PROSPECTIVE, COMPARATIVE VOLUMETRIC ASSESSMENT OF ALVEOLAR RIDGE PRESERVATION UTILIZING DIFFERENT BONE GRAFTING MATERIALS

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A thesis submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfilment of the requirements for the degree of Master of Science in Periodontology in the School of Dentistry.

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ABSTRACT

David Paul Semeniuk: Prospective, comparative volumetric assessment of alveolar ridge preservation utilizing different bone grafting materials
(Under the direction of Jonathan Reside)

Objectives: Characterize dimensional changes of the alveolus and soft tissues 3 months following post extraction ridge preservation with different grafting materials.

Methods: 80 patients were recruited. Post-extraction sockets were randomly treated with Allograft, Alloplast, or Xenograft bone graft with membrane coverage, or ungrafted control with membrane alone. CBCT imaging and impressions were taken at baseline and 3 months post extraction. Dimensional changes were evaluated using 3D Slicer. Implant planning using coDiagnostiX™ was used to evaluate the need for additional bone augmentation.

Results: 12 patients provided pilot data. No differences in volumetric or linear dimensional changes were seen between treatment groups, but trend for improved hard and sot tissue maintenance were suggested compared to the control group. Buccal plate thickness was inversely related to bone loss when not grafted. Ideal implant positioning in treatment groups is achieved, with the control group often requiring further bone grafting.

Conclusions: Ridge preservation procedures may reduce the amount of bone loss and reduce the need for additional bone grafting prior to implant surgery.

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LIST OF ABBREVIATIONS

.nrrd – nearly raw raster data file

.stl – stereolithography file

.vtk – visualization tool kit file

ACS – acellular collagen sponge

ADM – acellular dermal matrix

Ag – allograft

ANOVA – analysis of variance

Ap – alloplast

ASA – American society of anesthesiologists

BMP – bone morphogenetic protein

C - control

CAD CAM – computer aided design computer aided milling

CBCT – cone beam computed tomography

CT – computed tomography

CT – connective tissue

DBBM – deproteinized bovine bone matrix

DFDBA – demineralized freeze dried bone allograft

dPTFE – dense polytetrafluoroethylene

EPR – electronic patient record

ePTFE – expanded polytetrafluoroethylene

FDBA – freeze dried bone allograft

FGF – fibroblast growth factor

FGG – free gingival graft

GBR – guided bone regeneration

GTR – guided tissue regeneration

HA – hyaluronic acid

HA – hydroxyapatite

HbA1c – glycated hemoglobin

HFA – high frequency acceleration

HIPAA - Health Insurance Portability and Accountability Act

ID – identification

MTF – musculoskeletal transplant foundation

NIH – national institute of health

PDL – periodontal ligament

PI – primary investigator

PMN – polymorphonuclear leukocytes

RCT – randomized controlled clinical trial

REDCap – Research Electronic Data Capture

rhBMP-2 – recombinant human bone morphogenetic protein 2

ROI – region of interest

RR – relative risk

SD – standard deviation

TGF-β1 – transforming growth factor β1

TNF-α - tissue necrosis factor α

UNC – University of North Carolina

VEGF – vascular endothelial growth factor

X – xenograft

β-TCP - β tricalcium phosphate

LITERATURE REVIEW

The alveolar process houses the dentition, and begins to develop in conjunction with the eruption of the teeth. Its development and maintenance is dependent on this eruptive process (1) and the continued presence of the teeth. This can be clearly seen in cases of oligodontia in children, where the alveolar process fails to develop due to the absence of teeth (genetic failure to develop) (2). In these patients, the edentulous ridge is usually knife edged, with minimal thickness and height, mimicking the clinical appearance normally seen in adult patients who have been missing teeth for many years.

These examples highlight that bone is a dynamic organ. It responds to pressure and tension forces by producing bone resorption and apposition respectively, and it is a combination/interplay of these adsorption and absorption processes that allow the bone to adapt over time. When a tooth is removed, these stimulatory/regulatory stimuli cease to exist, creating an imbalance in the adsorptive/absorptive processes, with a net effect of bone loss over time (disuse atrophy).

In an ever-changing industry, along with increasing patient expectations, the demand for functional and cosmetic implant dentistry to replace missing teeth is

increasing. Our aim in both surgical and prosthetic implant dentistry is to try and mimic the natural dentition to best produce a functionally and esthetically ideal result for our patients. Consequently, the common dental phrase ‘the bone sets the tone, but the tissue is the issue’ is becoming more and more relevant. It highlights the important foundations set by the bony support base to the overlying soft tissue. With bone loss comes potential soft tissue loss, and possible compromises of the final cosmetic outcome. Preservation of the existing hard and soft tissue architecture following tooth extraction could allow us a greater chance at providing an ideal functional and esthetic final outcome for our patients.

Socket or ridge preservation is one such technique that can aid in maintenance of the pre-extraction dimensions of the alveolus and soft tissues. In this literature review, the effects of extraction on the alveolar ridge will be discussed, along with current techniques used to preserve the dimensions of the alveolar process and their clinical outcomes.

Extraction Socket Healing

Histological Healing of an Extraction Site

Post-extraction socket healing follows a well defined series of phases as seen in other forms or wound healing: (a) coagulation/hemostasis, (b) granulationtissue/matrix formation, (c) tissue repair or regeneration and (d) tissue maturation/remodelling (3-5). When a tooth is removed, the empty socket that remains is lined by a cortical bone-like layer called the bundle bone (seen radiographically as the lamina dura). This socket wall is covered in torn periodontal ligament fibers laterally, and surrounded by a band of gingival epithelium coronally (6). Immediately

following extraction, the socket fills with blood, forming a coagulum which seals the socket from the oral cavity (Figure 1a). This coagulum initially consists of erythrocytes, leukocytes and torn pieces of the periodontal ligament, which are embedded in a fibrin network. It provides the basis for a provisional matrix to facilitate epithelial and fibroblast cell migration and acts as a reservoir for growth factors released into the wound site from the surrounding cells.

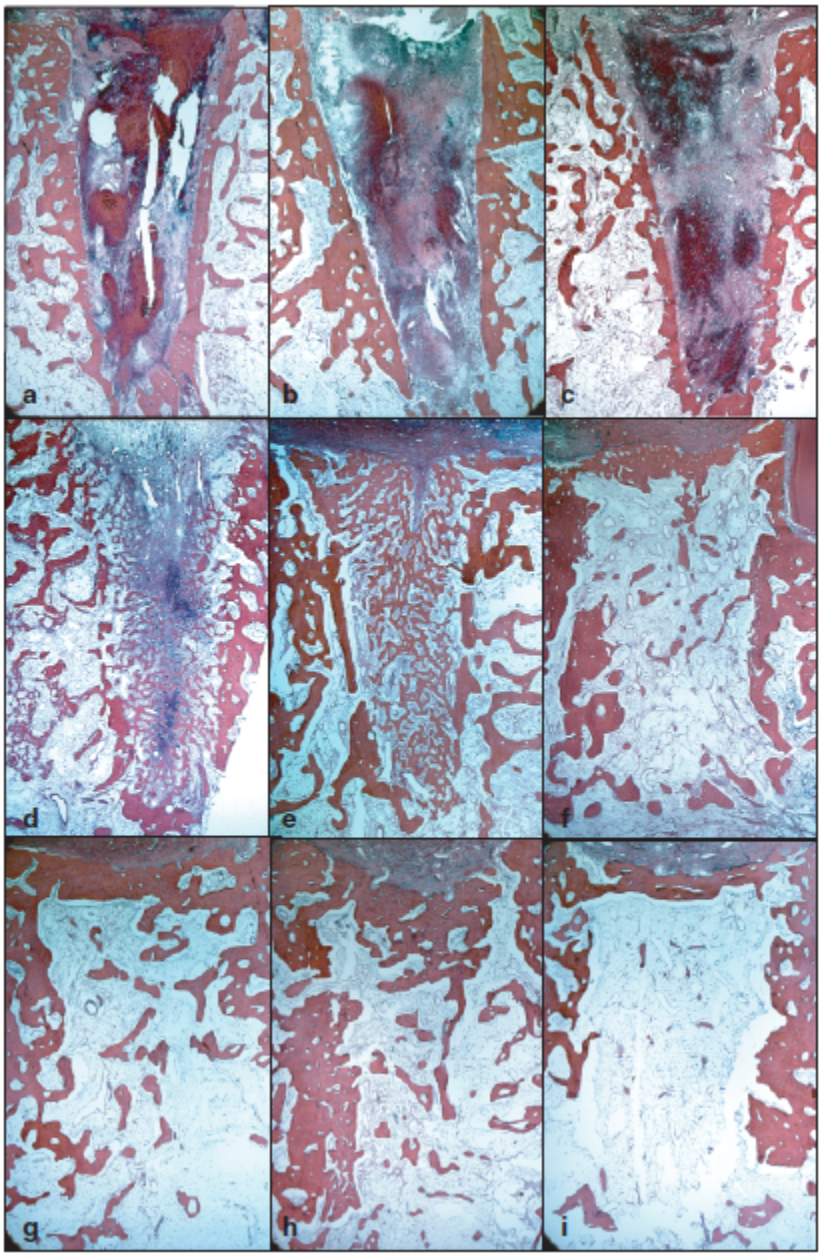


Figure 1: Mesio-distal sections illustrating histological wound healing events following tooth extraction in a dog model: (a) 1 day, (b) 3 day, (c) 7 day, (d) 14 day, (e) 30 day, (f) 60 day, (g) 90 day, (h) 120 day, (i) 180 day. H & E staining; original magnification x16. Reproduced with permission from John Wiley and Sons (3)

The inflammatory process begins within the first few minutes to hours following removal of the tooth. The first cell to migrate into the socket is the neutrophil (Polymorphonuclear leukocytes). Their main role is in phagocytosis, debriding the socket of any bacteria or debris. Macrophage numbers then begin to increase. Once in the wound they differentiate initially into the M1 pro-inflammatory and, later the M2 anti-inflammatory phenotypes. The M1 macrophages are responsible for producing an array of pro-inflammatory cytokines to further drive the inflammatory process in the initial stages, while a switch to the M2 phenotype allows production of anti-inflammatory chemokines (lipoxins, resolvins, protectins) and other growth factors (VEGF, FGF, TGF-β1) which push the wound healing cascade towards a regenerative or reparative phase.

Next, the center and then the peripheral areas of the provisional matrix begin to undergo coagulative necrosis through a centripetal process (7), and fibroblasts and capillaries begin to proliferate into the area, rapidly depositing vascular channels and collagen, converting the coagulum into granulation tissue. The granulation tissue is comprised of an organized collagen plug (beginning 7-10 days following injury) which can be seen in Figure 1b (8), which provides a scaffold for further connective tissue formation.

Peripheral epithelial cells dissolve their hemidesmosomal and desmosomal connections, allowing epithelial migration to begin 24 hours following extraction. The epithelium migrates under the fibrin clot and above the developing immature connective tissue, until it contacts the epithelium from the other side. This process typically results in complete soft tissue closure 24 -35 days post-extraction (8).

Myofibroblasts begin to differentiate around day 7 from local fibroblasts and other progenitor cells, aiding in wound closure through wound contraction produced by their actin-rich cytoskeleton.

Towards the end of this first week, osteoclasts begin to line up within the marrow space of the bundle bone (2) ready to begin the hard tissue remodeling. The bundle bone forming the periphery of the socket no longer serves a function and is removed through osteoclastic resorption (Figure 1d). The necrotic bone is sloughed off into the extraction socket (9). At 2 weeks, osteoprogenitor cells, preosteoblasts and osteoblasts are seen in the surrounding trabeculae, and the periodontal ligament is displaced to the center of the extraction socket (10).

At day 20, the granulation tissue goes through a maturation phase and begins to be replaced with collagen, producing a matrix for new bone formation (7). Bone deposition and mineralization begins at the base and periphery of the socket (centripetal bone formation), and tends to show a decrease in mineralization rate from the lingual to the buccal regions (7). As the bone begins to fill the socket, the epithelium moves coronally, becoming level with the adjacent gingiva (Figure 1e).

During the initial bone formation, fibroblasts and osteoblasts produce a callus, a fibrous haphazard collagenous matrix that fills the socket. This callus then begins to ossify, forming woven bone (Figure 1f, g). Finger-like projections of woven bone are first laid down around blood vessels, which extend into and infiltrate the granulation tissue. Granulation tissue is progressively replaced by the collagenous matrix and woven bone, with woven bone occupying 35% of the socket volume at the 6-8 week

time period. Over time, this woven bone is remodelled by osteoclasts, allowing the osteoblasts to form trabecular bone, which is oriented to more ideally resist the functional forces placed on the bone (11).

A layer of woven bone can be seen bridging the socket after 30 days of healing (5). Around the same time, collagen fibers from the new overlying mucosa become inserted into the new cortical bone, establishing a periosteum like structure (3, 12). Bone organization and architecture is often not complete by 24 weeks following extraction (7), and continues to go through a remodeling process (Figure 1h, i). Remodeling of the cortical bone seal can still be detected 90 days post extraction (corticalization), whereas the middle and apical regions appear to be more mature in their remodeling process (5). A high amount of bone marrow can be seen at 180 days after extraction (5).

Clinical Healing of an Extraction Site

Following tooth extraction, the alveolar process begins to resorb both in the horizontal and vertical dimension. The local anatomy of the extraction socket particularly the buccal plate thickness, can affect the volume of resorption seen. Some of these factors will be discussed.

The thickness of the palatal or lingual bone plate seems to influence the resorption and remodeling process. The buccal plate of both the maxilla and mandible is frequently thinner (13), contains a higher relative percentage of bundle bone, and is more fragile than the palatal or lingual plate(4). This can allow for more pronounced resorption following tooth extraction in comparison to the palatal aspect (4).

