VOLUMETRIC CHANGES IN EDENTULOUS ALVEOLAR RIDGE SITES UTILIZING GUIDED BONE REGENERATION AND A CUSTOM TITANIUM RIDGE AUGMENTATION MATRIX (CTRAM)

by

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CERTIFICATE OF APPROVAL

MASTER'S THESIS

This is to certify that the Master's thesis of

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has been approved by the Examining Committee for the thesis requirement for the Master of Science degree in Oral Biology at the June 2018 graduation.

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ABSTRACT

VOLUMETRIC CHANGES IN EDENTULOUS ALVEOLAR RIDGE SITES UTILIZING GUIDED BONE REGENERATION AND A CUSTOM TITANIUM RIDGE AUGMENTATION MATRIX (CTRAM)

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Introduction: Dental implant placement in a deficient alveolar ridge often requires site development in the form of hard tissue augmentation to achieve ideal functional and esthetic results. A relatively new technique involving use of a customized titanium ridge augmentation matrix (CTRAM) for guided bone regeneration overcomes various limitations and challenges associated with previous techniques. The deficient ridge is virtually augmented, a CTRAM is designed via computer aided design (CAD), fabricated via electron beam melting of Ti6AlV4 alloy powder, polished and sterilized prior to surgical implantation. To date, quantitative volumetric data describing bone gain following ridge augmentation with a customized titanium matrix has not been reported in the literature. The purpose of this prospective pilot study is to evaluate the dimensional change of the alveolar ridge following bone augmentation using CTRAM with freeze-dried bone allograft and a collagen membrane.

Methods: Nine subjects treatment-planned to receive a dental implant following bone augmentation using a CTRAM were enrolled. A pre-surgical cone beam computed tomography (CBCT) scan was obtained for CTRAM design/fabrication and to evaluate pre-surgical ridge dimensions. Surgical treatment consisting of full-thickness mucoperiosteal flap reflection and fixation of the CTRAM to the alveolar ridge was performed at each deficient site. Periodontal probe measurements were made from the CTRAM surface to the underlying alveolar bone. Freeze-dried bone allograft and a collagen membrane were placed prior to flap closure. A 2nd CBCT scan was obtained 7 months following CTRAM placement and bone grafting, and was used to quantify volumetric change in ridge dimensions compared to the pre-surgical CBCT scan. At 8 months, periodontal probe measurements were again made from the CTRAM surface to the underlying bone, CTRAMs were removed, and dental implants placed.

Results: Mean volumetric bone gain was 85.5% of planned dimension. Soft tissue wound dehiscence occurred in four cases; CTRAMs were removed prior to 8 months in three of these cases. When volumetric gain was stratified by soft tissue outcome, cases experiencing dehiscence achieved a significantly lower mean bone gain of 61.3%, versus 104.9% in those that maintained soft tissue closure ($p<0.05$). Mean vertical augmentation, assessed by clinical probing, was 2.86 mm, and mean horizontal gain was 3.02 mm. The average discrepancy between actual CTRAM placement compared with its planned location was 1.09 mm.

Conclusions: Customized titanium ridge augmentation matrices fabricated via CAD/CAM offer the significant benefits of rigid space maintenance during guided bone regeneration, reduced surgical time compared to commercially available mesh, and apparent complete regeneration of bone up to the intaglio surface of the matrix in most cases when soft tissue dehiscence can be avoided.

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LIST OF ABBREVIATIONS

AAOMR	American Academy of Oral and Maxillofacial Radiology
CAD	Computer Aided Design
CAM	Computer Aided Milling
CBCT	Cone Beam Computed Tomography
CT	Computed Tomography
CTRAM	Custom Titanium Ridge Augmentation Matrix
DMLS	Direct Metal Laser Sintering
EBM	Electron Beam Melting
EMD	Enamel Matrix Derivative
e-PTFE	Expanded Polytetrafluoroethylene
FDBA	Freeze-Dried Bone Allograft
GBR	Guided Bone Regeneration
mg	Milligram
mm	Millimeter
NSAIDS	Non-steroidal Anti-Inflammatory Drugs
q6h	Every 6 Hours
q8h	Every 8 Hours
stl	Stereolithography
WRNMMC	Walter Reed National Medical Military Center

CHAPTER I: INTRODUCTION

When a tooth is extracted, resorption of the supporting alveolar bone proper is inevitable, and alveolar ridge resorption amounting to half of the bucco-lingual dimension within the first year is likely to occur (Schropp 2003). Site preservation, which entails placement of a bone graft material within the socket at the time of extraction, can help minimize this resorption. In cases where site preservation is not performed following extraction of a tooth, the resultant atrophic alveolar ridges often require bone augmentation to facilitate dental implant placement. There are a variety of techniques currently available for hard tissue augmentation, several of which involve the placement of a bone substitute graft. Utilizing a fixed, rigid structure or material to immobilize and maintain space at the site of augmentation is key to a successful result.

One such example of a rigid structure that can be utilized for hard tissue augmentation procedures is commercially available titanium mesh. These have been in use in dentistry for over a decade, and have led to successful augmentation results in both the horizontal and vertical dimension (Louis 2008). Despite their excellent space maintenance properties, some limitations to these meshes exist (Louis 2008, Jensen 2014, Sumida 2015):

1. Additional intraoperative time is required to trim and adapt the mesh to the site.
2. Sharp edges along the periphery of the mesh predispose it to mucosal perforation/dehiscence during healing.
3. Difficult to precisely fit to defects in order to create ideal bony contours.

The integration of computer aided design (CAD) and 3D modeling has been

utilized to fabricate customized titanium meshes (matrices) that provide an intimate and precise anatomic fit to the defect without the need for intraoperative adjustments, which reduces surgical time. At the Naval Postgraduate Dental School (NPDS), Customized Titanium Ridge Augmentation Matrices (CTRAM) have been successfully utilized to achieve ideal restoration of deficient alveolar ridges. This approach to augmentation overcomes limitations associated with other techniques in addition to commercially available titanium mesh, such as ridge split (high technique sensitivity) and autogenous block grafts (patient morbidity due to graft harvest at additional surgical site, graft resorption during healing).

Figure 1 depicts a clinical case in which prior loss of molar teeth resulted in an atrophic alveolar ridge with dimensions insufficient to facilitate dental implant placement. After full-thickness flap reflection, intra-marrow penetrations are created in the area to be grafted (Fig. 1A), and the CTRAM is positioned over the defect and secured with fixation screws (Fig. 1B). Large "bone loading" ports on the buccal aspect of the CTRAM allow for easy placement of freeze-dried bone allograft (FDBA), and are subsequently covered with a resorbable collagen membrane (Fig. 1C, D). Tension-free primary closure is achieved (Fig. 1E), and a healing period of 8 months is allowed for formation and maturation of new bone within the space created by the CTRAM. Complete bone fill to the intaglio surface of the CTRAM was seen upon re-entry, and the new ridge dimensions replicate the planned, ideal dimensions as specified in the CTRAM design process utilizing CAD software (Fig. 1F). The post-augmentation dimensions of the ridge appear ideal and were optimal for facilitating implant placement (Fig. 1G, H). While this case depicts an ideal and frequently observed outcome of treatment with

CTRAM as observed at NPDS (complete restoration of deficient ridges to ideal dimension), quantification of bone gain resulting from this treatment protocol has not previously been documented.

