, one patient exited due to receiving a joint replacement, two were lost to follow-up and unable to be contacted, and four patients were lost due to COVID-19 diagnosis, exposure, and/or death that interfered with the implant timing protocol. This left 43 patients who completed the study, 19 males and 24 females, with an average age of 55 years (age range, 25–81). There were three light smokers (<10 cigarettes/day) in the ST group and one light smoker in the LT group. There were three patients with a history of well-controlled diabetes (HbA1c < 7.0%) in both the ST and LT groups (six total). Table 1 presents the distribution of tooth sites in both groups.

At the time of implant placement, all 43 patients completing the study had bone cores harvested and all patients

* ImageJ, National Institutes of Health, Bethesda, MD.

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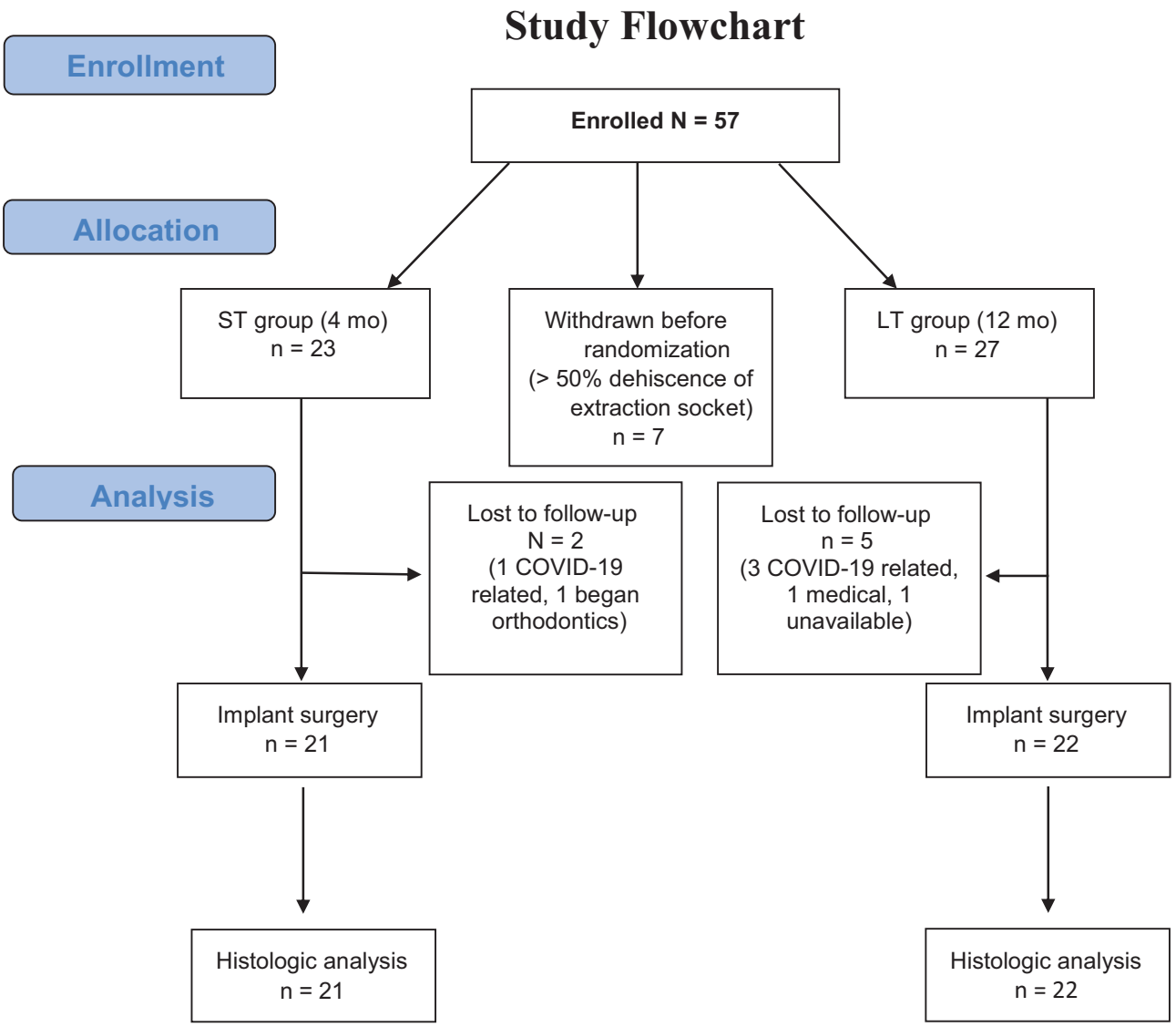