The bone and overlying soft tissues gain their blood supply from the periodontal ligament, periosteum and the bone marrow. The buccal plate is most likely thin (<1mm) (14) with minimal interstitial cancellous bone marrow containing bone, and is primarily composed of dense cortical bone. Nutrient supply may primarily originate from the overlying gingiva, periosteum, and the PDL. Following extraction, the PDL is effectively removed, and along with it one of two good sources of blood supply to the buccal plate. The exposed bone then subsequently undergoes necrosis. The thicker palatal bone contains more bone marrow/cancellous bone, which can provide a continual blood supply to the region following extraction, despite the removal of the blood supply from the PDL. Superficial necrosis of bone facing the extraction socket still occurs, however in this instance the area of necrosis may become more contained, with minimal resorption of bone due to greater vascular supply.

The increased rate of resorption of the buccal plate shifts the edentulous ridge to a more palatal/lingual position (15), with the extent of remodeling influenced by tooth position. Pietrokovski and Massler demonstrated that the amount of resorption appears to be greater in the molar region than in the incisor and premolar regions in both the maxilla and mandible when comparing the ridge dimensions of a previous extraction site to a contralateral site containing a tooth(16). Contrary to this study, Schropp *et al*. conducted a prospective study evaluating resorptive changes, and could not find any major difference in amount of resorption seen in different regions of the jaws (17). The differences may be related to study design (cross sectional vs prospective) along with differences in extraction technique.

On average, Schropp *et al*. identified a reduction of approximately 50% of ridge width, of which two thirds occurred during the first 3 months of healing (17) but continued for up to 6 months. From 6 to 12 months, this new bone shows some remodeling, however the size of any further loss remained comparatively unchanged from the 3 to 12-month period (17). Radiographically, remodeling of the lamina dura and the septum (multi-rooted teeth), was more pronounced in the period from 6 to 12 months after tooth extraction (17). The amount of horizontal loss reached a mean reduction of 3.8mm, along with a mean vertical reduction of 1.24mm (18). The loss in width is greater than the loss in height (19).

Schropp also observed that the new bone that formed into the extraction socket never reached the levels of the remaining bone situated at the tooth surfaces distal and mesial to the extraction site. The alveolar ridge morphology becomes curved between the mesial and distal boundaries of the previous socket, with the lowest point situated 1.2mm apical to these mesial and distal points (17). This observation suggests that the bone level at the extraction site dictates the level to which the bone crest heals to, rather than the bone level of the adjacent teeth.

Araujo *et al*. also assessed the dimensional changes following tooth extraction in a dog model through histology and clinical measurements (4). They indicated that the coronal portion of the bone walls was solely made up of bundle bone, with $\geq$1mm of the height of the buccal plate and <0.5mm of the lingual plate being comprised of bundle bone. They observed that at 1 week the buccal bone crest was located on average 0.3 $\pm$ 0.2mm coronal to the lingual crest, however at 2, 4, and 8 weeks of healing it was located consistently apical to the lingual crest at 0.3 $\pm$ 0.1mm, 0.9 $\pm$

0.3mm and 1.9 ± 0.2mm respectively. They demonstrated that following extraction, the amount of vertical bone loss was more pronounced on the buccal than the lingual plate, producing a relative height reduction of 2.2 ± 0.2mm (Figure 2). They concluded that resorption of the buccal/lingual walls of the extraction site occurs in two overlapping phases. Phase 1 involves the bundle bone and its loss of function following tooth removal. Resorption of the bundle bone occurs and replacement with woven bone. They indicated that as the buccal bone crest is made almost solely of bundle bone, the remodeling would be more substantial than the lingual bone plate, resulting in more vertical bone reduction of the buccal crest. The second phase involved the resorption of the bony walls from the external surface. It should be noted however that the extraction technique in this study involved flap elevation, where separation of the periosteum from the bone can cause vascular damage and acute inflammation, causing further resorption and bone loss. The lingual plate was also used as a reference point for measurement in this study, and only the difference in buccal vs lingual bone height were assessed, with potential underestimation on the total amount of bone height loss.

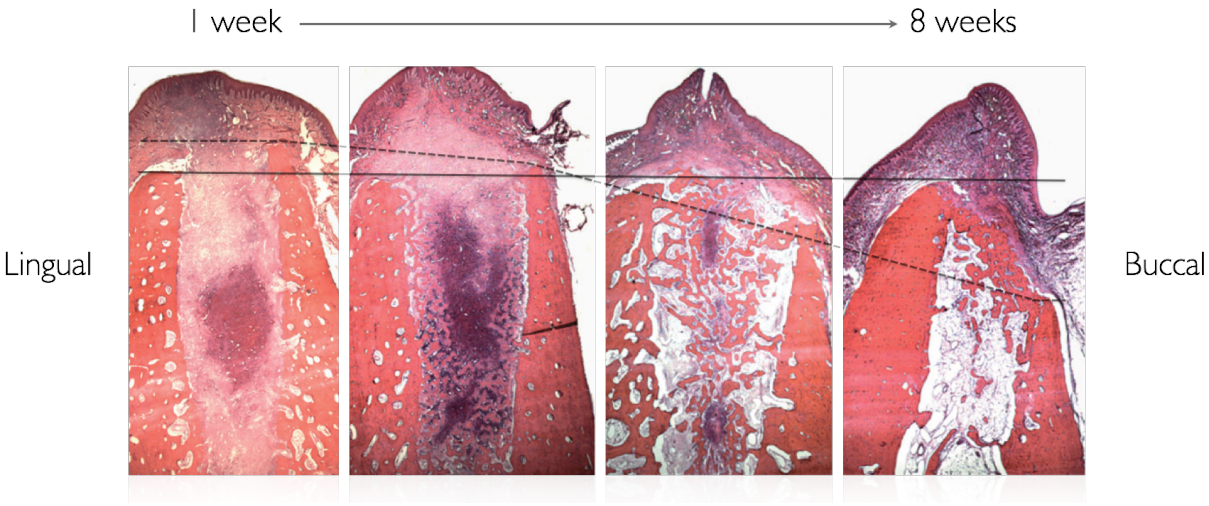


Figure 2: Change in buccal plate height (dashed line) compared to the lingual plate (solid line), following tooth extraction in a dog model. Adapted by J. Reside from Araujo *et al* 2005. Reproduced with permission from John Wiley and Sons (4).

The influence of periosteal flap elevation on post-extraction ridge alterations was further quantified in a further study by Araujo *et al*. They compared the relative alteration of the surface area as a percentage, in the coronal, middle and apical thirds of the edentulous ridge. Overall in the flapless group -17 ± 16% was lost compared to -14± 6% in the flap group, with no significant difference present. Thirty-five percent of bone was lost in the coronal portion in both groups, while 9% and 14%, and 6% and 5% were lost in the flapless and flap sites in the middle and apical portions respectively. The differences, again, were not statistically significant (20). These results, however, differ from other studies showing increased bone loss during the post-extraction healing period when a periosteal flap is raised (21, 22).

Loss of bone volume in a monkey model was assessed by Omran *et al*. In intact sockets following a 6 and 12-week healing period, a mean crestal volumetric bone

loss of 45% and 69%, respectively, was identified in a 0-3mm zone from the original height of the crest. At a position 6mm from the ridge crest a mean loss of 30% and 45% at 6 and 12-weeks respectively, occured. When a buccal dehiscence was present, a more pronounced loss of bone in the realm of 60 and 86% at 6 and 12 weeks in the 0-3mm zone was found if the socket was left ungrafted (23).

Schropp *et al*. studied the changes in the soft tissue profile following atraumatic extraction (17). Immediately following extraction, the height of soft tissue contour on the buccal aspect of the ridge was located 1.3mm apical to the height of soft tissue contour on the palatal or lingual aspect. Following 12 months of healing, the difference was reduced to 0.2mm. This was due to tissue gain at the extraction site of 0.3mm, along with a tissue loss of 0.8mm on the palatal or lingual side. Only slight changes (less than 1mm) in soft tissue height took place in both jaws during the 12 months of healing. This differs in what was found in other studies, where the reported height reduction was between 2.0mm to 4.5mm (19, 24).

Tan *et al*. completed a systematic review evaluating the dimensional ridge alterations following extraction in humans, further reiterating the data presented above (18). Following the evaluation of 20 different studies meeting their inclusion criteria, a mean horizontal reduction of 3.79mm and a vertical height reduction of 1.24mm on the buccal, 0.84mm on the mesial, and 0.80mm on the distal was seen. Reduction in ridge width amounted to 32% at 3 months, and up to 63% at 6-7 months' post extraction, and was substantially greater than that seen in the vertical dimension. Soft tissue changes showed a 0.4-0.5mm gain of thickness at 6 months on the buccal and

lingual aspects. Along similar lines, Ten Heggeler showed a reduction in ridge width ranging from 2.6mm and 4.6mm and 0.4mm and 3.9mm in height (25).

Factors Affecting Wound Healing of Extraction Sockets

Variations in the amount of bone resorption is seen, and can be dependent on various patient and procedure related factors. Factors such as patient age at time of extraction, the number (26) and type of tooth removed, and the region of the mouth have been identified as affecting healing post-extraction socket healing outcomes. Other factors such as loss of socket walls or height due to previous disease or trauma before or during the extraction procedure, extraction technique, flap, and smoking, can impact on bone loss following extraction (27). Control of these factors may promote a more ideal healing outcome in preparation for future dental implant placement. Some of these factors will be discussed.

Flap elevation with removal of the periosteum from the bone causes additional trauma to the underlying bone. Wood *et al*. in their classical study showed that flap elevation can produce an additional 0.6mm of bone resorption (28). This is echoed in a more recent publication from Fickl *et al*. where elevation of a flap showed a statistically significant higher resorption rate of 0.7mm on the buccal aspect after 4 months of healing (22). Contrary to this, Araujo and Lindhe reported similar post extraction ridge dimension changes in the flap and flapless group at a 6 month time period (20). They suggested that any initial acceleratory effects on bone resorption induced by flap elevation may be insignificant following 6 months of healing. Overall, flap elevation seems to have a negative impact on healing.

Buccal plate thickness has been associated negatively with bone loss following extraction (29). A thinner buccal plate is made up of considerably more bundle bone, with minimal interposing supportive bone marrow. Once the tooth is removed and the remodeling process starts, a thin buccal plate can experience complete resorption, creating a three-wall socket defect. This defect configuration is not as supportive and conducive to complete regeneration as a four-wall defect, providing inadequate space maintenance, allowing the collapse of the soft tissue into the wound space, and reeuced new bone formation. Support of this soft tissue in its original position would promote maximum new bone formation.

Cardaropoli *et al*. evaluated the relationship between the buccal bone plate thickness and the healing outcome following extraction (29). They found that the baseline thickness of the buccal bone plate and the amount of alveolar bone loss had a strong negative correlation (r=-0.752). However, when a graft was placed in the extraction socket, this correlation was absent (r=-0.05). This highlights the importance of defect morphology and space maintenance of a wound, promoting a more adequate environment for healing. This, however, is disputed in a more recent publication, where a weak correlation was found between the initial buccal plate thickness and ridge width reduction. It should be noted however that the teeth assessed were in the molar region, which tend to present with a thicker buccal plate than anterior teeth (30).

Regional variances in bone thickness and quality, along with tooth type, can affect the amount of resorption seen. More bone loss has been reported in the posterior maxilla, presumably due to the lower bone density and a more traumatic extraction (multi-rooted), while extractions in the mandibular premolar region show

less reduction in ridge width (31). This has been disputed in other studies, where resorptive changes in the mandible were found to be four times greater than what was seen in the maxilla (32). These results, however, came from completely edentulous patients who were wearing dentures, and as such the resorptive rates may be greater due to time and effects of an overlying denture.

Ridge width reduction tends to be greater following removal of molar teeth rather than premolar teeth (17). With wider sockets, more time is needed to fill in the defect with new bone. In this situation, the balance between the resorption and apposition phases of healing may be tipped to favor resorption. Even more so, the amount of bone loss seen in the anterior maxilla can be larger, primarily related to the usually thinner buccal plates (14) and considerably higher percentage of bundle bone in the buccal plate than in the premolar and molar regions (33). With esthetics being of primary concern in the anterior region, greater bone loss can lead to a reduction in the final restorative esthetic outcome.

Smoking is well known to alter the bodies healing potential, and it is no surprise that it can negatively affect the amount of dimensional ridge reduction post tooth extraction. Saldhana and colleagues evaluated the radiographic bone changes following tooth extraction in smokers and non-smokers over a 6-month time period (34). It was demonstrated that smokers experienced more significant horizontal alveolar ridge resorption (14 vs 6 mm), 0.5mm greater reduction in vertical bone height, along with a reduced radiographic bone density in the center of the post extraction socket. These negative healing outcomes have been attributed to the effects of nicotine on the body:

- Bone mass (affecting the initial bone density in smokers)
- Inhibition of gingival fibroblast proliferation
- Increased collagenase activity
- Inhibition of fibroblast synthesis of fibronectin and type I collagen (Extracellular matrix formation)
- Inhibition of angiogenesis and vasoconstriction, which may limit the infiltration of important growth factors into the area.

Flap elevation, buccal plate thickness, tooth type, and smoking status are just a few of the many factors which could possibly produce adverse healing outcomes. Identification and control of pre- and post-operative factors could allow for more ideal extraction site healing.