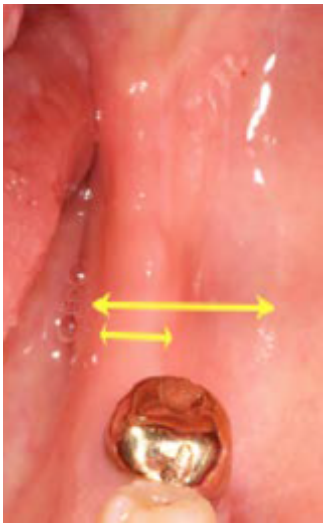
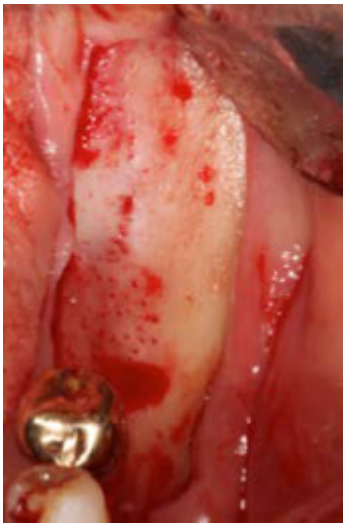


Figure 1A



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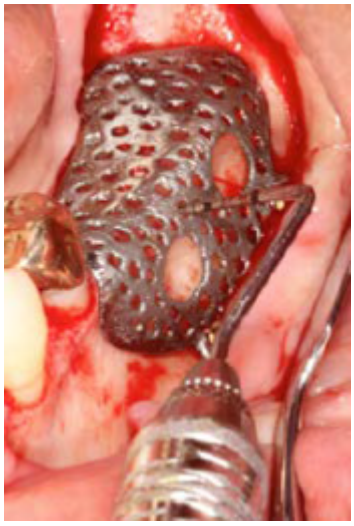
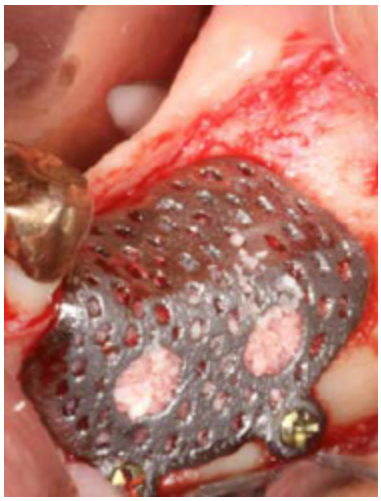


Figure 1C



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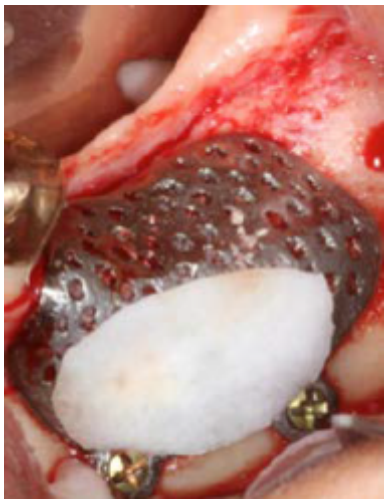

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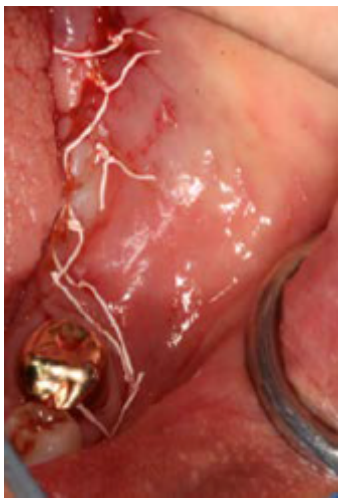


Figure 1F

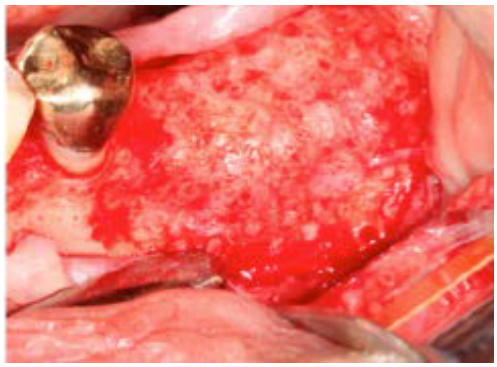


Figure 1G

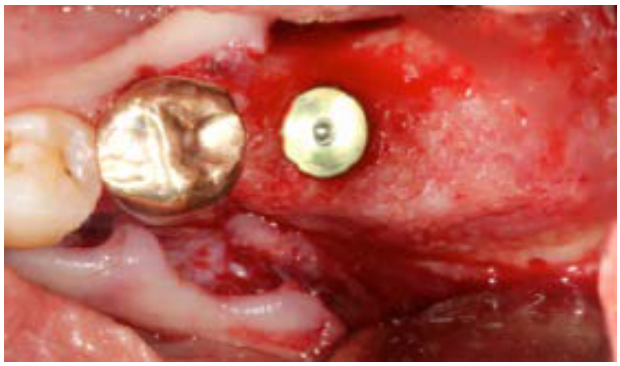


Figure 1H

To date, no published studies have documented volumetric changes in ridge dimension when utilizing a customized titanium mesh with bone graft to augment an edentulous ridge.

If the data from this prospective pilot study indicate that predictable augmentation approximating the dimensions of the custom-designed CTRAM can be achieved, it may be possible to consider elimination of the need to obtain a second cone beam computed tomography (CBCT) scan prior to re-entry surgery as is commonly performed for assessment of bone gain.

CHAPTER II: REVIEW OF THE LITERATURE

Dental implant treatment is a complex modality requiring careful planning and consideration to achieve successful outcomes. One of the most commonly encountered challenges when considering implants is the atrophic alveolar ridge. Following the extraction of a tooth, resorption of the alveolar bone occurs due to the loss of vasculature associated with the periodontal ligament. The amount of resorption that occurs has been described (Schropp, 2003) as comprising approximately 50% of the horizontal dimension of the alveolar ridge one year after extraction, with roughly 1/3 of this amount occurring within the first 3 months. Site preservation techniques have been developed to minimize the extent of resorption, but oftentimes the clinician is nonetheless faced with the prospect of inadequate osseous dimensions to support a dental implant in its ideal position.

If a dental implant is placed into a ridge with inadequate bucco-lingual dimension, a clinical result such as that depicted in Figure 2 may result. Implant threads that are not enclosed in bone facilitate bacterial colonization and may contribute to the development of peri-implantitis leading to further complications and possible loss of the implant (AAP Position Paper, 2013).

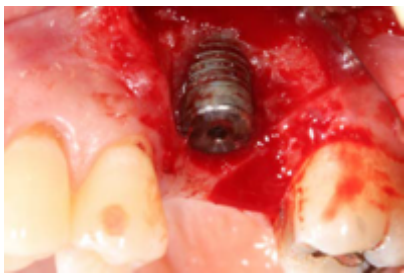


Figure 2

In order to augment the dimensions of the alveolar ridge to facilitate dental implant placement, numerous techniques have been described in the literature. Guided bone regeneration (GBR), which consists of the use of a membrane with or without the

use of a graft material, takes advantage of the cell-occlusive properties of the membrane to selectively allow for population of the area of augmentation with cells that favor deposition of new bone. The initial introduction of this technique involved the use of membranes placed over bone grafts during spinal fusion in a canine model (Hurley, 1959). Later, Buser (1993) utilized membranes in deficient maxillary sites in humans to exclude fibroblasts and epithelial cells during a nine-month healing period, resulting in successful regeneration of bone.

The forms of particulate allograft materials typically used in GBR procedures are freeze-dried bone allograft (FDBA), and demineralized freeze-dried bone allograft (FDBA). Nevins (1998) reported that implants placed into bone regenerated from either DFDBA, FDBA or autogenous bone all had similar survival rates to those placed into native bone. Cammack (2005) found nearly identical percentages of new bone formed after ridge augmentation performed with FDBA and DFDBA (41.89% and 41.74%, respectively). These studies indicate that utilization of these allografts is a viable option for regenerating bone when placement of dental implants is the intended therapeutic endpoint.

Another option for ridge augmentation is the use of either autogenous or allograft bone blocks. While both can be effectively utilized for this purpose, significant drawbacks to each approach have been described. Block autografts are associated with increased patient morbidity due to the frequent need for a second surgical site for block harvest, and rates of resorption of these blocks have been reported at up to 25% (Misch, 1997). Allograft blocks are an alternative to autogenous block grafts which avoid the morbidity associated with graft harvest, however materials cost and graft resorption are

both significant drawbacks to this approach. Keith (2006) found localized resorption ranging from 0.5-2.0 mm associated with block allografts in 31% (23/75) of subjects studied. Lyford (2003) similarly identified surface resorption from 1.0-2.0 mm in three of five block allograft cases studied.

Titanium mesh is a biocompatible, space maintaining material that has been utilized successfully in cranioplasty applications. A case report by Gundesliogu (2013) documents the use of a titanium mesh in a 58-year old patient following cranioplasty. The mesh became exposed soon after placement. Eight years later, the patient returned seeking treatment for "discharge" emanating from the area, as well as a foul odor. The titanium mesh was subsequently removed, and significant new bone formation was observed to have occurred beneath the mesh. Histological assessment showed a chronic inflammatory response to "the inverted scalp" but not to the mesh itself, which demonstrates the biocompatibility of titanium mesh in the event of exposure.