FIGURE 3 Study flowchart

TABLE 1 Distribution of tooth sites by group

Treatment group	Tooth type					
	Max incisor	Max canine	Max premolar	Max first molar	Mand premolar	Mand first molar
ST group	6	1	11	0	0	4
LT group	0	1	12	2	1	5

received dental implants. Three patients in the short-term group and two patients in the long-term group required additional bone grafting at the time of implant placement due to a buccal plate that was <1 mm in thickness after final osteotomy preparation. All implants achieved primary stability, with an average implant torque value of 28 N/cm. A total of 21 bone cores in the ST group and 22 in the LT group were harvested and analyzed histologically.

4 | HISTOLOGIC OBSERVATIONS

The histomorphometric analysis for the primary outcomes is summarized in Table 2. There was a significantly higher vital bone percentage in the LT group (51.38% ± 20.41) compared with the ST group (31.39% ± 18.78) ($p = 0.003$), significantly less residual graft particles in the LT (18.04% ± 15.17%) compared with

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TABLE 2 Primary histologic outcomes

Variables	4-month mean (SD)	[95% CI]	12-month mean (SD)	[95% CI]	*p* value
Vital bone (%)	31.39 (18.78)	[22.9–39.9]	51.38 (20.41)	[42.3–60.4]	0.003
Residual graft particles (%)	28.16 (15.47)	[21.1–35.2]	18.04 (15.17)	[11.3–24.8]	0.029
CT/other (%)	40.38 (14.07)	[34.0–46.8]	30.59 (13.63)	[24.5–36.6]	0.017

TABLE 3 Frequency distribution of percent residual graft material in patients from ST and LT groups

	Vital bone (%)					
Treatment group	0%–10%	10.1%–20%	20.1%–30%	30.1%–40%	40.1%–50%	50.1%–60%
ST ($n = 21$)	4	3	4	4	4	2
LT ($n = 22$)	8	6	4	1	2	1

the ST group (28.16% ± 15.47%) ($p = 0.029$), and significantly less CT/other in the LT group (30.59% ± 13.63%) compared with the ST group (40.38% ± 14.07%) ($p = 0.017$).

There were no significant correlations found between vital bone percentage and presence or absence of a dehiscence ($p = 0.36$), maxillary versus mandibular site ($p = 0.15$), molar versus nonmolar sites ($p = 0.12$), patients with diabetes versus patients without diabetes ($p = 0.34$), need for additional grafting at time of implant placement ($p = 0.51$), or patient age ($p = 0.51$). There was a trend for greater vital bone formation in nonsmokers compared with light smokers ($p = 0.08$), but there were few smokers enrolled in the study ($n = 4$). There was a moderate negative correlation found between bone type quality according to the Lekholm and Zarb classification[16] and percent vital bone percentage (rho > −0.2, $p = 0.01$), with type 2 bone having the highest new vital bone formation.

5 | DISCUSSION

The primary objective of this study was to histologically compare the wound healing and vital bone formation up to 12 months in patients receiving ridge preservation using a combination 70%/30% mineralized/demineralized allograft. The fate and turnover timing of allograft particles remains unknown beyond 6 months, and patients often delay implant placement following ridge preservation longer than 3 to 4 months for a variety of reasons. From this study, it is evident that it takes >1 full year for residual graft material to become fully incorporated within newly forming vital bone tissue, as the average residual graft percentage found even in the 12-month healing group was 18.04%. Indeed, after 12 months of healing, only 8 of 22 patients had <10% residual graft material, 6 of 22 had 10.1% to 20%, 4 of 22 had 20.1% to 30%, and 4 of 22 had 30.1% to 60% residual graft material (Table 3).