Ridge Preservation

Rationale

Soft tissue healing progresses much faster than bone formation, and with the inevitable resorption of the buccal plate, the soft tissue collapses into the socket space (27), reducing the potential size of the blood clot and provisional matrix, reducing the volume of new bone formation. The ridge width at time of extraction is on average 12mm (8.6-16.5mm), however after 12 months it can be reduced to just 5.9mm (2.7-12.2mm). Placement of a standard body implant requires a minimum of 6-7mm in ridge width, and so implant placement can become more complicated.

Ridge width posteriorly naturally is greater and as such any horizontal resorption may still allow for sufficient ridge dimension to place a dental implant. Anteriorly, the ridge is naturally narrower and the buccal plate is often <1.5 to 2mm thick (35), as such normal physiologic resorption in this area can be more dramatic,

making placement of an implant in a favorable prosthetic and esthetic position difficult. To correct this an additional grafting procedure (35) or sinus procedure, along with the associated discomfort and expenses, would be required.

Utilization of a grafting material with or without a membrane (alveolar ridge preservation) provides additional support for blood clot stabilization and space maintenance, reducing bone loss from 69% to 25% or less (23). Alveolar ridge preservation aims to reduce bone loss, provide soft tissue support, and reduce the need for additional bone (1) and sinus augmentation procedures(36); ultimately providing for easier implant placement and a higher potential of achieving an esthetic restorative outcome.

Indications for ridge preservation procedures include (35):

- Sites with buccal plate thickness less than 1.5-2mm (most anterior and esthetic zones).
- Sites with damage or loss of one or more socket walls.
- Sites where maintaining bone volume is crucial to minimize the risk to adjacent anatomical structures
- Patients with high esthetic demands such as a high lip line and thin biotype, which are more prone to tissue loss.
- Patients where many teeth are being extracted and preservation of bone is important for further restoration.

There have been many different ridge preservation techniques proposed, with the most common being a placement of a grafting material into the socket, and covering with a membrane and coronally advanced flap (37). The procedure typically

involves atraumatic extraction of the tooth, curettage of the socket, and placement of a graft material with or without an overlying collagen membrane or plug or primary closure.

Histologic Healing following ridge preservation

Insertion of a graft material into an extraction socket initiates a host response, resulting in increased inflammation, macrophage and osteoclastic activity, which has been suggested to cause a delay in socket healing (38, 39). The persistence of the material has been suggested as a cause for this, reducing space available for revascularization, and bone apposition, and depending on the grafting product source, a possible risk of disease transmission (27). Despite this, the success of implants placed in ridge preserved sites has been shown to be no different than in native bone (40).

Histologically, ridge preservation has been shown to produce higher percentages of trabecular bone and total mineralized tissue when compared to spontaneous healing alone (41), however when compared to the use of an autogenous graft, a reduction in mineralized bone volume is seen (31). Conversely, graft particles embedded inside connective tissue (42) has been shown, which could affect bone quality for implant placement (43-46). The histologic healing characteristics of the extraction socket largely depends on the characteristics of the material being used. The most researched grafting material used in ridge preservation is deproteinized bovine bone matrix (DBBM).

DBBM has a low turnover rate (47). Evaluation of sites grafted with DBBM after 3 years *in situ* revealed that the DBBM particles still made up 38% of the tissue

volume, while new bone constituted 26% of the tissue volume, with connective tissue and bone marrow making up 34% (48). This is similar to a study by Lindhe *et al*. who saw 22.6% of tissue volume made up of residual graft particles present after 6 months and 30.8% still present after 9 months (49, 50). Depending on the situation, a high residual particle content may be advantageous in space maintenance, however its persistence may interfere with bone maturation. When DBBM is incorporated into a collagen matrix a faster resorption rate is seen, where only 19% present after 6 months of healing (51), which may offer an improved histologic profile. Despite the high volume of residual graft particles still present in the non collagenated form, the residual particles are not thought to have a significant effect on osseointegration. This was addressed in a recent systematic review, which showed a high percentage of direct contact between bone and implant as well as a lack of graft materials contacting the implant surface, demonstrating that the residual graft particles did not compromise the osseointegration of the implants. (27)

After 5 months of healing, DBBM particles are surrounded by immature woven bone, while sockets which were left to heal spontaneously showed more new mature bone and marrow spaces (52). This suggested that the DBBM particles may slow down the healing process. This is further supported by looking at the local chemokine and enzyme expression profiles during would healing. Alkaline phosphatase, osteopontin, osteocalcin (53) and BMP-2 (52) expression in healing extraction sockets grafted with DBBM has been shown to be reduced, along with osteoblastic proliferation (54) is decreased, while TNF-α is increased (52). This suggests a reduction or delay in the bone formation phase, while prolongation of the resorptive

and inflammatory phase of bone healing. Despite these potential initial upsets, implants placed in DBBM grafted sites do show good osseointegration without an inflammatory reaction.

When comparing DBBM to allografts, one study has shown that grafting with DBBM produces more intimate contact with the new bone, more new bone formation, and less fibrous tissue surrounding the graft particles than an allograft (47). The allograft however can be actively resorbed and incorporated into the new bone, however new bone formation can be irregular and separated, with thick bony trabeculae which are rarely connected (47), suggesting that the quality of formed in DBBM grafted sites may offer greater implant stability. The difference in histological (and clinical) outcomes between DBBM and allografts is related to their resorption rates, and it was suggested that DBBM may provide more adequate volume maintenance when used in defects that are not self-containing, whereas an allograft would be better suited to use in those sockets with intact bony walls (47).

Leblebicioglu *et al.* assessed histologically the effects of FDBA with a collegan membrane on bone formation in posterior mandibular and maxillary extraction sites (55). Histologically they found that the mandibular sites showed more new bone in the coronal portion than in maxillary sites, however when looking at the entire socket, the amount of mature bone, new bone, new cellular bone or immature tissues showed no statistical difference between jaws. They also saw a higher rate of mineralization in the mandibular arch, along with higher angiogenic activity in the mandible than the maxilla, although not significant. They suggested that healing outcomes could be

affected by the position of the site, where clot stability may be greater in mandibular sites.

Guided bone regeneration principles call for the use of an occlusive membrane to prevent the ingrowth of the faster moving epithelium into the regenerating bone, increasing the quality of the newly formed bone. The adjunctive use of a collagen membrane over the grafting material has been shown to result in higher new bone formation and lower connective tissue formation than spontaneous healing alone (41). However, other studies have identified similar amounts of new bone formation to untreated sockets, with more vital bone seen in the untreated sockets (42), possibly due to the space occupying nature of the grafting material during new bone formation.

While histologlically a membrane can produce better quality bone, it can also interfere with the vascularization of the flap, impairing soft tissue. Studies have shown that when a membrane is placed over a grafting material for protection, the mucosa after healing was thinner than it was at baseline (42, 56). Pellegrini completed a split-mouth randomized controlled clinical trial evaluating the effect of a collagen membrane on the overlying soft tissues following a grafting procedure (57). After 5-weeks of healing there was significantly lower tissue vascularization when a membrane was used when compared to no, however these differences were not present after 12 weeks of healing. They also noted that in the membrane group, collagen content and fiber organization was reduced, with a more acute inflammatory reaction indicating an initial delay in soft tissue healing, most likely due to membrane resorption. Despite this, later healing periods showed augmentation of collagen fibers and higher tissue maturation levels than those sites without a membrane, reaching

values comparable to those of the healed no treatment group. They concluded that use of a membrane may initially delay the vascularization of the soft tissue healing and caused a transient inflammatory acute response, however, the membrane did provide a protective role for the coagulum first and the granulation tissue later, accelerating the soft tissue maturation. This acceleration in soft tissue healing may allow for less soft tissue reduction post tooth extraction (42).

When looking at systematic reviews, the histologic advantages and disadvantages of ridge preservation procedures is unclear. In one systematic review (58), it was noted that only two of eight included studies reported a statistically significant higher trabecular bone volume following a ridge preservation procedure (41, 59), when compared to normal socket healing. Likewise, 2 studies reported significantly more connective tissue in the site when no grafting was performed (41, 45), however another study reported more vital bone in the normal socket healing groups (42). A vast difference in histological healing outcomes is seen following a ridge preservation procedures, and depends on the study and grafting material.

Ridge Preservation Materials

Many different materials are available for ridge preservation procedures, from the use of autogenous bone harvested intraorally at time of extraction, donated human source cortical and cancellous bone (allograft), xenografts from bovine, porcine, and equine origins, and synthetically produced grafting products (alloplast). Some of these products and selected studies will be presented.

Autograft

Although autogenous grafts are considered the gold standard, using native bone for space maintenance in an initial resorptive process, can make it a less than ideal grafting material due to the ease in which the activated osteoclasts can resorb it.

Shultz *et al.* compared alveolar ridge width dimensions between sites treated with autogenous bone and a DBBM and porcine collagen grafting material, after 6 months of healing. The autogenous bone group showed a -14.31 $\pm$ 21.41% change compared to -9.45 $\pm$ 10.51% seen in the DBBM and collagen group (31). Araujo and Lindhe completed a similar study, evaluating the use of DBBM and autogenous bone chips in dogs (60). After three months of healing it was found that in the coronal portion of the ridge there was approximately 25% resorption in the autogenous bone group, while in the xenograft group only 3.6% resorption was seen, demonstrating the superior effects of the non-autogenous bone graft. The amount of residual grafting particles in the xenograft group was 24.4%, compared to 1.9% in the autogenous bone group, highlighting the importance of the space maintainability of the DBBM particles compared to autogenous bone. The more rapid resorption of the autogenous graft did not offer adequate space maintenance for a sufficient time to counteract the resorptive phase of extraction site healing.

Allograft

Allografts are composed of human sourced cadaveric bone, and are primarily used in North America. The grafting material essentially come in two forms, a mineralized freeze dried bone allograft (FDBA) and a demineralized freeze dried bone

allograft (DFDBA). The demineralized form is said to be osteoinductive due to the release of the Bone Morphogenetic Proteins (BMP) from the graft material. When the graft is in the mineralized form, the BMP is trapped within the graft material and is therefore not available to stimulate the initial healing processes. This does not make the mineralized form a less than ideal grafting material, as its slower resorption profile may act as a better scaffold and space maintainer throughout the healing process. The longer resorption profile is related to the prolonged osteoclastic phase needed to break down the particles due to the mineral content.

Wood and Mealey compared FDBA with DFDBA (61). The graft was sourced from one donor, a 47-year-old female, and was made available in the mineralized and demineralized form. After 4-5 months of healing they found no difference in ridge height or width reduction between the two graft forms, suggesting that the effects of BMP release on dimensional stability was minimal. They did however find that the DFDBA group showed more vital bone (81.3%) and less residual graft content (18.74%) compared to the FBDA group (50.63% and 49.37%). This could be due to the more rapid resorption rate of the demineralized graft, allowing for more space for new bone ingrowth. The DFDBA used in the study had a lower degree of inductivity which could have affected the outcome, with the osteoinductivity of DFDBA dependent on the age and the sex of the donor (62). With vast variability in osteoinduction and BMP concentration seen in donor bone, use of a synthetically produced biomimetic with a consistent BMP concentration profile may produce more consistent results.

Clinically, Leblebicioglu *et al.* found that after 4.5-month healing period, FDBA prevented height loss, however a 2.5mm loss in ridge width was seen (55). Comparing these outcomes to a similar study using a xenograft, the results were very similar (63).

Xenograft

Various preparations of xenografts from bovine, porcine and equine origin are currently available on the market, and have been evaluated in ridge preservation procedures. These grafting materials (particularly from bovine sources) display large popularity outside of North America, with an extensive amount of research been done on these graft materials.

Nevins *et al*. evaluated the use of DBBM in the anterior maxilla in high risk patients (prominent teeth and thin buccal plate) (64). 19 extraction sites were allocated to the test group which was grafted with the xenograft (Bio-oss), while 17 were allocated to the control group and were allowed to heal spontaneously. CT scans were taken immediately following the extraction procedure and again at 30 – 90 days after the extraction. The height of the ridge at which 6mm of width was first found was recorded (minimum width required for implant placement) as a height reference point. Control sockets lost 5.24 $\pm$ 3.72mm in height, while the sites grafted only lost 2.42 $\pm$ 2.58mm in crestal height. This difference amounted to more than two times the amount of height loss in the non-grafting group compared to the grafted group. Crest height was maintained (showing a loss of less than 20%) in 84% of grafted sites, versus only 29% maintaining crestal height, and more importantly 71% of sites showing loss of more than 20% in height in the control group.

The study did indicate that some sites can heal adequately without grafting, however it was not possible to identify these sites before extraction. It was suggested that due to the possibility of considerable height reduction and its effects on the final esthetic outcome, grafting of the socket to help preserve the ridge dimensions was important to avoid possible complications later on.

Sbordone *et al*. assessed retrospectively the amount of bone volume loss in the premolar and molar region, following a ridge preservation with DBBM and a resorbable barrier membrane. These sites were compared to extraction sites with no graft (65). CT scans acquired preoperatively and 6-months post operatively were used for analysis. The grafting group showed a bone volume loss of $72mm^3$ (9.9%), while the no grafting group showed a bone volume loss of $274mm^3$ (34.8%), a statistically significant difference. They suggested that following grafting, clinicians should expect less than a third of the resorption seen when the site is allowed to heal naturally.

A mixture of 90 % DBBM and 10% porcine collagen is commercially available, and its use in ridge preservation with an overlying bilaminar collagen membrane in molars and premolars was assessed by Cardaropoli. Following a 4-month healing period, the control group lost an additional 3.33mm in width and 1.11mm in height when compared to the treatment group. This difference amounted to an additional 32.92% (7.23±9.24% in test and 40.15±8.29% loss in the control) of bone volume lost when a ridge preservation procedure was not completed (29).