Commercially available titanium mesh has been utilized as an effective means to achieve rigid space maintenance to successfully augment deficient alveolar ridges. Von Arx (1998) reported on the use of titanium mesh in conjunction with autogenous bone to augment deficient ridges at the time of implant placement in 6 patients (10 implants). No complications were noted, and after 6-9 months the mesh was removed and >90% of the augmented ridge dimension was maintained. A prospective study by Pierri (2008) involving treatment of 19 deficient ridge sites with titanium mesh with an autogenous/xenograft bone mix found an average horizontal gain of 3.71 mm and vertical bone growth of 4.16 mm. Dental implant treatment was successfully completed at all sites.

Despite the advantages of utilizing commercially available titanium mesh for space maintenance in hard tissue augmentation procedures, these meshes require trimming for proper adaptation to the patient's ridge intraoperatively that can increase intraoperative time, and the trimming often results in sharp points along the edges of the mesh that can perforate the mucosa. In a review of 6 studies employing titanium meshes with particulate bone graft for ridge augmentation (Ricci, 2013), 22.78% (18/79) of patients were reported to have had mesh exposure during weeks 5-12, and 9 patients required the mesh to be removed. Two other retrospective studies evaluating titanium mesh also reported rates of exposure ranging from 26-52% (Her 2012, Louis 2008).

Customization of titanium using computer-aided design/computer-aided manufacturing (CAD/CAM) technology in medicine was first reported by Joffe (1999). 148 patients undergoing cranioplasty were treated by CAD/CAM fabricated titanium plates. Of these plates, 97 fit passively over the defect, and it was noted that the surgical time was minimal in comparison to alternative approaches. Only one case required plate removal due to infection. This technique was not only effective but also represented an increase in the level of precision and a reduction in surgical time (versus previous techniques requiring manual adaptation of the titanium plates to the skull defect) and minimal post-operative complications.

The use of CAD/CAM and additive manufacturing of titanium mesh for alveolar ridge augmentation was first described in a case report by Ciocca (2011). Utilizing a pre-operative CBCT scan and CAD to design a custom mesh 0.6 mm thick with square 1.0 mm pores throughout the surface, they then utilized direct metal laser sintering (DMLS) techniques to three dimensionally print the customized mesh from titanium alloy

(Ti6AlV4). A second CBCT was obtained 8 months after the mesh was surgically implanted over the deficient ridge, and a mean vertical increase of 2.57 mm and horizontal increase of 3.41 mm in alveolar ridge dimension were reported.

Jensen (2014) similarly used CAD/CAM methodology to fabricat a customized titanium mesh for ridge augmentation. TiAl4V powder was used in a different additive manufacturing process known as electron beam melting. Although no quantified outcome data was reported with regards to the degree of augmentation achieved, he reported an intimate fit of the mesh to the defect, which shortened the surgical procedure and reduced the surgical difficulty compared with the aforementioned stock titanium mesh techniques.

In addition to the precise and intimate fit achieved when utilizing customized titanium mesh, other advantages have been described in the literature. The elimination of the need to trim and adapt the mesh, as is necessary with stock mesh, results in a reduction of intraoperative time and elimination of sharp edges along the periphery of the mesh that have the potential to lead to mucosal perforation during healing. Sumida (2015) compared customized versus commercially available titanium mesh, and reported an average surgical time of 75.38 minutes for customized mesh, vs. 111.9 minutes for stock mesh. In addition, the rate of mucosal perforation was 7.7% for customized vs. 23.1% for stock mesh, and significantly fewer fixation screws were required to stabilize the customized mesh. These reported benefits were echoed in a case series published by Connors (2016), which also discussed the advantage of the provider having full control over the contours/borders of the desired bone regeneration.

CHAPTER III: MATERIALS AND METHODS

Nine patients (6 males, 3 females), with ages ranging from 42 to 66, were enrolled in this prospective pilot study evaluating the volumetric changes in alveolar ridge dimension following treatment with the CTRAM technique. Inclusion criteria for study participation included military healthcare beneficiaries 18 years or older, geographic presence within the National Capital Region for the duration of the study, and the presence of an edentulous alveolar ridge site deficient in bone with at least 3 natural teeth adjacent to the area. All patients were treatment planned for dental implants and ridge augmentation using CTRAM by their periodontics provider (periodontics residents at the Naval Postgraduate Dental School, Bethesda, MD). Exclusion criteria included female patients who were pregnant or nursing, current smokers, patients with clinically significant or poorly controlled systemic diseases which may affect healing (ASA 3 or higher), allergies to medications or materials used in the study, active infections, and poor oral hygiene.

Once a suitable candidate for the study was identified, the patient's periodontics provider supplied a one-page study brief explaining the nature of the study, as well as the research interventions involved in the study. If they were interested in participating, they were then provided a full consent packet by one of the investigators, and the study was discussed in detail prior to consenting or denying consent to participate.

The full course of the study is outlined graphically in Appendix A ("CTRAM Prospective Study Flow Chart"). This flow chart depicts where and when study

interventions occur within the typical CTRAM treatment workflow. The only clinical interventions that differ from the normal course of ridge augmentation treatment with CTRAM are the clinical probing measurements obtained through the CTRAM at the time of matrix placement and removal.

Following consent, the baseline CBCT scans (previously obtained by the subject's periodontics provider during treatment planning stage) were imported into the 3D CAD software (Mimics, Materialise). Thresholding was performed for the osseous tissues, and a stereolithography (STL) file was then exported to produce a 3D-printed physical model of the jaw to be augmented. These models acted as a tool for communication between the treating periodontist and the biomedical engineer to define the extent of ridge augmentation desired through treatment with CTRAM.

The STL files of the deficient ridges were then imported into Geomagic Freeform Modeling Plus (3D Systems). An additional digital body file for each case was then fabricated to approximate the desired post-augmentation ridge dimensions, which could be fine-tuned with input from the surgical provider until the precise desired ridge dimension (based on the planned eventual implant positions) was achieved. An example of this is shown in figure 3, where the virtually augmented ridge dimension is depicted in turquoise. The body of the CTRAM, represented by this ideal ridge dimension, was then created as a solid surface file with an approximate thickness of 0.5 mm. This

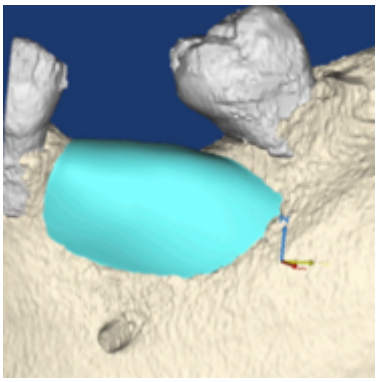


Figure 3

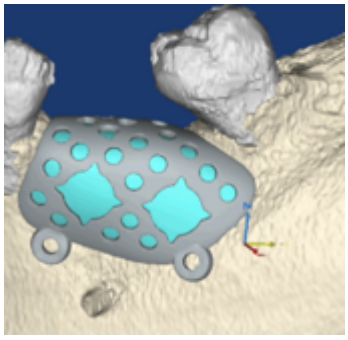


Figure 4

"crude" CTRAM was then further digitally manipulated to include one or two large bone loading ports (to allow placement of graft material), multiple smaller nutrient ports (to allow for the passage of gasses and nutrients from the flap to the underlying graft), and two fixation "feet" along the perimeter of the CTRAM for placement of fixation screws. Four notches, 90-degrees apart were designed into the edges of each bone loading port to serve as references for horizontal clinical probing measurements (figure 4). Four nutrient ports on the occlusal surface of the CTRAM were also uniquely designed in a cam-shaped fashion to similarly allow for attainment of repeatable vertical probing measurements.

The completed STL file of each CTRAM was then exported to an electron beam melting machine (Arcam) for fabrication using TiAl6V4 titanium alloy powder. The resultant piece was then cleaned and polished to remove excessive surface roughness, and sterilized in an autoclave.

Prior to the surgical procedure, each subject's periodontics provider determined whether sedation was indicated, and the patients were given the option to have the procedure completed with either 1) only local anesthesia, 2) local anesthesia and oral anxiolysis with triazolam, or 3) local anesthesia with intravenous moderate sedation. All surgical providers (periodontics residents at the Naval Postgraduate Dental School) were briefed on the CTRAM surgical protocol.