This is the third study within the authors' research group with a study design using the 70%/30% combination allograft. Between these studies, there are now three different time points with histological analysis: 8–10 weeks, 18–20 weeks, and 12 months. Nelson and Mealey[9] showed at 8 to 10 weeks of healing an average vital bone formation of 18.17%, with 41.54% residual graft particles. At 18 to 20 weeks of healing, Borg and Mealey,[7] Nelson and Mealey,[9] and the current study had average vital bone percentages of 36.16%, 40.32%, and 31.39%, respectively, with average residual graft percentages of 18.24%, 23.59%, and 28.16%, respectively. At 12 months of healing, the current study showed an average of 51.38% vital bone formation and 18.04% residual graft particles. Studies demonstrate a decrease in the absolute percentage of residual graft particles between the 8- to 10-week and 18- to 20-week healing ranging between 13% to 23%. Conversely, between 18 to 20 weeks and 12 months, the absolute percentage of residual graft decreased only 0.1% to 10%. The difference in percentages of vital bone and residual graft between the studies may be related to inherent differences in the osteoinductivity of bone from the different tissue donors. In the current study, osteoinductivity of donor bone in the athymic mouse gluteal muscle model was scored as 1 on a scale from 0 to 4, while the donor bone in the other studies had a score of 2 (Nelson and Mealey[9]) and 3 (Borg and Mealey[7]). Across all three studies, it can be concluded that the longer the clinician waits for dental implant placement following ridge preservation, the grafted site will contain more vital bone and fewer residual graft particles compared with earlier time points.

The relationship between the amount of vital bone present at the time of implant placement and the final amount of bone-to-implant contact is unknown. Implants do not attain 100% bone-to-implant contact in animal models or in humans, and the percentage of bone-to-implant contact is highly dependent on implant materials and

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surface textures.[17–19] The relationship between vital bone percentages and implant-related outcomes has not been established in the literature. It is also not clear the amount of time needed for the particulate bone allograft to be entirely replaced with new vital bone. At 6 months, Wen et al.[10] showed an average residual graft percentage of 14.82%; however, the graft material was not procured from a single donor. Following allograft placement in intrabony defects with DFDBA, Reynolds and Bowers[20] showed that 72% of sites had residual graft particles at re-entry 6 months after graft implantation. It is unclear with any bone graft implantation at what time point the graft particulate bone is no longer detectable.

The results of the current study suggest that after 12 months of healing, residual allograft is frequently present at ridge preserved sites, usually in relatively small amounts. However, this study used a single type of allograft, a combination of 70% mineralized and 30% demineralized FDBA. Results of this study cannot be extrapolated to other types of allografts which may have different wound healing outcomes. Xenografts may be used in circumstances when slow bioabsorption and turnover rates are desirable.[21] For example, xenografts tend to have slow bioabsorption and may be present for an extended period when used for sinus augmentation.[22] Relatively high percentages of residual graft material have also been seen when xenograft is used for ridge preservation.[4] That said, in a separate study by the authors' study group, a commonly used bovine xenograft has a similar percentage of residual graft (13.5%) at 21 weeks after ridge preservation as compared with the LT group in the current study (18%).[23] It is impossible to speculate how long implanted allograft materials remain present at the site. A previous publication by the authors' study group examined ridge dimensional changes in this patient population and found no significant differences in loss of ridge width or buccal and lingual ridge height between the ST and LT groups.[24] It is unknown whether the increase in vital bone percentage seen in the LT group plays a role in dimensional stability over time. Future studies are needed to evaluate longer healing periods beyond 1 year and to evaluate the correlation between vital bone formation, residual graft, and implant outcomes. In addition, split-mouth studies would further reduce variables in wound healing that may be unique to individual patients.

6 | CONCLUSIONS

There is a significantly greater amount of vital bone present 12 months following ridge preservation procedures with a combination allograft when compared with 4 months. Should circumstances prevent patients from having an implant placed at time points shortly after extraction and ridge preservation, clinicians can be confident that vital bone formation will continue at the site. Conversely, it is incorrect to assume that 12 months after ridge preservation, there will be no allograft remaining at the site. The amount of time required for a particulate bone allograft to be entirely replaced by new host bone remains unclear.

AUTHOR CONTRIBUTIONS

Drs. Zellner, Allen, and Mealey each contributed to conception, design, data acquisition and interpretation, and drafting and revising the manuscript. Dr. Kotsakis contributed to data analysis and interpretation and to drafting and revising the manuscript. All authors have given their final approval of the version to be published.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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