Similarly, Araujo and Lindhe evaluated the use of a DBBM and porcine collagen graft in a dog model (66). Following 6 months of healing, linear dimensional changes were found to be three times larger in those sites not grafted than the sites grafted.

Initial histological analysis showed similar amount of new bone formation in the grafted and control group, however the grafting group showed more residual graft material and less bone marrow initially (66)., however, after 6 months the differences between test and control sites were minimal (39). DBBM and porcine collagen therefore did not seem to negatively impact the histological characteristics, and did not enhance histological bone formation, acting as a scaffold only. The grafting material did allow for significant ridge volume preservation.

Despite these good outcomes, there has been reports that DBBM placed in an extraction site may not show integration in the coronal most aspect of the socket (67). Consequently, when an implant is placed, osseointegration in the coronal aspect of the implant may be compromised, with subsequent formation of a vertical defect (67). The results from this particular study however came from a small number of dogs, and the particles were mixed with a fibrin sealer. The sealer could have interfered with the healing and integration of the graft particles, as has been shown in another study (68).

Barone *et al*. conducted a multicenter randomized clinical trial evaluating the change in ridge volume at molar or premolar sites using a porcine grafting material. A collagenated cortico-cancellous porcine bone graft or cortical porcine bone grafting material covered by a collagen membrane was used (63). Plaster casts from the pre-operative, 1-month and 3-month time period were digitized for the analysis. Following a 3-month healing period, the collagenated porcine grafting group lost significantly less bone volume than the porcine graft with membrane ($244mm^3$ vs $349mm^3$), suggesting that the collagenated form was a more effective grafting material. Linear measurements showed a 1.8 and 2.0mm reduction in height and a 1.8 and 2.5mm

reduction in ridge width in the collagenated porcine bone graft and the porcine bone graft with membrane respectively. This loss in volume was greater than what was seen in a study using DBBM and an overlying collagen membrane, where a mean bone volume loss of 193mm^3 was seen (252.19mm^3 in the non-grafted control group) (69). The latter study evaluated volume loss based on bone changes (CBCT) only, whereas this study utilized soft tissue and bone. The donor source and processing of the porcine and bovine xenograft materials is different, and this could prolong the space maintainability and support of the wound for longer in one material versus the other, producing greater ridge preservation.

The same group evaluated the difference in clinical ridge dimensions with or without placement of a cortico-cancellous porcine graft and collagen membrane, along with histomorphometric analysis following a 7-month healing period (41). Significantly greater horizontal resorption was seen at the non-grafted sites compared to the grafted sites (4.3 and 2.5mm respectively), along with more significant vertical ridge height reduction at the buccal (3.6 and 0.7mm respectively) and lingual (3 and 0.4mm respectively) sites. They highlighted the importance of preserving this vertical height to allow the development of adequate esthetics and placement of a longer implant. Histologic analysis revealed higher amounts of trabecular bone (26 and 36%) and less connective tissue (59 and 37%) in the grafted group than the non-grafted group, suggesting that the increased mineralization seen in the porcine xenograft may be more suitable for implant placement.

The same group compared the clinical outcome following a ridge preservation procedure or not in a human prospective clinical trial (70). A total of 29 premolar and

molar teeth in each of the test and control group were extracted and treated with a cortico-cancellous porcine bone graft and collagen membrane or placing a silk suture alone in the control group to support the blood clot. Following a healing period of 4 months it was found that in the control group vertical bone resorption was1, 2, 1, and 2mm at the mesial, vestibular, distal and lingual sites respectively. The amount of horizontal bone resorption was 3.6mm. When a grafting procedure was completed an average of 0.3, 1.1, 0.85, and 0.9mm of vertical resorption was seen at the mesial, vestibular, distal and lingual sites respectively; along with only 1.6mm of horizontal resorption. This amounted to about half the amount of vertical and horizontal bone resorption.

Thalmair also evaluated the use of porcine grafting materials however with the addition of free gingival grafts (FGG) (71). They found that when a porcine graft was covered with FGG, ridge reduction as measured by change in soft tissue profile, amounted to 0.79 $\pm$ 0.5mm in the buccal lingual direction. A FGG alone produced a reduction of 0.85 $\pm$ 0.6mm, while using the bone graft alone gave an average 1.45 $\pm$ 0.7mm ridge width loss. The control group in comparison showed a 2.29 $\pm$ 1.1mm loss in ridge width.

Change in ridge volume was also addressed in this study. Treatment with a porcine graft and FGG showed a change of 19.92mm^3, FGG alone 24.89mm^3, Porcine graft alone 32.89mm^3, and no graft 41.41mm^3. Use of a porcine graft with a FGG and use of the FGG alone significantly less volume loss when compared with the control group. Use of a soft tissue seal lead to a statistical influence on bone shrinkage. Use of a filler or not was not found to be significant, and these results were not affected by

tooth type or if it was in the maxilla or mandible (71). It was concluded that use of a soft tissue graft to promote 'primary' closure may have a greater influence on post-operative outcome than if a graft was used or not. Use of a FGG may promote clot stabilization, while faster soft tissue coverage could limit soft tissue ingrowth in to the would site, allowing a more adequate healing response.

Alloplast

Alloplasts are synthetically produced, inert grafting materials. These grafting materials can include β-tricalcium phosphate, hydroxyapatite, and bioactive glass to name a few.

Bone ceramic is composed of hydroxyapatite and β-tricalcium phosphate. It was developed with the idea that the more soluble tricalcium phosphate would be replaced by bone while the less soluble hydroxyapatite would remain, maintaining the space. In a comparison study between bone ceramic and DBBM, Mardas *et al* found the bone ceramic maintained 1mm more ridge width than the DBBM group (72). However, the quality of the bone formed when using bone ceramic was questioned in another study where at implant placement, the new bone was consistently poorer than sites that healed without a graft, with looser connective tissue and less woven bone (73).

β-Tricalcium Phosphate blocks have been used in sites with a buccal plate deficiency in a dog model. After 2-months of healing there was considerably less loss of ridge width both in the coronal and middle portions of the socket, when compared to control sites (3.2 and 3.6mm ridge width compared to 1.2 and 2.0mm) (74).

Magnesium enriched hydroxyapatite has recently been evaluated histologically in site preservation procedures (75), with the premise that an increase in the local concentration of magnesium, calcium and phosphate ions can promote the formation of mineralization sites in bone. The healing pattern at 4 and 12 months was assessed, however no comparison was made to natural healing or a different grafting material. At 4 months 32% of bone was present, with around 41% of residual particles remaining. Bone formation increased to 41% at 12 months, while the amount of residual grafting material reduced to 26. Comparison was made to results from other studies using other grafting materials, showing similar results, however a small sample size was used in this study.

Froum *et al* utilized bioactive glass in a ridge preservation procedure, and found that the mean new bone formation after 8 months healing was 59.5%. This was higher than that seen in sites grafted with DFDBA (34.7%) or a no graft control group (32.4%) (45). The results however were not statistically significant.

Resorbable and non-resorbable membranes

Membranes are regularly used in guided tissue generation procedures. The premise for their use stems from the compartmentalization theory behind tissue regeneration (76). Epithelium rapidly migrates, while bone moves comparatively slower. This gives the opportunity for soft tissue to infiltrate into the defect site/socket, reducing the space available for bone regeneration, and ultimately the quantity and quality of bone formation. In ridge preservation, membranes have been used for their occlusive properties, preventing the ingrowth and collapse of the soft tissue into the extraction socket, along with stabilizing the bone graft and blood clot *in situ*.

Lekovic investigated the use of a glycolide and lactide polymer resorbable membrane only (no graft) (77). They found that membrane usage alone reduced the amount of vertical and horizontal bone loss at a 6-month period following ridge preservation. They highlighted the potential of the membrane to prevent epithelial and connective tissue migration into the defect, along with providing the clot with increased stability, producing a superior result.

The same group investigated the use of an ePTFE membrane only in ridge preservation (78). After 6-months the sites were reassessed and showed that there was significantly less loss of ridge height and width when the membrane was used. Increased bone infill was also seen in the membrane group compared to no membrane. It was however reported that 30 percent of membranes became exposed, resulting in clinical outcomes similar to the control group.

dPTFE membranes have pore sizes less than 0.2 micrometers which unlike ePTFE membranes can resist bacterial ingression into the wound site when left exposed. These membranes have been assessed alone and in combination with bone grafting materials in an open healing model. Following membrane removal within 4-8 weeks, a significant reduction in loss of ridge dimensions along with bone formation was seen (79-81).

These few studies suggest that when choosing a membrane, use of a resorbable membrane may give superior results compared to non resorbable, however with the advent of newer dPTFE membranes, sufficient outcomes may still be possible.

More commonly, membranes are used in combination with an underlying bone graft. Brkovic *et al*. evaluated whether or not the adjunctive use of a collagen membrane over bone grafts had a positive effect on ridge preservation outcomes (82). The sockets were filled with β-tricalcium phosphate and type I collagen with or without a covering collagen membrane, and primary closure was obtained. After a 9-month healing period the sites were re-entered surgically and ridge measurements were taken. No statistically significant difference in preservation of ridge dimensions was found between those who did or did not have a membrane. Histomorphometric analysis also failed to show any difference in the amount of new bone formation, suggesting that using a GTR-like strategy did not improve the clinical and histologic outcome. The results also suggest that the space maintenance effects of the bone graft may play a more important role in ridge preservation outcomes than if a membrane is or is not used.

This is contradicted by a systematic review by Vittorini Orgeas *et al.* who evaluated the use of bone grafts alone, barriers alone and a combination of both (83). They found that when barriers were used alone 0.9mm more bone in height and 2.9mm in bone width was preserved when compared to a control group. Grafts alone and a combination of grafts and barriers showed less preservation. They suggested that use of barrier membranes alone could improve normal wound healing in extraction sites.

Acellular dermal matrix (ADM) is produced from donated human dermis, and is commonly utilized in mucogingival surgery as a means to increase soft tissue thickness. ADM has also been used as a membrane and has been assessed together

with DFDBA in ridge preservation by Fowler *et al*. The dermal matrix was placed under the buccal flap and left exposed over the socket opening. They found that tissue height after healing was suitable for implant placement, with minimal loss of ridge dimensions, and suggested use of dermal matrix when primary closure could not be achieved. Their results should be interpreted with caution as it was a report of two cases and did not provide in-depth evaluation pre-and post operatively to assess ridge dimension changes.

Fernandes *et al*. also evaluated the use of ADM in combination with an allograft, in a larger clinical trial in humans (84). Primary closure was not obtained over the sockets. 19 patients were split between a treatment and control group and were re-evaluated and compared both clinically and histologically after 6 to 8 months of healing. They found less reduction in alveolar ridge width and height, however the differences between test and control were minimal and not significant. Histologically there was significantly more mineralized tissue in the test sites (+7%).

Use of an 'autogenous membrane' such as a free gingival graft (FGG) has been advocated by studies (71, 85). Unlike ADM, a FGG contains live cells along with blood vessels which can provide the opportunity for speedier reestablishment of blood flow and faster graft integration. Its use could allow for more ideal ridge preservation. The dimensional changes at 4 month following a porcine bone graft with and without FGG was compared to no treatment (71). A porcine graft with a covering FGG allowed a ridge reduction on 0.79 ± 0.5mm in the buccal lingual direction. A FGG alone produced a reduction of 0.85 ± 0.6mm, while using the bone graft alone produced greater ridge width loss averaging 1.45 ± 0.7mm. The control group in comparison showed a 2.29

± 1.1mm loss in ridge width. This study suggested that use of an FGG alone could be sufficient to reduce dimensional alterations in the ridge.

Fickl *et al*. evaluated a FGG combined with a DBBM and porcine collagen graft. Comparisons were made to DBBM with porcine collagen alone, or spontaneous healing. The addition of a free gingival graft produced significantly less horizontal ridge resorption, however in the vertical dimension dimensional changes were the same. The free gingival graft was noted to help stabilize the buccal soft tissue and prevent it from collapsing. However when no graft or a collagen plug was inserted underneath the free gingival graft, no beneficial effect of using a free gingival graft was seen in one of their studies (86), suggesting that the presence of a grafting material may produce all of the benefit.

Ridge Preservation Outcomes

Factors Affecting Outcome

The amount of alveolar bone loss can vary not only between subjects but also within the same subject (87). Factors such as number of neighboring teeth being extracted, number of roots, socket morphology, integrity of the buccal and lingual plates, tissue biotype, flap or flapless extraction, grafting material, smoking status, systemic disease and patient compliance, can affect the amount of ridge resorption seen following tooth extraction and a grafting procedure (87).

Avila-Ortiz *et al*. systematically reviewed the effect of different alveolar ridge preservation techniques and materials, in non-molar human teeth. Studies were compared to non-grafted controls, and were evaluated following a minimum of 12 months of healing (87). 6 studies were included for quantitative analysis. They found

that grafting produced a significant effect on dimensional changes (bucco-lingual 1.89mm, mid buccal 2.07mm, mid lingual 1.18mm, mesial 0.48mm). In agreeance with some and contrary to other studies, flap elevation had a beneficial effect on preservation of the midbuccal and midlingual alveolar bone height, along with the use of a barrier membrane, however this may be due to the grafting technique employed. The use of a xenograft or allograft had a greater effect on midbuccal bone preservation when compared to alloplastic materials. They concluded that flap elevation, membrane usage, and use of an allograft or xenograft may contribute to superior outcomes, although complete preservation of ridge volume is not attainable.