The general surgical technique included sulcular incisions around teeth adjacent to the site to be augmented, with a paracrestal or crestal incision traversing the edentulous ridge. Vertical releasing incisions were included if necessary. Full-thickness mucoperiosteal flap reflection was completed, CTRAM was positioned and assessed for

appropriate fit, and corticotomies were made through the underlying cortical bone. The CTRAM were then fixated with either one or two fixation screws as necessary to achieve complete immobilization. Following fixation, periodontal probe measurements were

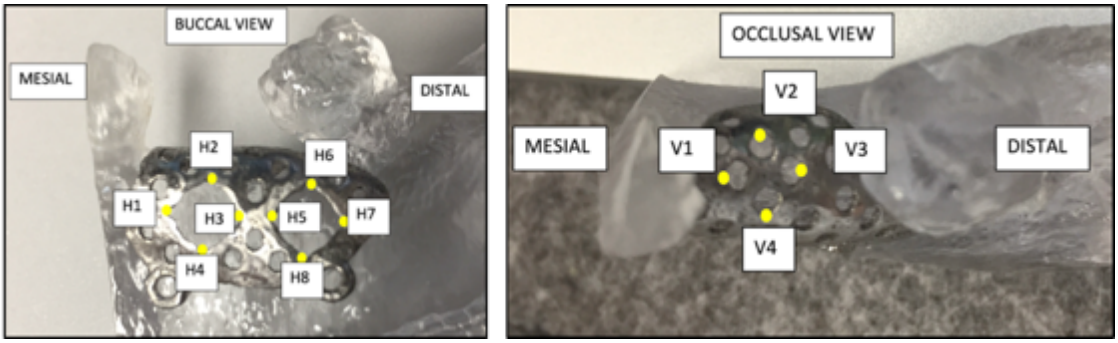


Figure 5

taken by one of three designated board-certified periodontists to the nearest 0.5 mm with a UNC-15 periodontal probe through the four designated vertical locations and either four or eight horizontal locations on the CTRAM to the underlying bone (figure 5). FDBA was then placed through the bone loading ports, and the CTRAM was covered by a collagen membrane. Periosteal releasing incisions were made as necessary to facilitate tension-free primary closure, and the areas of the flap were sutured with monofilament non-resorbable suture material (other areas were sutured with either a resorbable or non-resorbable suture material).

A standardized post-operative medication regimen was administered, consisting of ibuprofen (800 mg PO TID), hydrocodone/acetaminophen (5/325 mg, 1-2 tabs PO q6h as needed), amoxicillin (500 mg PO TID for 10 days), 0.12% chlorhexidine gluconate rinse (BID), and Medrol (methylprednisolone) Dosepak 4mg (if needed). Subjects allergic to penicillin were given clindamycin (300 mg, q8h for 10 days) instead of amoxicillin. Written and verbal post-operative instructions were provided, and patients

were seen at weeks 1, 2, 4 and 8, as well as 3, 5 and 7 months after surgery for post-operative care.

In the event that soft tissue dehiscence resulting in exposure of the CTRAM occurred during the post-operative course, surgical providers were given the discretion to treat the areas with local measures (topical application of 0.12% chlorhexidine gluconate) and monitor for signs of adverse healing, or to intervene by removing the CTRAM early. If significant pain or signs of infection, including purulent exudate, were detected the CTRAM was removed.

Seven months following placement of the CTRAM, a second CBCT scan was taken to assess the degree of bone fill beneath the CTRAM. At 8 months post-insertion of the CTRAM, the second surgical procedure involving removal of the CTRAM and implant placement was completed. Surgical steps were completed as previously described to uncover the CTRAM (figure 6). Clinical probing measurements were again made by one of the designated investigators at the specified points through the CTRAM to the underlying bone with a UNC-15 probe. Fixation screws and the CTRAM were removed. Dental implant placement was completed according to the manufacturer's guidelines, and standard post-operative care was given at weeks 1, 2, 4 and 8.

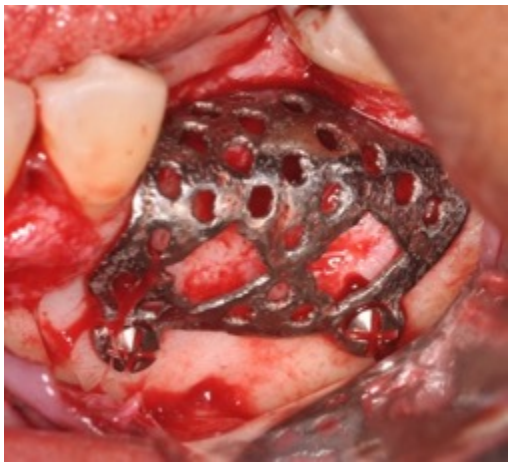


Figure 6

The volumetric analysis of the changes in alveolar ridge dimension achieved through treatment with CTRAM and FDBA was divided into two specific aims: Specific Aim 1

involves comparison of the pre-surgical and post-surgical cone beam CT scans to determine the amount of radiographic bone fill attained beneath the CTRAM, as well assessment of the accuracy of the surgical placement of the CTRAM versus its digitally planned location. Specific Aim 2 involves assessment of the bone fill by comparing pre- and postsurgical clinical probing measurements made at designated points from the CTRAM surface to bone.

Volumetric Analysis and Assessment of CTRAM Placement (Specific Aim 1):

3D reconstruction of post-treatment osseous anatomy was completed using the previously outlined CAD methodology based on the 7-month CBCT scan. The CTRAM was segmented separately and maintained as a separate file. Global registration allowed for pre- (figure 7A) and post- treatment scans to be overlaid for comparison. Bone fill was measured by subtracting the post-operative osseous dimension (figure 7B) from the initial reconstruction (Figure 7C) using a Boolean subtraction operation. The result of this subtraction is a volume (representing "new bone") that can be compared with the planned dimension of augmentation to yield a percentage bone fill.

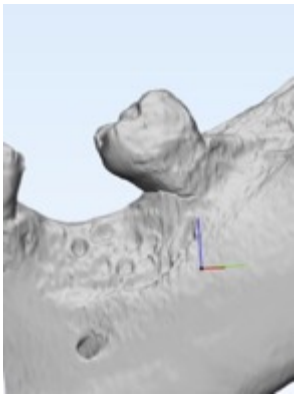


Figure 7A

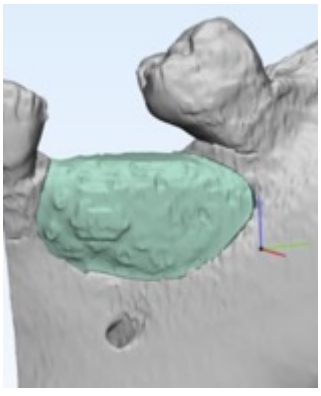


Figure 7B

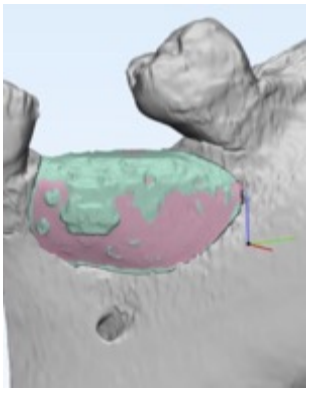


Figure 7C

Global registration of the preoperative 3D reconstruction (which includes the "planned CTRAM") and the post-operative reconstruction (which includes the CTRAM in its actual position in the mouth) was performed to assess the accuracy of CTRAM placement in relation to the intended position. Four points on each subject's CTRAM were chosen as points for comparison: the mesial and lingual vertical measuring points (V1 & V2), and the most distal and most disto-apical horizontal measuring locations (H3 & H4 or H7 & H8 if the CTRAM design contained two bone loading ports). After registering the two reconstructions and isolating the CTRAMs from each, linear measurements were taken between each point on the and its corresponding point on the other model (figure 8). Measurements were recorded as absolute values on a three dimensional coordinate system.

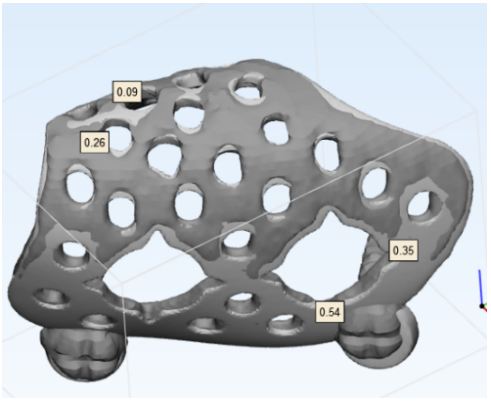


Figure 8

Means and standard deviations were calculated on both a subject level and overall for percent bone fill and CTRAM placement discrepancy. A Wilcoxon rank-sum test was performed to compare differences in percentage mean bone fill between subjects who experienced soft tissue dehiscence, and those who did not.