Elevation and advancement of a full thickness flap has been shown to cause resorption of bone, along with tissue recession at adjacent teeth, alterations to the papillae and loss of keratinized tissue (88). Barone investigated the effect of primary closure on healing outcomes and found that there was no change in the facial soft tissue level, however there were significant negative changes in the width of keratinized tissue (1.77mm loss in flap group vs 1.8mm gain in flapless group) and bone width (loss of 3.5mm in flap group and 1.7mm loss in flapless group) when a flap was raised (88). Barone also found that the height of the buccal aspect of the ridge was consistently 0.5mm higher in the flap group, indicating that more buccal height was preserved when a flap was raised (88).

Similar outcomes were observed by Fickl *et al.* in dogs, who also showed less resorption when a flap was not raised (21). However a study by Araujo and Lindhe, found that raising a flap only influenced the short term outcome, and after 6 months of healing, these differences were negligible (20).

The different results seen in these studies may be related to the differing methodology. Barone and Fickl utilized direct soft tissue measurements rather than bone measurements. Soft tissue profile can give an indication of the underlying bone profile; however, this is not always the case, and could represent a source of error. Araujo and Lindhe on the other hand evaluated the dimensions of the bone through the use of block bone biopsy. Biopsies were taken after 3 months and the adjacent mesial root (distal root was the extraction site) was used as the baseline measurement in which the control and test sites were compared to. In this sense, assumptions were made that the bone height around the extracted root was the same as the adjacent control root. Flap elevation (involved the mesial root), and natural bone remodeling as a result of removing the distal root, could produce bone loss around the mesial root, underestimating the amount of bone loss.

In a systematic review by Darby *et al*, the effect of primary closure (flap elevation) on the long-term healing outcomes was not able to be determined, and they suggested that ridge preservation can be successful with or without soft tissue closure (37). They did suggest that if a membrane is being used, not obtaining primary closure and leaving the membrane exposed may negatively influence healing. However, in other studies this has not negatively influenced the regeneration of bone (70, 89, 90).

Extraction of multiple adjacent teeth could increase the amount of bone loss due to the loss of the bundle bone of both sides of the interdental septum. This is easily seen in cases of full mouth extractions in preparation for complete dentures. Bone loss following single or multi tooth extraction and ridge preservation was assessed in a dog model by Al-hamoudi *et al*. (91). They found that there was no

significant difference between sites that had one tooth vs multiple teeth removed, however the change over time from baseline was not assessed, making comparison with other studies difficult.

Factors affecting ridge preservation outcomes were also assessed by Leblebicioglu *et al*. (55). Analysing the clinical results following grafting with FDBA and a collagen membrane, the factors affecting ridge height included a combination of healing time, mid buccal clinical attachment level and the mid buccal keratinized tissue amount significant affected the outcome. When evaluated individually, none of these parameters significantly affected the outcome. Alveolar ridge width loss was also negatively associated with root length and buccal plate thickness. This negative effect of a thicker buccal plate opposes the majority of other studies. They also found that initially wider ridges lost more width, however when expressed as a percentage this was not the case.

The size of the socket can affect the healing outcome. Larger sockets need more time to completely bridge the socket with new bone than narrower sockets, and with the faster moving epithelial and connective tissues, bone formation loses out. Along the same lines, those sites which have experienced a horizontal pattern of periodontal bone loss also heal quicker, as the socket dimensions are reduced in all dimensions. Bone dehiscence's or fenestrations present at the time of extraction can predispose to formation of a fibrous connective tissue rather than bone, and can infiltrate into and fill a large portion of the socket (37).

Bone loss in the anterior region can reduce the chance of obtaining an esthetic implant restoration. High risk patient characteristics includes an incomplete buccal

wall and/or a thin scalloped gingival biotype. Cosyn *et al*. evaluated healing outcomes in those patients assumed to be at high risk of adverse healing outcomes (92). Patients were grafted with a DBBM and porcine collagen grafting product only, and re-evaluated 4 months after extraction. The mean alveolar ridge remodelling was 14%, with 38% of patients experiencing less than 10% bone loss and 24% experiencing more than 20% bone loss. They concluded that 76% of high risk cases showed less than 20% bone loss when a ridge preservation procedure was undertaken, suggesting that these high-risk characteristics may not necessarily translate into a reduced preservation outcome, with the bone graft counteracting these effects. It was also found that central incisors and canines had more alveolar bone loss than lateral incisors and premolars. Teeth which presented initially with a periodontal abscess and buccal bone loss also showed more bone loss than those without.

When the buccal plate is partially or completely missing, use of the ‘ice cream cone’ technique has been advocated by some authors (93). In this technique, the collagen membrane is cut into an ice cream cone shape and inserted in the socket covering the buccal plate dehiscence and then the socket is filled with an allograft. The membrane is left longer in the vertical dimension so that it can be folded over and secured on the palatal aspect. Buccolingual loss at 6 months was assessed after using this technique. Bone loss was found to be between 1.28 and 1.36mm, depending if CBCT or direct cast measurements were used. These results are similar to outcomes seen in intact socket grafting protocols as evaluated in a recent systematic review (27), but substantially less than seen in other studies (41). The differences may be

due to non-standardization of the measurement position between studies, along with difference in healing time, and procedural technique.

The ice cream technique places heavy emphasis on the use of a membrane covering the buccal defect, however this may not be a requirement. Sisti *et al*. in a multicenter randomized study, placed hydroxyapatite only, in sockets with a buccal plate dehiscence greater than 5mm together with an overlying collagen plug and ovate pontic (94). After 3 months of healing, CBCT analysis revealed retention of the ridge width and height, with implants being placed in all sites without the need for additional grafting (mean ridge width 7mm). Sites that were not grafted required additional grafting at time of implant surgery. They reported that the same outcome as a more expensive GBR procedure could be achieved through a relatively inexpensive ridge preservation procedure, but indicated that the additional soft tissue support provided by the fixed ovate pontic could also have played a role in the results obtained.

Grafting products are available in different particle sizes. The particle size affects the packability of the particles, and could influence the ingrowth of the provisional matrix and ultimately effect bone formation. Larger particles do not pack tightly, allowing more space between particles for tissue ingrowth, possibly producing less delay in extraction site healing. Hoang and Mealey assessed the effect of particle size on ridge preservation outcomes, and found that the size of the bone grafting particles had no effect on the clinical efficacy of ridge preservation, along with the histologic outcome (95).

Clinical and Histologic Outcomes

It has been reported numerous times that ridge preservation procedures cannot prevent all bone remodeling following tooth extraction (25). Naturally, additional buccal grafting/guided bone regeneration (GBR) at the time of extraction and ridge preservation has been proposed. Fickl *et al.* evaluated the dimensional changes after using a buccal overbuilding technique in beagle dogs (22). Extraction sites were assigned to one of four groups: grafting with DBBM and porcine collagen covered with a free gingival graft from the palate; augmentation of the buccal plate by a GBR technique, filling the socket with DBBM and porcine collagen and covering with a free gingival graft; forcing the buccal plate buccally and filling the socket with DBBM and porcine collagen and covering with a free gingival graft; and filling the socket with DBBM and porcine collagen and a combination of a free gingival and connective tissue graft to cover the socket orifice and augment the buccal contour. All groups showed horizontal and vertical bone loss, with the mean vertical bone loss significantly lower in the combination FGG/CT group. No differences could be seen between the treatment groups when looking at the change in the horizontal dimension. They concluded that overbuilding the buccal aspect at the same time as ridge preservation did not compensate for reduction in ridge width seen following tooth extraction (22). This indifference in outcome could be associated with the additional trauma (i.e. flap raising and release) produced when carrying out this over building procedure.

Morjaria *et al*. conducted a systematic assessing the bone healing response with or without the use of an intervention (27). 9 trials were included which ranged from radiological, clinical, histological studies and combinations of each. The studies

showed great heterogeneity, each involving different extraction techniques (flap or flapless, socket perforations etc.), along with different graft materials (rh-BMP-2 with ACS, bioactive glass, DFDBA, Calcium sulfate hemihydrate, autologous bone marrow, mineralized FDBA, porcine cortico-cancellous bone, glycolide and lactide polymer), and different follow-up periods ranging from 3-12 months.

Clinical outcomes in control sites showed a linear dimensional loss of width of between 2.46 (SD 0.4mm) to 4.56mm (SD 0.33mm), and 0.9 (SD1.6mm) to 3.6mm (SD 1.5mm) of bone loss in height. The test groups showed between 1.14 mm (SD 0.87 mm) to 2.5 mm (SD 1.2 mm) width loss, and a range of bone height gain of 1.3mm (SD 2mm) to a loss of 0.62mm (SD0.51mm). The majority, except for one study, showed a significant difference between test and control groups. Overall there was approximately 1mm less vertical resorption and 2mm more bone fill in the test groups. The average residual ridge width was approximately 6mm in the test and 3mm in the control sites, with a difference of 3mm noted by the author to significantly impact on future implant treatment. Overall the authors noted there was limited data comparing ridge preservation therapies to a control group, and no robust conclusions could be drawn as to if one treatment regimen is better than another (27).

A systematic review by Vignoletti *et al*. also evaluated the different materials used for ridge preservation. They found that there were no significant differences in outcomes between various materials (grafts and membranes) or if primary closure was obtained, along with the technique used for primary closure (soft tissue punch, connective tissue graft, barrier membrane, soft tissue replacement matrix). The only

exception was for the use of a collagen plug alone which failed to maintain the ridge width (96).

A recent Cochrane systematic review by Atieh *et al.* assessed the clinical effects of various materials and techniques for alveolar ridge preservation, comparing them with each other or extraction alone (97). 8 RCT's with a total of 233 extraction sites met the inclusion criteria, one study with an unclear risk of bias, and the remaining included studies with a high risk of bias.

When comparing grafting materials to extraction alone, only xenografts and allografts were compared. 2 trials compared a xenograft material to extraction without grafting (1, 98), with reduction in ridge loss by 1.97mm in the bucco-lingual direction and 2.6mm in the height, when compared to extraction alone. They indicated a significant benefit for ridge preservation using xenografts. Out of these two studies, only one (1) evaluated the need for additional bone augmentation in the test and control groups, showing no difference between the two groups. Risk of implant failure also showed no difference (1).

One trial compared the use of an allograft to extraction alone, and reported a statistically significant difference in bone loss in favour of the allograft (2.2mm difference in height and 1.4mm in width) (42).

Five trials were included which compared different grafting materials to each other. One trial compared an alloplast (nanocrystalline hydroxyapatite) material to a xenograft (DBBM), showing no statistical difference between the two groups (99). Similarly, another study compared Bone Ceramic to DBBM, also showing no significant different in clinical and radiographic parameters between the two groups

(100). Meta-analysis including these two studies showed no difference in need for additional augmentation between the materials.

One trial compared an alloplast (β-TCP with type I collagen) with and without a collagen membrane (82). They observed significant reductions in the alveolar ridge height and width in the non-membrane group compared to the membrane group (width 0.43mm difference, height 0.38mm difference). Another trial compared use of acellular dermal matrix and anorganic bovine bone matrix with and without peptide P-15 (101). No statistically significant differences were found between the two groups when comparing reduction in ridge width and height. One trial compared an alloplast (demineralized bone matrix) of different particle sizes, where no significant differences were found between the two groups (95).

The review concluded that all techniques produced a statistically significant reduction in loss of ridge width and height when compared to extraction alone, however there was no difference seen between the different materials or procedures. It was however noted that the evidence comparing different techniques was low and had moderate study quality. They noted that it is still premature to conclude which material is superior to others and whether barrier membranes provide any additional benefit. They also noted that there was no convincing evidence that a ridge preservation procedure would improve implant or prosthodontic success, as evidenced by similar needs for additional augmentation in both control and test groups.

More recently, MacBeth *et al* addressed two questions: (1) what is the effect of alveolar ridge preservation on linear and volumetric alveolar site dimension,

keratinized tissue measurements, histological characteristics and patient-based outcomes when compared to unassisted socket healing; and (2) what is the size effect of these outcomes in three different types of interventions (guided bone regeneration – GBR, socket grafting, and socket seal) (102).

Eight randomized controlled clinical trials and 1 controlled clinical trial were included for question 1; and 29 randomized controlled clinical trials, 7 controlled clinical trials, and 1 case series was included to address question 2. All studies needed a minimum of 10 patients. The risk of bias was listed as unclear or high in most of the included studies.

The standardized mean difference in vertical mid-buccal bone height between the treatment group and control was 0.739mm, while the proximal vertical bone height difference was 0.796mm. The difference in horizontal mean width change was 1.198mm. Amount of vital and trabecular bone, keratinized tissue width and thickness showed significant variation between the techniques.

A pooled effect reduction in mid-buccal alveolar ridge height of -0.467mm was seen in GBR procedures, and -0.157mm for socket grafting. The horizontal width reduction in the GBR group was -1.45mm and -1.613mm in the socket grafting group. When looking at the width in keratinized tissue, two reported an increase, while two reported a reduction. Histology revealed a great amount of variation between materials and protocols. The most common post-operative complication reported in 29 studies was soft tissue inflammation and infection.

The review concluded that ridge preservation procedures result in a significant reduction in the vertical bone dimension change when compared to extraction alone.

The reduction in the alveolar bone width however was variable. There was no evidence supporting one intervention over another in regards to bone dimension preservation, bone formation, keratinized tissue dimensions and patient complications.

Jambhekar *et al*. carried out a systematic review of RCTs comparing the clinical and histologic outcomes at 12 weeks of sockets grafted with differing grafts following flapless tooth extraction (103). 32 RCT's were identified, published up until July 2014. The mean bucco-lingual loss in width at the crest was lowest for xenografts (1.3mm), which was then followed by allografts (1.63mm), alloplasts (2.13mm) and finally sockets which were not grafted (2.79mm). The mean loss in buccal wall height was lowest again for the xenografts (0.57mm), followed by allografts (0.58mm), alloplasts (0.77mm), and those without grafts (1.74mm). Histology showed the highest vital bone content in socket grafted with alloplasts (45.53%), followed by those with no grafting (41.07%), xenografts (35.72%), and allografts (29.93%). The highest amount of connective tissue was seen in those with no grafting (52.53%), and then allografts (51.03%), xenografts (44.42%) and alloplasts (38.39%). They speculated that xenografts and allografts resulted in the least loss of socket dimensions, with alloplasts showing the maximum amount of vital bone and least amount of remnant graft material and connective tissue. It should be noted however that there was no attempt at meta-analysis and these most likely represent strict means in each group, with true comparison between materials to determining superiority not undertaken.