Clinical Probing Assessment of Ridge Augmentation (Specific Aim 2)

Subtracting the probing measurements obtained at the time of CTRAM removal from the initial probing measurements (at time of CTRAM fixation) yields a linear dimension of ridge augmentation. Mean subject level and overall

horizontal and vertical augmentation dimensions and standard deviations were obtained by pooling these values.

CHAPTER IV: RESULTS

Nine patients treatment-planned for hard tissue augmentation with CTRAM were enrolled in the study (6 men, 3 women; age range 42-66). Five patients completed the treatment sequence as described in the protocol, with CTRAM removal performed 8 months after graft placement. In three cases, CTRAM was removed early at the discretion of the surgical provider due to early exposure. Four patients experienced dehiscence of the CTRAM through the soft tissue (44.4%); three of these comprised the aforementioned early-removal group, and the other was maintained in-situ until the prescribed removal time at 8 months.

The overall mean percentage bone fill as assessed through volumetric analysis was 85.5 ± 30.9%. Volumetric results are summarized in Table 1 and Figure 9. The overall average positional discrepancy between a point on the planned CTRAM and the same point's actual position following surgical placement, across all subjects, was 1.09 ± 0.81 mm, with error bars denoting the subject-level minimum and maximum values. These results are summarized in Table 3 and depicted graphically in Figure 11

Clinical probing data, assessed at baseline and at re-entry, is summarized in Table 4. The mean baseline vertical probing measurement through the CTRAM was 4.49 ± 0.71 mm, and mean baseline horizontal probing measurement was 3.91 ± 0.50 mm. Subject-level mean horizontal and vertical probing values were calculated by averaging the values of all designated horizontal and vertical probing sites on the patient's CTRAM. The mean horizontal and vertical increases in ridge dimension achieved, assessed by comparing pre- and post-graft probing measurements, was 3.02 ± 0.84 mm and 2.86 ±

1.09 mm, respectively. Clinical measurements at the time of removal were not obtained on subjects #5 and 7, whose CTRAM were removed early.

In cases where closure of the soft tissue over the CTRAM was maintained (no dehiscence occurred) until matrix removal at 8 months, the mean bone fill percentage was 104.9 ± 15.5%. In the four cases involving soft tissue dehiscence of the CTRAM, the mean percentage bone fill was 61.3 ± 33.7%. This difference was found to be statistically significant ($p=0.03$, Wilcoxon rank sum test). Volumetric bone gain stratified by soft tissue outcome is displayed in Table 2 and Figure 10.

No significant complications were noted at any time point in any of the subjects. Only one patient (subject 1) exhibited purulent exudate at the site of soft tissue dehiscence of the CTRAM. Dehiscence occurred 2.5 months after CTRAM placement, and exudate was detected 1.5 months thereafter, at which time the CTRAM was removed. Despite early removal of the CTRAM, the percentage bone gain was 93.8%, and dental implant placement was possible with no further ridge augmentation required.

Two subjects had CTRAM removed due to early exposure prior to obtaining the second CBCT scan. In these subjects, volumetric analysis was still completed according to the previously described methods. The CTRAM in subject 5 was removed at 2.25 months after placement due to the provider's concern with the significantly large area of the CTRAM exposed to the oral cavity. The soft tissue was allowed to heal by secondary intention following removal, and a CBCT scan obtained three months later revealed a bone gain representing 68.8% of the planned augmentation volume. Primary soft tissue closure was not achieved during the placement of the CTRAM in subject 7, and the CTRAM remained exposed to the oral environment until its early removal 2.5 months

after placement. During this period of time, the exposed area was treated topically with 0.12% chlorhexidine rinse. Percentage bone fill for subject 7 was only 13.9%, the lowest of any subject by a significant margin.

Dental implant placement was accomplished at all sites in all subjects enrolled in the study without the need for further hard tissue augmentation.

TABLE 1

Volumetric Bone Gain (Specific Aim 1)				
Subject ID	**Baseline volume (mm3)**	**Virtual Model Increase (mm3)**	**Post-Grafting Volume (mm3)**	**% Bone Fill**
1	0	311.29	292.06	93.82
2	0	507.44	614.64	121.13
3	0	259.70	283.34	109.10
4	0	242.68	238.84	98.42
5	0	804.80	553.93	68.83
6	0	297.45	203.88	68.54
7	0	341.20	47.74	13.99
8	0	299.01	243.33	81.38
9	0	157.23	179.60	114.23
Overall	**0**	**357.87± 180.99**	**295.26 ± 169.29**	**85.49 ± 30.88**

TABLE 2

Volumetric Gain Stratified by Soft Tissue Outcome			
Case outcome	**Mean planned augmentation volume**	**Mean post-graft volume**	**Mean % Bone Fill**
Soft tissue dehiscence	438.687	274.403	61.296 ± 33.69
No soft tissue dehiscence	293.211	311.948	104.851 ± 15.52
p value*	**0.287**	**0.778**	**0.0355**

*Wilcoxon rank sum test

FIGURE 9

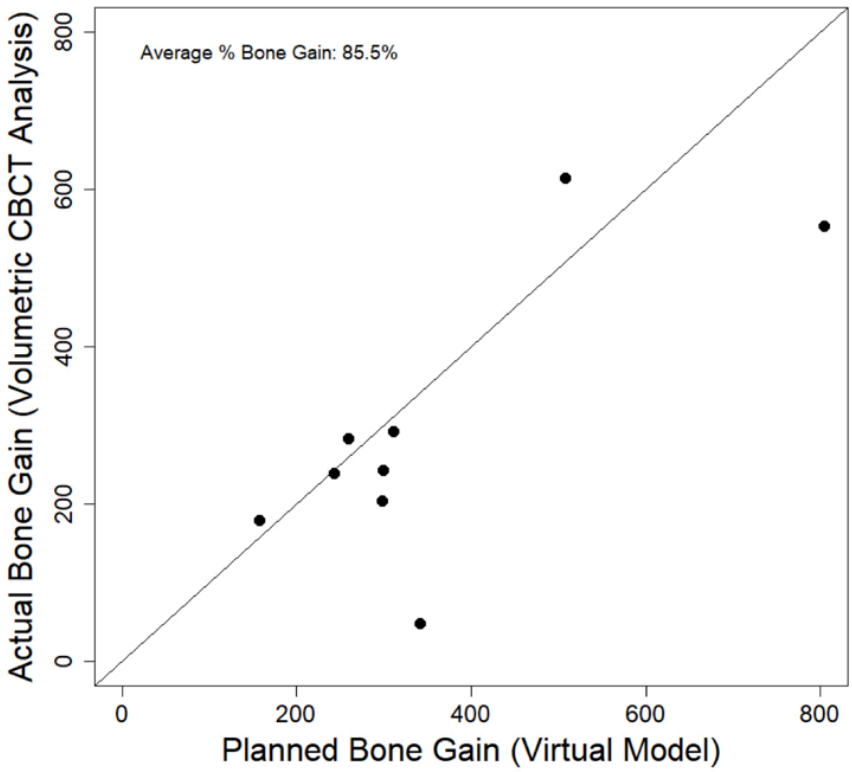


FIGURE 10

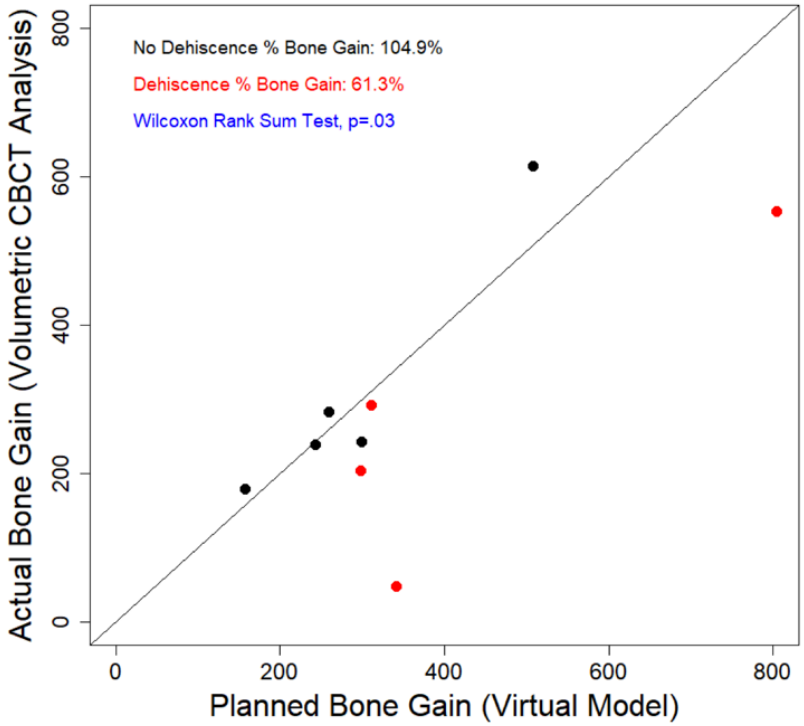


TABLE 3

CTRAM Placement Discrepancy (Specific Aim 1)					
Subject ID	**Point 1 Difference (mm)**	**Point 2 Difference (mm)**	**Point 3 Difference (mm)**	**Point 4 Difference (mm)**	**Mean Difference (mm)**
1	0.56	0.31	0.31	0.41	0.39
2	0.26	0.09	0.35	0.54	0.31
3	1.07	1.13	0.76	0.68	0.91
4	0.65	0.98	0.83	0.92	0.85
5	N/A	N/A	N/A	N/A	N/A
6	0.89	1.61	1.97	0.85	1.33
7	N/A	N/A	N/A	N/A	N/A
8	2.47	2.2	3.64	3.37	2.92
9	0.47	0.9	1.16	1.11	0.91
Overall					**1.089 ± 0.81**

FIGURE 11

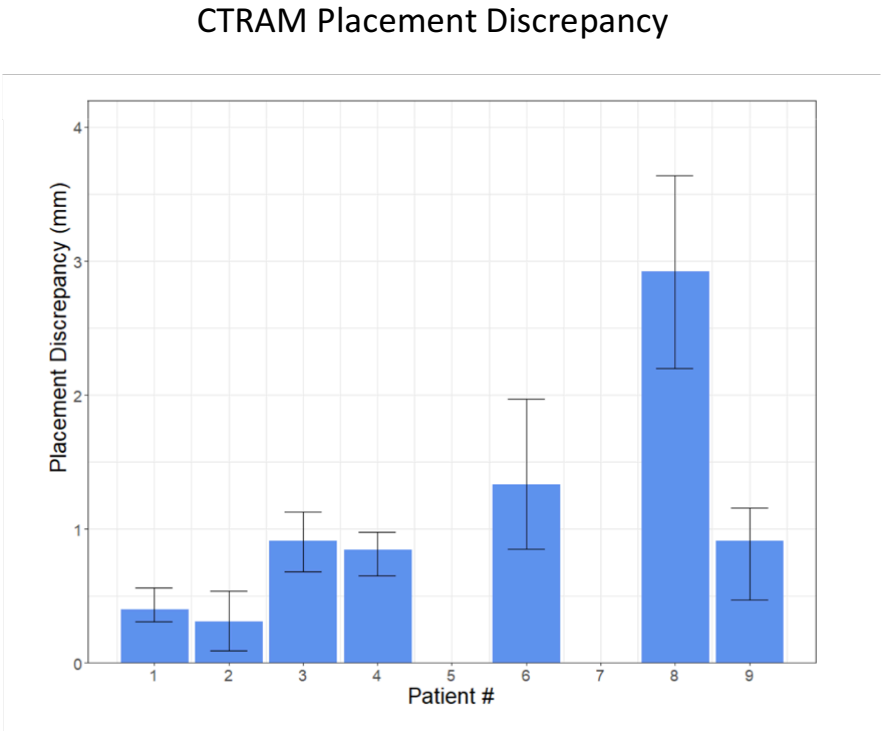


TABLE 4

Clinical Probing Measurements (Specific Aim 2)						
Subject ID	**Baseline Horizontal**	**Baseline Vertical**	**Final Horizontal**	**Final Vertical**	**Mean Horizontal Gain**	**Mean Vertical Gain**
1	3.875	5.2	1.75	2.5	2.125	2.7
2	4.125	5.6	0.5	1	3.625	4.6
3	4.5	5	0.125	1.25	4.375	3.75
4	4	3.8	0.25	0.625	3.75	3.175
5	4	4.2	---	---	---	---
6	4.5	5	1.25	2.5	3.25	2.5
7	3.5	4.4	---	---	- --	---
8	4	3.8	1.75	3	2.25	0.8
9	2.75	3.4	0.625	0.5	2.125	2.9
OVERALL	**3.92 ± 0.50**	**4.49 ± 0.71**	**0.89 ± 0.63**	**1.63 ± 0.94**	**3.024 ± 0.84**	**2.86 ± 1.09**

CHAPTER V: DISCUSSION

Ridge augmentation using CTRAM is a viable modality for alveolar ridge augmentation to facilitate placement of dental implants. While previous reports in the literature and cases completed at NPDS have documented the success, predictability, safety, and efficiency properties of these devices, no publications to date have reported on the volumetric dimensional changes of the augmented ridges in a prospective trial.

When CTRAM experienced soft tissue dehiscence in the present study, statistically significantly less mean bone formation was achieved (61.3% vs. 104.9% when no dehiscence occurred). Machtei (2001) described the impact that the shift from an essentially sterile environment in a GBR site with soft tissue closure maintained, to one that is contaminated by bacteria following wound dehiscence and exposure has on the amount of bone regeneration achieved. In their review of relevant literature, they found that 24 non-exposed GBR sites gained 6-times as much new bone (3.01 +/- 0.38 mm) compared with 36 sites (0.56 +/ 0.45 mm) that became exposed. The present study also found a much wider range (13.99-98.22%) in bone fill achieved in sites that experienced wound dehiscence versus sites which maintained primary soft tissue closure until re-entry at 8-months post-insertion of the CTRAM (81.38-121.13%). This suggests that another consequence of soft tissue dehiscence is a higher degree of unpredictability with respect to the amount of bone regeneration that can be expected.

The rate of soft tissue dehiscence resulting in CTRAM exposure in the present study (4/9 cases, 44.4%) is higher than the rate reported by Sumida (2015) which is the only other custom titanium mesh study in the literature with a similar or greater number

of cases reported. Their rate of wound dehiscence for customized titanium mesh was 1/13 or 7.7%, versus 3/13 (23.1%) for stock titanium mesh. One explanation for the higher rate of dehiscence noted in the present study is the fact that surgical procedures were performed by multiple different providers and all surgical providers were periodontics residents, which included first- through third- year residents of varying surgical experience.

Soft tissue dehiscence resulting in exposure of the CTRAM to the oral cavity does not, however, seem to necessitate immediate removal of the CTRAM. This finding was previously described in a CTRAM case series by Connors, where CTRAM which had become exposed due to soft tissue dehiscence were maintained in health for months through topical application of 0.12% chlorhexidine gluconate and regular postoperative monitoring. In the present study, the decision to remove a CTRAM early was left to the discretion of each individual surgical provider (NPDS Periodontics residents) and their attending staff periodontist. In three out of the four cases where wound dehiscence resulting in CTRAM exposure occurred, the CTRAM was removed early. Subject #6 presented with CTRAM exposure at the one-week post-operative follow up. The site was managed via local application of chlorhexidine as previously described until removal at 8-months post insertion. 68.54% bone fill was achieved, despite the exposure which occurred within the first week of healing, and dental implant placement was accomplished with no complications.

Several sites were found to have achieved over 100% bone fill. While this finding may initially seem counterintuitive, it can be explained by several factors. First, the reference volume consists of the volume bound by the alveolar ridge at baseline and

the CTRAM in its digitally planned location. When the CTRAM is placed clinically, slight deviations in placement versus the planned position can result in a larger "real" potential augmentation volume. Additionally, bone was shown in several cases to have regenerated beyond the dimension bound by the intaglio surface of the CTRAM, particularly in the region of the large bone loading ports. This is illustrated in figure 9, where the pink surface represents the digitally planned augmentation, and the green represents the actual bone fill.

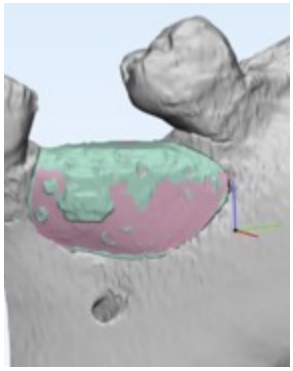


Figure 12

In all but one case, the mean deviation in placement of CTRAM relative to the planned position was found to be less than 1.5 mm. In the case with the highest mean deviation (subject 8), which measured 2.92 mm, the deviation did not impact the ability to place the implant in its intended location. One explanation for the high discrepancy value in this case is that the site was not tooth-bound (site #19 with teeth numbers 17 and 18 missing), which created the potential for the CTRAM to be inadvertently fixated in a stable, but distally displaced, location. The degree of deviation is notable in this case, however, because the volumetric bone fill achieved (81.4%) was the lowest of all cases not experiencing soft tissue dehiscence during healing. While other cases without dehiscence achieved close to 100% volumetric bone fill, the lower percentage gain in this case may be due in part to a consequence of this positioning discrepancy.