De Risi *et al* evaluated and compared the histology and histomorphology over time (3-7 months), of allografts, xenografts, alloplasts and control sites, through meta-

analysis of 38 papers (104). Many techniques and materials were used (graft alone, graft and membrane, membrane alone), however the data was only analyzed based on the grafting product only. It was found that the best percentage of bone was seen in the alloplast group at 3 months (54.4%), with the lowest percentage seen in the xenografts at 5 months. It was suggested that this lower percentage of bone growth at a later healing time point may indicate possible inflammatory foreign body reaction related to the presence of the bone graft, however the resorption of the graft particles may also need to be taken into account.

When evaluating the percentage of connective tissue, the highest mean percentage was seen in the allografts and lowest in the alloplasts after 7 months. Comparing the different materials to each other and the control group over the 7-month time period revealed no statistically significant difference in bone and connective tissue percentage. They suggested that there was no difference in the histological healing outcomes at any time point between any of the materials evaluated, along with spontaneous healing by itself. They suggested that placement of a bone graft did not accelerate or improve the histological healing of the site, and that an implant could be placed at an earlier time point, as early as 3 months. Dimensional changes in the ridge was not evaluated.

Darby *et al* completed a systematic review which in included 37 human studies, along with 10 animal studies (37). They indicated that ridge preservation techniques are effective in limiting ridge dimensional changes following extraction, with no evidence of one technique being superior to another. They indicated that membranes should be covered to maximize the outcome, however primary closure is not always

necessary. Despite the positive outcomes, there was no conclusive evidence that ridge preservation procedures improve the ability to place implants.

The reported systematic reviews indicate that comparative data between techniques and grafting materials is limited, with the available data suggesting that there may be no significant difference in outcome seen between ridge preservation materials and procedures.

Clinical Outcome – Additional grafting needs, Ability to place implant.

The vast majority of studies evaluating the outcome of ridge preservation procedures report on the percentage of width reduction following the procedure. While this provides helpful insight into the expected ridge dimensions following a ridge preservation procedure, they do not directly address the main reasons why ridge preservation procedures are recommended, easier implant placement. Whether or not ridge preservation reduces the need for additional bone augmentation and permits easier implant placement, is a constant discussion point between academics. A more appropriate end point outcome may be need for additional bone grafting and ability to place implant, which few studies have addressed.

Barone evaluated the need for additional grafting in molars and premolars at the time of implant placement in sites that did nor did not undergo a ridge preservation procedure (70). Forty two percent of control sites required an additional bone augmentation procedure at time of implant placement, compared to only 7% of the test sites, representing an 83% reduction in the need for additional bone grafting. Additionally, longer and larger implants were more frequently able to be inserted in the grafted sites compared to the non-grafted sites. The placement of small diameter

and short implants was considered less than ideal by the authors, however more recent studies suggest similar success and survival of short and narrow diameter implants (105-107), especially when utilizing more recently developed stronger alloys such as titanium-zirconia (108).

The need for further additional grafting following an alveolar ridge preservation procedure in both compromised (partial or complete buccal plate loss), and non-compromised (buccal plate intact), was assessed using CBCT at 4-6 months (109). Compromised sockets were treated with flap elevation, release and over grafting, while intact sockets received a bone graft covered with a collagen membrane. Virtual implants were placed in the ideal prosthetic position on the CBCT scan utilizing digital implant planning software, and the number of implants showing an exposed buccal surface was calculated. Sockets which presented a compromise in the buccal plate showed that 26% of anterior implants, 28% of premolar implants and 37% of molar implants had exposed buccal surfaces and would require additional grafting. In the non-compromised group, 44% of anterior implants, 22% of premolar implants and 23% of molar implants had exposed surfaces; with no significant difference between the two groups. These results indicate that despite grafting in compromised and non-compromised situations, not all bone volume can be maintained and some additional grafting may be anticipated. This study questioned the validity of ridge preservation procedures in preventing the need for additional grafting.

In comparison, Walker *et al*. found that 5 out of 20 (25%) implants placed in molar sites which did not receive a ridge preservation procedure required additional grafting at time of implant placement, whereas only 2 of 20 (10%) in the grafting group

required grafting. They did however note that the 2 requiring additional augmentation in the grafting group was due to poor graft material integration rather than implant exposure (30). They suggested that non-grafted molar sites were not negatively impacted and all could still receive implant treatment. These numbers are comparatively lower than what was found in another study (40), which identified only 1 out of 24 (4%) implants placed at ridge preservation sites requiring additional grafting, whereas 14 out of 24 (58%) required additional grafting if they were left to heal without ridge preservation.

Dies *et al* reported that 8/12 (66.7%) subjects could receive implants following grafting of sockets with a buccal plate dehiscence using DBBM or DFDBA (110), while Sandor found only 17.6% of sites could have an implant placed without additional grafting following ridge preservation with coral granules (111). As a comparison, Fiorellini *et al*. observed that 55% of sockets allowed to spontaneously heal required additional augmentation (112). Cardaropoli *et al* found that 7% of molar or premolar sites that underwent a ridge preservation procedure needed additional grafting, whereas 58% of those sites who did not receive a graft needed additional grafting (40).

Mardas *et al.* completed a systematic review evaluating two questions, is there any additional benefit of ridge preservation techniques over unassisted healing in terms of implant placement feasibility, need for further augmentation, implant survival, implant success and marginal bone loss; and what are the estimated size effects of implant placement feasibility, need for further augmentation, survival and success, and marginal bone loss of implants placed following different ridge preservation

techniques (113). They included ten articles to answer the first question and 30 to answer the second. All studies had an unclear or high risk of bias. They found that implant placement was feasible in ridge preservation treated sites and unassisted socket healing sites, with implant survival and success rates, along with marginal bone levels being similar. The need for further augmentation decreased when a ridge preservation procedure was performed (RR 0.15). Implant feasibility following use of a bone graft and membrane was 100%, and in those which used a graft only, feasibility was between 88.9-100%. When a socket seal technique was used, implants were able to be placed in 100% of sites.

It was reported that ridge preservation will significantly decrease the need for further ridge augmentation during implant placement compared to unassisted socket healing, however implants could be placed in those who received the preservation procedure and those that did not. There was no clear evidence that a ridge preservation procedure increased implant placement feasibility, improved the survival or success of the implants or contributed to the maintenance of marginal proximal bone levels better than unassisted socket healing. When comparing types of intervention used, not one material or technique was more superior to one another.

The vast majority of these studies only assessed posterior teeth. It is expected that the percentages of extraction sites requiring additional grafting without a ridge preservation procedure would be higher in anterior teeth and so ridge preservation would be more crucial. The data from the study by Koutouzis (109) suggests a 44% chance of needing additional grafting even if the ridge preservation procedure is performed, questioning the additional benefit of the ridge preservation procedure. The

majority of these studies highlight that not all bone loss is prevented with a ridge preservation procedure, however the possibility of needing additional major grafting may be reduced. Despite these results, the effects on the soft tissue profile and overall final esthetic evaluation of the cases were not evaluated in the studies, and a ridge preservation procedure may allow for a greater chance of achieving better soft tissue esthetics.

Immediate Implants and Extraction Site Healing.

The addition of grafts into an extraction socket aims to provide additional support for the initial blood clot formation, along with an osseoconductive and possibly osseoinductive stimulus for bone regeneration. Immediate placement of a dental implant has been proposed as a method of supporting the remaining alveolar bone and blood clot, reducing the amount of ridge reduction. This concept has been assessed and disproved in a dog model by Araujo *et al* (114). After 1 month of healing, bone was observed to be above the level of the first thread on the buccal aspect. After 3 months of soft healing, the bone level receded to below the first thread as a result of buccal plate remodelling. All implants placed into experimental sites failed to prevent the remodelling of the buccal socket, consistently leading to exposure of the buccal surface of the implant. In the anterior region, immediate placement of a dental implant could lead to esthetic nightmares in certain cases, potentially warranting future implant removal and tissue augmentation.

Naturally the next step assessed was whether a simultaneous buccal GBR procedure at time of immediate implant placement produced a satisfactory outcome. This concept was assessed using DBBM and a collagen membrane, in Labrador dogs

by Favero *et al*. (115). Similarly to Aruajo *et al*. (114), the immediate placement of an implant and graft did not preserve the volume of hard and soft tissues at a 3 month time period (115), however they indicated that the grafting at time of implant placement did reduce the amount of volume shrinkage. It was concluded that contour augmentation using DBBM and a collagen membrane was not able to maintain the tissue volume.

Botticelli *et al* followed and characterized the healing of 21 immediate implants placed in incisor, canine or premolar regions was studied (116). There was no attempt to place any membranes or grafting materials in the remaining socket defect at the time of extraction and implant placement. After 4 months of healing, they found that a 1.9mm (56%) buccal crest width reduction and 0.9mm (30%) palatal/lingual crest width reduction occurred. A loss of 0.3mm in bone height on the buccal, 0.6mm on the lingual, 0.7mm on the mesial and 0.5mm on the distal also occurred. This reduction in bone height was smaller than that seen by Araujo *et al*. who identified a 2mm mean reduction in crestal height (114). They identified that those initial defects which showed a horizontal distance of more than 3mm from the implant shoulder to buccal bone plate was filled with bone 84% of the time. They concluded that in humans, the extraction socket may predictably heal with new bone formation around the implant, however the implant did not prevent bone loss.

The results from the above studies was confirmed in a systematic review by Chen *et al* (117). Implants placed immediately into extraction sockets did not prevent vertical or horizontal resorption. They also indicated that grafting the buccal aspect at the time of implant placement helped reduce (but not stop) the reduction in horizontal

ridge resorption, however it failed to prevent resorption in the vertical dimension. This further highlights the fact that grafting cannot completely negate the resorptive phase of extraction socket healing.

New Technologies and Developments in Ridge Preservation

BMP-2 is an osteoblastic differentiation inducer and can promote and accelerate bone formation. rhBMP-2 and an absorbable collagen sponge (ACS) has been assessed in a buccal dehiscence type model, in a randomized and controlled clinical trial. Use of 1.5mg/ml of rhBMP-2/ACS produced a height reduction of -0.02mm at 4 months compared to -1mm if the collagen sponge was used alone. Change in width at the coronal aspect of the socket was 3.27mm, compared to 0.82mm when the sponge was used alone. The results when the socket was left to heal spontaneously without a graft was similar to the sponge alone. When using implant placement as the long-term outcome, in the test group, 86% of patients were able to receive implants without any further grafting, while in the control group, only 45% of patients were able to receive an implant without any additional bone grafting procedures (112). This study however defined adequate alveolar dimension as 6mm in width, allowing for only a 3mm implant to be placed with 1.5mm on each side. Not every site may be suitable to receive a narrow diameter implant.

Lee *et al*. compared the effects of adding rhBMP-2 to a bovine bone graft, in extraction sockets with buccal dehiscence's (118). Using a dog model, they observed that sites grafted with DBBM and rhBMP-2 or DBBM and a membrane showed a greater area of new histologic bone formation and less bone loss than those sites which were not grafted or received DBBM alone. There however was no difference

between the DBBM + rhBMP-2 or DBBM + membrane groups, and one treatment method was not shown to be superior to the other. The addition of BMP-2 to a graft or BMP-2 alone may not provide superior clinical and histological outcomes and its use should be weighed up with the considerable additional cost to the patient.

An electrospun cotton wool-like nanocomposite which incorporated amorphous calcium phosphate nanoparticles into a biodegradable synthetic copolymer poly(lactide-co-glycolide) has been developed and the healing outcome in a sheep model has been assessed (119). Following 16 weeks of healing, the wool like material showed a fine trabecular pattern, compared to non-grafted sites which showed thick trabeculae separated by areas of fibrovascular connective tissue. The wool treated sites showed less residual graft material than a bovine bone grafted group. Bone formation between the groups however was not statistically significant.

A more rigid, purported easier to use, resorbable and non resorbable barrier devices have been developed for use in intact sockets, along with sockets with buccal plate dehiscence's. SocketKAP is a dome shaped non-resorbable device made from polypropylene, and contains channels on the superior surface to allow the placement of sutures. SocketKAGE is a resorbable device consisting of rigid interconnecting ribs made from poly-L-lactide, and is used to support sockets that present with buccal dehiscence's (120).

In intact sockets using the socketKAP device only, 53.7% (volume loss of 46.3%) of bone was preserved in comparison to only 32.6% (volume loss of 67.4%) seen in the negative control group at 6 months, however the results were not statistically significant. When the intact socket was filled with DBBM along with use of

the SocketKAP, 74.9% of bone was maintained (volume loss of 25.1%), which was significant in comparison to the negative control group. The majority of bone lost was in the coronal 1-3mm of bone height.

When sockets did not have an intact buccal plate, the SocketKAGE device with DBBM was used and compared to a negative control group. At 6 months, the negative control group lost 62.5% of alveolar bone volume in the crestal 3mm, while the experimental group lost only 23.8%. It was noted that in the absence of an intervention, only 10-30% of the crestal 3mm of bone remained, whereas the experimental groups preserved between 40 to 80% of crestal bone volume.

A biodegradable macroporous composite scaffold made of poly DL-lactide-co-glycolide/calcium phosphate was used in 16 sockets and compared to extraction alone at 4 months (121). The scaffold was premade into a cylindrical shape, and was inserted into the socket to aid in blood clot retention. It did not fill the socket in its entirety in the occlusal aspect. Measurements obtained from pre-and post-operative CBCT images showed 45.3% bone loss when the control group, compared to 28.7% bone loss seen when the scaffold was used. The difference was statistically significant.

Mechanical stimulation of bone using High frequency acceleration (HFA) has been shown to trigger skeletal adaptation to the additional mechanical loading (122). The effect of HFA following tooth extraction on alveolar bone loss and rate of bone formation was investigated in a rat model (122). Following use of HFA for 5 minutes per day for up to 56 days, an increase in bone volume in the extraction site and surrounding alveolar bone by 44% was seen when compared to a static load,

preserving the alveolar bone height and width. Expression of osteogenic markers and intramembranous bone formation was increased in the HFA group, while a decrease in expression of osteoclastic markers, bone resorption activity, and inflammatory markers was seen, highlighting the potential advantage of using HFA during the healing period.

Hyaluronic acid (HA) can promote cell migration and differentiation during tissue formation, purportedly through stimulation of BMP-2 and osteopontin production, and can play a role in wound healing (123). Kim *et al*. evaluated the use of HA on the healing of infected extraction sockets in dogs. They observed an increase in mineralized bone by 15.5% and a decrease by 15.75% in bone marrow in those sockets treated with HA. While the direct effects on preservation of alveolar ridge dimensions were not assessed, the use or addition of HA into a grafting material for clinical use could enhance the healing outcomes post extraction.

The Socket shield technique was originally proposed by Hürzeler *et al.* as a means of retaining the buccal bundle bone, limiting resorption of the buccal plate. The premise behind this it that the attached PDL will retain functionality of the bundle bone and so resorption of the buccal plate will be minimal. The procedure involves decoronation of the tooth 1mm under the height of the bone crest, sectioning of the root, removal of the palatal portion and leaving the buccal portion intact and attached to the buccal plate (124). The implant is then placed immediately behind the buccal fragment of tooth, and then the gap surrounding the implant is grafted with a slow resorbing bone grafting material. It was also suggested as a more economic option, as no grafting and membrane material was used (125).

The same group also published a histological, clinical and volumetric observational study (125). Three dogs were used for histology, while one human clinical case was used for volumetric evaluation. The teeth included presented with vertical root fractures and when performing the technique, an additional trough was created between the two buccal fragments to allow for tissue ingrowth, removing a potential bacterial nidus. They showed that after 4 months of healing, in the coronal portion between the implant and dentin of the tooth fragment, new bone formed. This was similar along the remainder of the implant length. New bone also formed within the gap created between the buccal root fragments. Buccal bone loss showed a mean of 0.66mm, however depending on the position of measurement, there was a range of loss from 1.16mm to 0.01mm.

A more recently published systematic review evaluating this technique found that evidence was limited, and has cautioned use of this technique (126). They found that all articles were case reports and series, with 75% of them not following the cases past 12 months. They noted that histology from animal studies showed mixed results, with formation of PDL and/or cementum on the implant surface, CT encapsulation, or reported bone formation. Some clinical reports suggested a stable outcome at 12 months, however others listed problems with infection and resorption of the socket shield. They indicated that loss of this shield would ultimately lean to loss of the buccal plate and possible implant exposure. While good outcomes have been shown for this treatment protocol, more research is needed to assess the long-term efficacy and predictability of the treatment

Conclusions

The evidence to date undisputedly shows that alveolar ridge dimensions change drastically following tooth extraction, and that, by providing a ridge preservation procedure, the degree of ridge resorption can be somewhat controlled. There are many techniques and materials available, however, due to the limited number of RCTs comparing multiple different grafting materials and differing study designs, comparisons between materials and techniques through meta-analysis has produced equivocal results. Furthermore, the clinical implications (making future implant placement more feasible and cost effective with potentially more long term results) of this additional grafting procedure and the costs associated, has been questioned. Therefore, more well designed randomized clinical trials evaluating different grafting materials and ungrafted control group is required, comparing and contrasting the outcomes and their effects on future dental implant placement.

AIMS AND OBJECTIVES

Limited data is available regarding volumetric changes of the alveolus following tooth extraction and ridge preservation procedures. This has direct effects on subsequent dental implant treatment. Successful ridge preservation enhances proper implant placement. Furthermore, it is necessary to better define the effects of different grafting materials on the clinical outcomes following ridge preservation. This study has been designed to treat a clinical scenario commonly encountered in clinical practice.

A common and non-invasive approach used for site assessment following a grafting procedure is the use of cone-beam computed tomography (CBCT) images (127). Several studies have demonstrated the reproducibility and accuracy of CBCT (128-131); concluding that there was no significant difference between the radiographic and clinical measurements. CBCT is now acknowledged by the American Academy of Oral and Maxillofacial Radiology, for the pre-surgical implant planning and augmentation procedures as the imaging modality of choice for preoperative cross-sectional images of potential implant sites (132). CBCT may be used to measure the alveolar bone condition prior to implant therapy and following ridge preservation. Therefore, when serial CBCT data is available, the direct volumetric assessment of ridge preservation outcomes will be possible.

Primary objective

The primary objective is to compare the volumetric changes in the alveolus through cone beam computed tomography (CBCT) analysis, following a post-extraction ridge preservation procedure. Three different treatment groups utilizing three different bone-grafting materials will be used and compared. Additionally, a non-grafted control group utilizing a membrane only is included for comparison (control).

Hypothesis: No significant differences in ridge volume maintenance are anticipated among the three grafting groups. The combined use of particulate graft material with a resorbable collagen membrane will maintain a greater ridge volume than the use of a resorbable collagen membrane alone.

Secondary objectives

Secondary objectives of the study are to evaluate and compare:

- Bucco-lingual and vertical linear dimensional changes of the alveolus in each treatment and control group
- Bucco-lingual and vertical linear dimensional changes of the soft tissue in each treatment and control group
- Ability to place a standard diameter implant (3.6mm (lateral incisor) or 4.1mm (premolar, central incisor, canine) diameter x 9mm) after healing without the need for additional grafting.

Additionally, this study also intends to provide statistically robust evidence that Symbios® demineralized cortical-cancellous mix, Symbios® OsteoGraf LD-300, and Symbios® OsteoGraf/N-300 combined with Symbios® OsteoShield Collagen resorbable membrane, can adequately support the alveolus during ridge preservation

procedures, reducing the dimensional changes of both the alveolus and the overlying soft tissues.

MATERIALS AND METHODS

This study is designed as a randomized controlled prospective clinical trial lasting a period of three months from tooth extraction. The study population will consist of individuals requiring an extraction with ridge preservation, within sites 4-13, 20-22, 27-29.

80 subjects will be included. Each subject will be randomized into one of three bone graft treatment groups or one membrane only treatment group:

- Group A - Symbios® demineralized cortical-cancellous granule mix, and Symbios® OsteoShield Collagen Resorbable Membrane (Allograft)
- Group B - Symbios® OsteoGraf/LD-300, and Symbios® OsteoShield Collagen Resorbable Membrane (Alloplast)
- Group C – Symbios® OsteoGraf/N-300, and Symbios® OsteoShield Collagen Resorbable Membrane (Xenograft)
- Group D - Symbios® OsteoShield Collagen Resorbable Membrane only (Control)

Prior to grafting and after a 3-month healing period, a CBCT will be taken, along with pre-and post-operative soft tissue impressions for analysis of volumetric and linear dimensional changes (Figure 3)

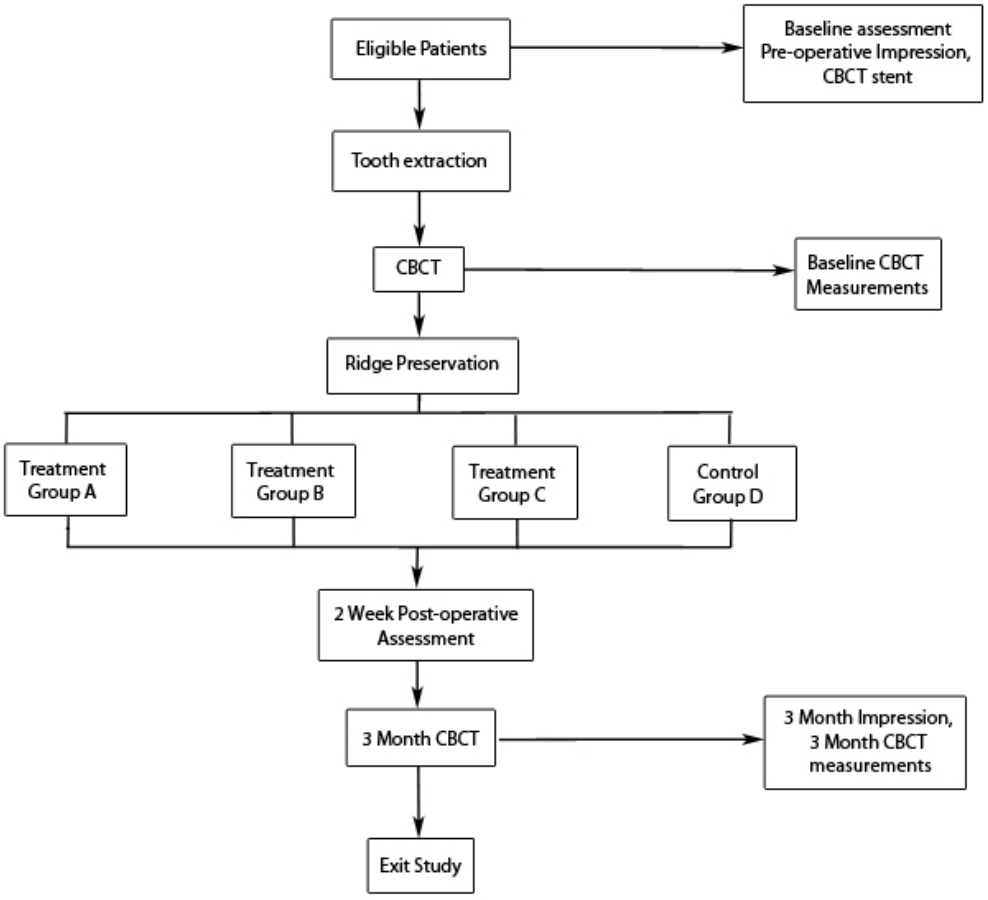


Figure 3: Study flow chart

Graft Products

Symbios® demineralized cortical-cancellous granule mix is a human allograft product obtained from the Musculoskeletal Transplant Foundation (MTF), which mimics the natural bone anatomy, providing space maintenance and surface area for bone formation. The material contains 80% cortical and 20% cancellous bone, displaying a particle size of 200-1000 microns.

Symbios® OsteoGraf/LD-300 is a 100% pure synthetic hydroxyapatite bone product that shows 56% porosity and high surface area. It is conducive to solution-mediated resorption, producing a readily available source of calcium for bone regeneration. This low density resorbable grafting material presents as 250-420 micron particles.

Symbios® OsteoGraf/N – 300 is a sintered natural anorganic bovine-derived microporous hydroxyapatite, displaying a particle size of 250-420 microns. The hydroxyapatite is conducive to cell-mediated resorption and provides a scaffold for new bone growth, holding the space until host bone takes over. There are no extractable proteins present in the product.

Symbios® OsteoShield Collagen resorbable membrane is made from Type-I bovine collagen from the Achilles tendon. It has a resorption time of between 26 and 38 weeks. It is a multi-layered membrane, which assists in healing of the bone and surrounding tissues, and helps prevent cellular and bacterial down growth.

Inclusion and Exclusion Criteria

Inclusion criteria

For inclusion in the study subjects must fulfil all of the following criteria:

1. Provision of informed consent
2. ≥ 18 years and ≤ 75 years
3. Good physical health (ASAI/II)
4. Extraction of maxillary premolar, canine or incisor, or mandibular premolar and canine required (#4-13, 20-22, 27-29).
5. Teeth adjacent (mesial and distal) to study site must consist of two stable natural teeth with minimal restorations, without signs of periodontal bone loss (> 3 mm) and/or significant soft tissue deficiencies

Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Buccal plate dehiscence and/or fenestration >3mm at study site following extraction
2. Untreated rampant caries and uncontrolled periodontal disease
3. Inadequate oral hygiene (estimated plaque score >20%)
4. Smokers using more than 10 cigarettes or equivalent per day
5. Smokeless tobacco use or e-cigarette use
6. Compromised physical health and/or uncontrolled or severe systemic diseases including:
    - ASA III/IV
    - Metabolic bone disease

- History of malignancy
- History or radiotherapy or chemotherapy for malignancy in the past 5 years
- History of autoimmune disease
- Long-term steroidal (20mg cortisol or equivalent for 2 weeks duration in past 2 years) or antibiotic therapy (antibiotic therapy exceeding 2 weeks in past 1 year)
- Uncontrolled diabetes (HbA1c ≥7)
- Known alcohol or drug abuse

7. Systemic or local disease or condition that would compromise post-operative healing
8. Use of any substance or medication that will influence bone metabolism
9. Pregnancy at time of screening
10. Unable or unwilling to return for follow-up visits for a period of 3 months
11. Unlikely to be able to comply with study procedures according to investigators judgement
12. Involvement in the planning and conduct of the study
13. Previous enrolment or randomization of treatment in the present study

Sample size calculation

A sample size of 20 participants per treatment group (80 total) was selected following power calculations and allowing for 10% patient dropout. A sample size of 18 patients was calculated for the primary outcome variable (volumetric bone changes) with the assumption that the detectable difference would amount to 0.5mm^3

with a standard deviation of 0.5. The type I error probability was set at 0.05 and the statistical power was set at 80%.