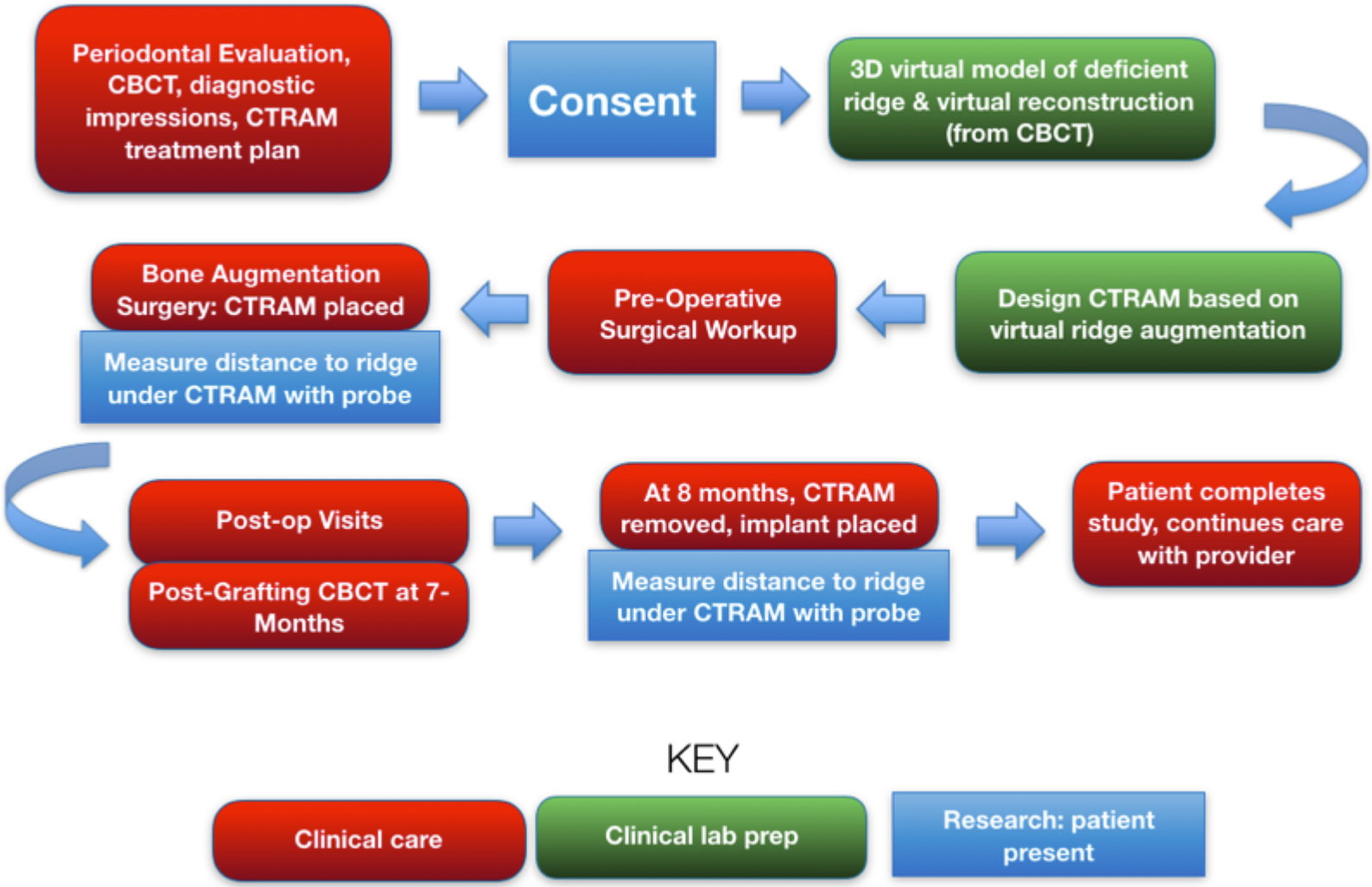
In clinical practice, CBCT scans are often obtained to assess bone gain after GBR procedures to assess results and plan for dental implant placement. If a ridge augmentation technique is able to predictably and repeatedly regenerate close to 100% of

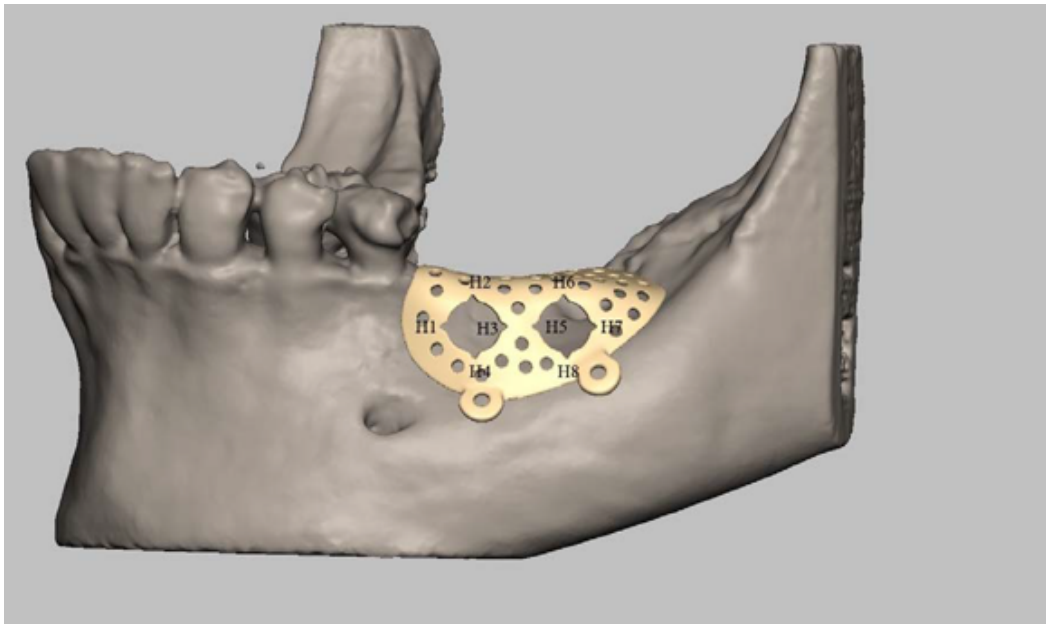
the intended volume, and the location of this gain can be controlled by the clinician, it may be justifiable to forego this post-augmentation scan. While CBCT imaging does impart less radiation on patients than medical-grade CT scans (White and Pharoah 2009) and provides the greatest diagnostic yield for cross-sectional imaging with an acceptable radiation dose risk (Tyndall 2012), ionizing radiation in any form does pose some degree of risk to patients. In the present study, the finding that sites which healed uneventfully with no soft tissue dehiscence yielded a mean bone fill of 104.6% suggests that the CTRAM technique fits the criteria of a predictable method for ridge augmentation that also gives the clinician control over the precise location of the augmentation and thus a second CBCT scan (taken prior to re-entry surgery and implant placement) may not be necessary when the healing after CTRAM placement is uneventful.

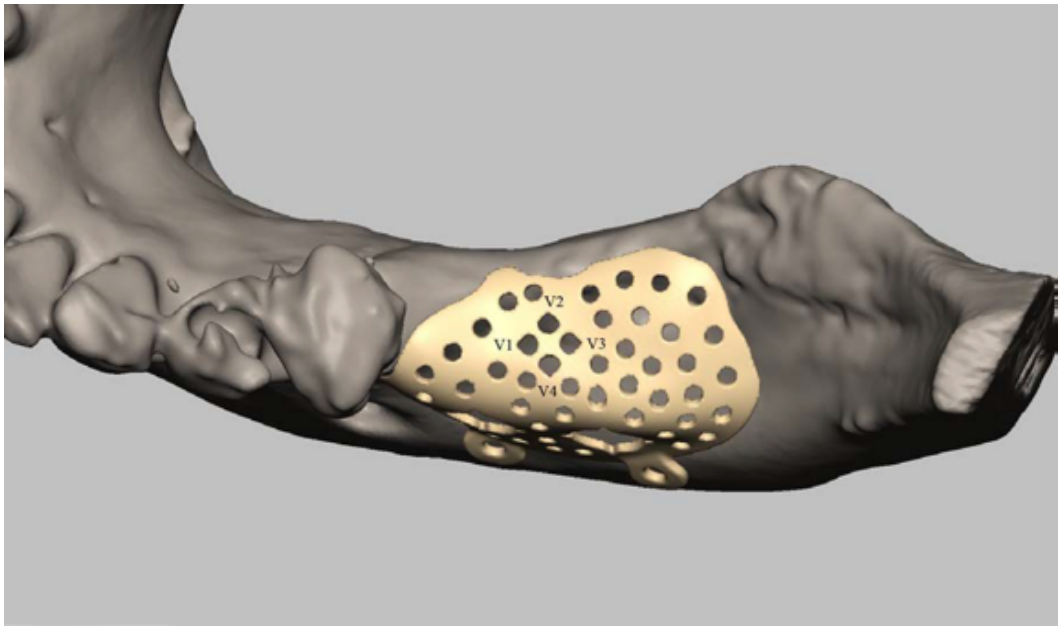
CHAPTER IV: CONCLUSION

Hard tissue ridge augmentation utilizing CTRAM and FDBA results in predictable gains in alveolar ridge dimensions and represents a technique with multiple practical advantages over alternative techniques. In cases where soft tissue closure is maintained, bone fill approximates the entire volume encompassed by the CTRAM, which indicates that a second CBCT scan prior to re-entry may not be necessary. Further longitudinal studies with larger patient populations are necessary to validate these findings.

APPENDIX A: CTRAM PROSPECTIVE STUDY FLOW CHART


Periodontal Evaluation, CBCT, diagnostic impressions, CTRAM treatment plan
Consent
3D virtual model of deficient ridge & virtual reconstruction (from CBCT)
Design CTRAM based on virtual ridge augmentation
Pre-Operative Surgical Workup
Bone Augmentation Surgery: CTRAM placed
Measure distance to ridge under CTRAM with probe
Post-op Visits
Post-Grafting CBCT at 7-Months
At 8 months, CTRAM removed, implant placed
Measure distance to ridge under CTRAM with probe
Patient completes study, continues care with provider
KEY
Clinical care
Clinical lab prep
Research: patient present





REFERENCES

Albrektsson T, Zarb G, Worthington P, Eriksson AR. The Long-Term Efficacy of Currently Used Dental Implants: A Review and Proposed Criteria of Success. Int J Oral Maxillofac Implants 1986; 1(1):11-25.

American Academy of Periodontology Glossary of Periodontal Terms, 4th Edition, 2001, Chicago, Illinois 60611-2690

American Academy of Periodontology Position Paper. Peri-Implant Mucositis and Peri-Implantitis: A Current Understanding of Their Diagnoses and Clinical Implications. J Periodontol 2013; 84(4):436-443.

Buser D, Dula K, Belser U, Hirt H, Berthold H. Localized Ridge Augmentation Using Guided Bone Regeneration. I. Surgical Procedure in the Maxilla. Int J Periodont Rest Dent 1993; 13:29-45.

Cammack GV, Nevins M, Clem DS, Hatch JP, Mellonig JT. Histologic Evaluation of Mineralized and Demineralized Freeze-Dried Bone Allograft for Ridge and Sinus Augmentations. Int J Periodont Rest Dent 2005; 25:231-237.

Ciocca L, Fantini M, De Crescenzio F, Corinaldesi G, Scotti R. Direct Metal Laser Sintering (DMLS) of a Customized Titanium Mesh for Prosthetically Guided Bone Regeneration of Atrophic Maxillary Arches. Med Biol Eng Comput 2011; 49:1347-1352.

Connors CA, Liacouras PC, Grant GT. Custom Titanium Ridge Augmentation Matrix (CTRAM): A Case Report. Int J Periodontics Restorative Dent. 2016 Sep-Oct;36(5):707-14.

Gundeslioglu OA. Exposed Titanium Mesh and Dura Persisting for 8 Years After Cranioplasty. J Craniofac Surg 2013; 24(2):655-656.

Her S, Taeheon K, Fien M. Titanium Mesh as an Alternative to a Membrane for Ridge Augmentation. J Oral and Maxillofac Surg 2012; 70:803-810.

Hurley LA, Stinchfield FE, et al. The role of soft tissues in osteogenesis. An experimental study of canine spine fusions. J Bone Joint Surg Am 1959;41A: 1243-54.

Jensen OT, Lehman H, Ringeman JL, Casap N. Fabrication of Printed Titanium Shells for Containment of BMP-2 Composite Graft Materials for Alveolar Bone Reconstruction. J Oral Maxillofac Implants 2014; 29e103-e105.

Joffe J, Harris M, Kahugu F, Nicoll S, Linney A, Richards R. A Prospective Study of Computer-Aided Design and Manufacture of Titanium Plate for Cranioplasty and its Clinical Outcome. Br J Neurosurg 1999; 13(6):576-580.

Keith JD Jr, Petrungaro P, Leonetti JA, Elwell CW, Zeren KJ, Caputo C, Nikitakis NG, Schöpf C, Warner MM. Clinical and histologic evaluation of a mineralized block allograft: results from the developmental period (2001-2004). Int J Periodontics Restorative Dent 2006; Aug:26(4):321-7.

Louis P, Gutta R, Said-Al-Naief N, Bartolucci AA. Reconstruction of the Maxilla and Mandible with Particulate Bone Graft and Titanium Mesh for Implant Placement. J Oral Maxillofac Surg 2008; 66:235-245.

Lyford RH, Mills MP, Knapp CL, Scheyer ET, Mellonig JT. Clinical evaluation of freeze-dried block allografts for alveolar ridge augmentation: a case series. Int J Periodontics Restorative Dent 2003; Oct;23(5):417-25.

Machtei EE. The effect of membrane exposure on the outcome of regenerative procedures in humans: a meta-analysis. J Periodontol. 2001 Apr;72(4):512-6.

McAllister BS, Haghighat K. Bone Augmentation Techniques. J Periodontol 2007; 78(3): 377-396.

Misch C. Comparison of Intraoral Donor Sites for Onlay Grafting Prior to Implant Placement. Int J Oral Maxillofac Implants 1997; 12:767-776.

Nevins M, Mellonig JT, Clem DS, Reiser GM, Buser DA. Implants in Regenerated Bone: Long-Term Survival. Int J Periodont Rest Dent 1998; 18:35-45.

Pieri F, Corinaldesi G, Fini M, Aldini NN, Giardino R, Marchetti C. Alveolar Ridge Augmentation with Titanium Mesh and a Combination of Autogenous Bone and Anorganic Bovine Bone: A 2-Year Prospective Study. J Periodont 2008; 79:2093-2103.

Ricci L, Perrotti V, Ravera L, Scarano A, Piattelli A, Iezzi G. Rehabilitation of Deficient Alveolar Ridges Using Titanium Grids Before and Simultaneously with Implant Placement: A Systematic Review. J Periodontol 2013; 84:1234-1242.

Schropp L, Wenzel A, Kostopoulos L, Karring T. Bone Healing and Soft Tissue Contour Changes Following Single-Tooth Extraction: A Clinical and Radiographic 12-Month Prospective Study. Int J Periodontics Restorative Dent 2003; 23:313-323.

Sumi Y, Miyaishi O, Tohnai I, Ueda M. Alveolar Ridge Augmentation with Titanium Mesh and Autogenous Bone. Oral Surg Oral Med Oral Pathol Oral Radio Endod 2000; 89:268-70.

Sumida T, Otawa N, Kamata YU, Kamakura S, Mtsushita T, Kitagaki H, Mori S, Sasaki

K, Fujibayashi S, Takemoto M and others. Custom-made titanium devices as membranes for bone augmentation in implant treatment: Clinical application and the comparison with conventional titanium mesh. J Craniomaxillofac Surg 2015;43(10):2183-8.

Tyndall DA, Price JB, Tetradis S, Ganz SD, Hildebolt C, Scarfe WC. Position statement of the American Academy of Oral and Maxillofacial Radiology on Selection Criteria for the Use of Radiology in Dental Implantology with Emphasis on Cone Beam Computed Tomography. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:817-826.

von Arx T, Kurt B. Implant Placement and Simultaneous Peri-Implant Bone Grafting Using a Micro Titanium Mesh for Graft Stabilization. Int J Periodont Rest Dent 1998; 18:117-127.

Wallace SS, Froum SJ, Tarnow DP. Histologic evaluation of a sinus elevation procedure: a clinical report. Int J Periodont Rest Dent 1996; Feb:16(1):46-51.
White SC and Pharoah MJ. Oral Radiology: Principles and Interpretation. 7th Edition. 2009.