Clinical Visits

Four Clinical visits over a span of three months were completed:

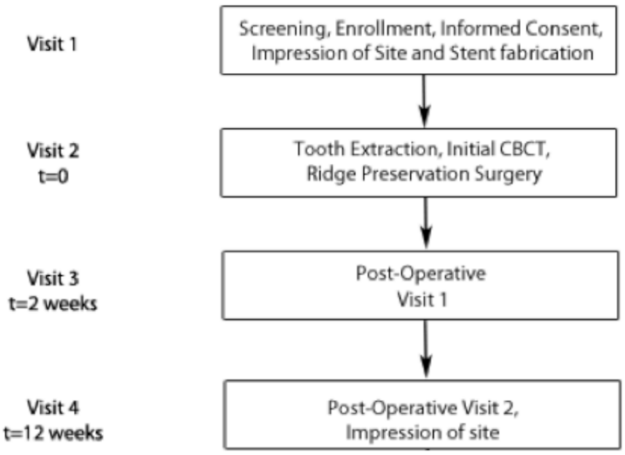


Figure 4: Appointment flow chart

Visit 1: Screening

Before any assessment or examination is carried out, informed consent and HIPAA authorization was obtained. Individuals meeting all initial inclusion and exclusion criteria were further evaluated through clinical and radiographic examination. Quadrant impressions were made using a hydrocolloid impression material (alginate) of the planned extraction site. The impression was then immediately poured in type III dental stone. One cast was used for the fabrication of a radiographic stent for ease of pre-and post-operative CBCT superimposition,

another providing baseline soft tissue data, and the final to allow for fabrication of a temporary tooth (essix retainer) if required.

Baseline clinical and demographic information was recorded in the REDCap online data management system.

Radiographic stent fabrication

The radiographic stent was fabricated by first blocking out any large undercuts on the stone model, and then a 0.5 mm thermos plastic material (Pro-form coping material) was heated and sucked down over the cast. Three Suremark 2.3mm CT marking labels were placed in a staggered formation on both the buccal and lingual surfaces of adjacent teeth. An additional layer of 0.5 mm thermos plastic material was then heated and adapted over the first layer. Excess material was trimmed so as to produce a radiographic stent which extended approximately 5mm from the gingival margins of the surrounding teeth, leaving the soft tissue in the site of the extraction exposed (Figure 5).

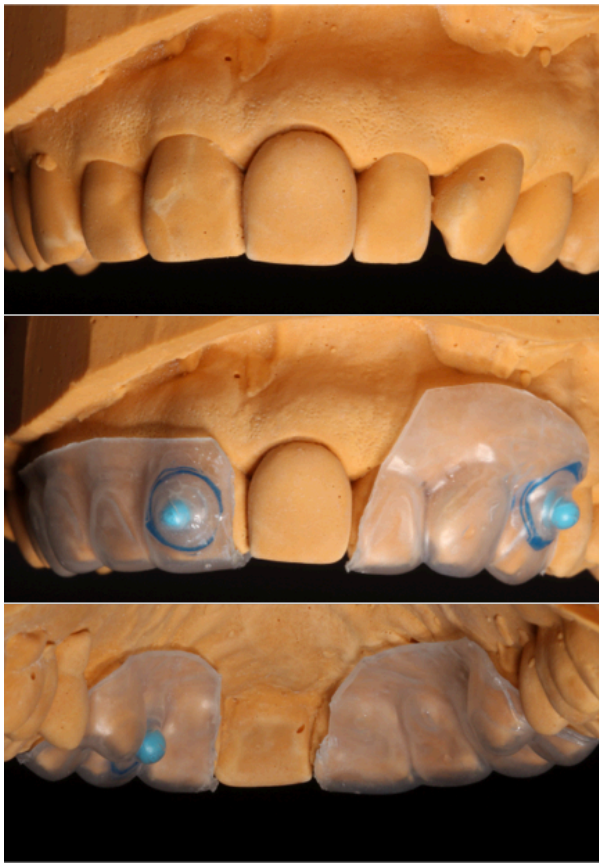


Figure 5: Radiographic stent.

Visit 2: Extraction, Initial CBCT, and Socket Preservation Surgery

Randomization and Stratification

Subject numbers (subject ID) were consecutively allocated in series at day of inclusion (Visit 1) starting at number 1. Enrollment will continue until 80 subjects have been allocated a subject ID. If a subject discontinues, the subject number will not be reused.

Subjects were randomized strictly sequentially at day of extraction and ridge preservation (Visit 2), after integrity of buccal plate was confirmed. Treatment group

randomization was completed using an opaque envelope randomization method (Figure 6).

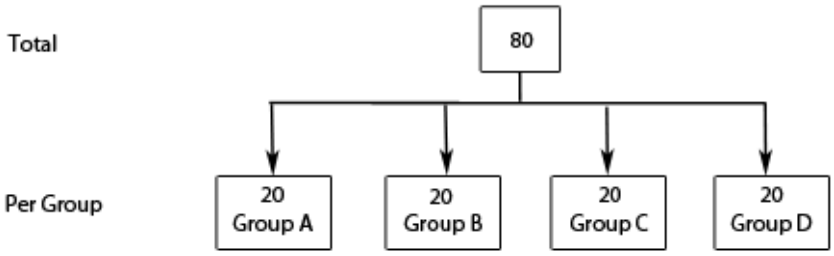


Figure 6: Randomization and stratification of subjects

Pre-Surgical, Surgical, and Post-Surgical Care (at surgical appointment)

Pre-surgical, surgical and post-surgical care were given at the discretion of the Investigator and recorded in appropriate sections in the RedCap and EPR systems:

- Antibiotics
- Analgesics
- Anaesthesia
- Anxiolysis

Antibiotics:

Pre-surgical antibiotic prophylaxis was provided for patients at risk for infective endocarditis or with total joint replacement according to current guidelines provided by the American Dental Association, American Heart Association (133), and the American Academy of Orthopaedic Surgeons (134).

Post-surgical antibiotic coverage was provided to patients, consisting of a 7-day course of 500mg Amoxicillin every 8 hours or 300mg Clindamycin every 6 hours.

Analgesics:

Post-surgical analgesics were provided, consisting of 800mg Ibuprofen every 6-8 hours and 5/325mg Acetaminophen/Hydrocodone every 4-8 hours.

Anxiolysis:

Options were discussed with the patient and the decision to use 1-2mg Ativan to reduce the patients surgical anxiety was made on a case-by-case basis.

Anesthesia:

The mucosa at the site of extraction was dried with gauze and 20% benzocaine topical anesthesia was placed on the mucosa for 1 minute. Infiltration anesthesia using 2% lidocaine with 1:100,000 and 2% lidocaine with 1:50,000 epinephrine was provided.

Post-surgery, infiltration anesthesia with 0.5% bupivacaine with 1:200,000 was provided at patient request.

Pre-Surgical Procedures

Buccal and crestal photographs of the planned surgical site were obtained using a Canon 50D digital camera body with a Canon 100mm f/2.8 macro lens and a Canon MR-14EX macro ring flash.

Surgical Procedure

A circumferential sulcular incision was placed around the teeth to be extracted. Periotomes and luxators were used to extract the tooth with minimal trauma to the adjacent tissues. The socket wall was examined for any dehiscence greater than 3mm

or fenestrations. If they were present, the patient was excluded from the study. In the case of dehiscence, fenestration, infection, or other surgical complications encountered during treatment and/or healing, appropriate site preservation procedures and/or debridement and/or infection control steps were implemented, and referred back to their general dental providers for follow-up treatment.

Following extraction, the socket was curetted, irrigated with sterile water and gauze was placed in the area to produce wound hemostasis.

Immediately following tooth extraction, the radiographic stent was placed and cotton rolls inserted into the vestibule, aiding in soft tissue retraction. The patient was then escorted to the Department of Radiology and a cone beam computed tomography (CBCT) image was produced whilst wearing the radiographic stent, and appropriate radiographic protective devices. The Sirona Orthophos XG 3D CBCT machine was utilized with standard parameters set and a voxel size of 0.3mm.

Following CBCT imaging, the socket was rinsed with sterile water and a ridge preservation procedure was completed as follows:

- Group A: Symbios® demineralized cortical-cancellous granule mix reconstituted in sterile saline was used to augment the socket and covered by a trimmed Symbios® OsteoShield Collagen resorbable membrane.
- Group B: Symbios® OsteoGraf/LD-300 reconstituted in sterile saline was used to augment the socket and covered by a trimmed Symbios® OsteoShield Collagen resorbable membrane.

- Group C: Symbios® OsteoGraf/N-300 reconstituted in sterile saline was used to augment the socket and was covered by a trimmed Symbios® OsteoShield Collagen resorbable membrane
- Group D: Socket covered with a trimmed Symbios® OsteoShield Collagen resorbable membrane and no grafting material, allowing socket to heal spontaneously.

All barrier membranes were secured over the socket orifice using 5-0 chromic gut sutures in a horizontal cross mattress and simple loop configuration, engaging the membrane (Figure 7).

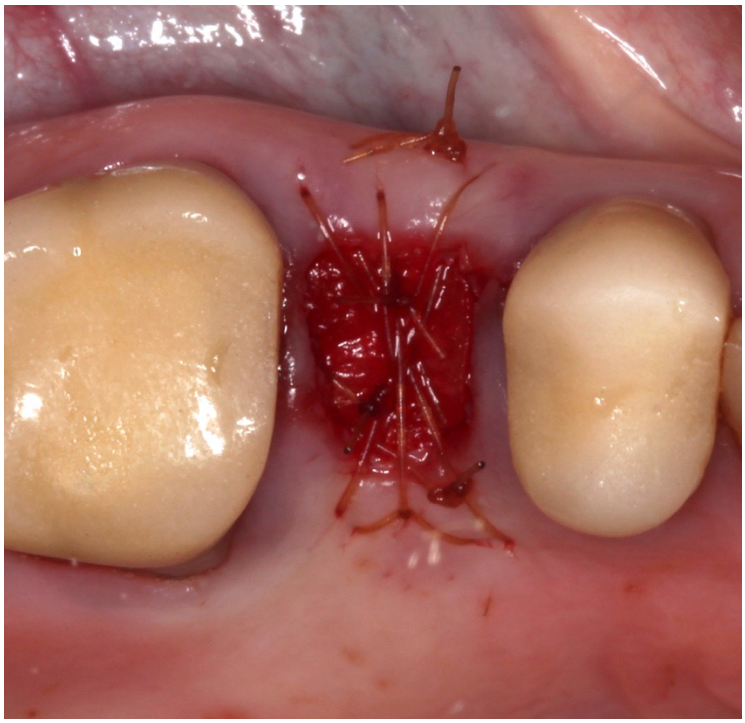


Figure 7: Post-operative suturing of membrane over socket

Post-Surgical Procedures

Buccal and crestal photographs of the surgical site were obtained. Standard UNC post-operative instructions were given which includes the use of a Chlorhexidine rinse 2 times daily for 2 weeks.

Restrictions Following Surgical Procedure

Subjects were advised of the following restrictions during the study period:

- To avoid disruption of wound healing during the initial study period the subject should have a restricted diet for at least 3-5 days and were instructed to avoid manual oral hygiene in the site for 2 weeks (printed instructions were distributed to the subjects at Visit 2)
- For current smokers, interim cessation will be encouraged and no more than 10 cigarettes per day were allowed
- No dentures overlaying the site were allowed, except for the use of an interim essix retainer.

Visit 3: Post-Operative Visit (14 days ± 2 days)

The stage of healing was clinically assessed. Remaining suture material was removed. Buccal and crestal photographs of the surgical site were obtained using a Canon 50D digital camera body with a Canon 100mm f/2.8 macro lens and a Canon MR-14EX macro ring flash. Any adverse events were recorded.

Visit 4: Cone Beam Computed Tomography Imaging (12 weeks ± 7 days)

Cone beam computed tomography (CBCT) imaging whilst wearing the radiographic stent was obtained for all patients 3 months following surgical treatment. The healing of the surgical site was clinically assessed, buccal and crestal

photographs of the surgical site were obtained, along with an alginate impression of the site.

Data Collection and processing

Primary outcome variable – Volumetric osseous changes

Pre-and post-operative CBCTs were imported into 3D Slicer 4.6 (NIH) (135). Fiducial points were placed in the position of the radiological stent markers, along with other anatomical markers (sinus septa, nasal spine, greater palatine foramen, nasopalatine foramen, greater and lesser wings of the spenopalatine bone, apices of roots), and the post-operative CBCT was aligned to the pre-operative CBCT using the affine registration method in the 'landmarks registration' module of 3D slicer. Following this, both pre-and post-operative scans were manually rotated using the 'Transform' module to allow for segmentation in a buccal lingual orientation in subsequent software (ITK Snap). The pre-and post-operative transformed/aligned CBCTs were then resampled at this new orientation using the 'Resample Scaler/Vector/DWI volume' module and exported as a .nrrd file.

Next, the .nrrd files were imported into ITK Snap (136). The area of the extraction site and surrounding teeth and bone, were segmented using the 'Active Contour Segmentation' module setting a lower threshold of 400 and a smoothness value of 10. The segmentation was then corrected by hand going slice by slice in all dimensions using the 3D round shaped paintbrush set at 5 slices thick. The socket space in the baseline CBCT was closed over by drawing a line from the buccal to palatal plate peaks, creating an idealized bone volume for comparison. The segmentation files were exported in the .vtk format to form a 3D model.

Following segmentation, the segmentations of the pre-and post-operative CBCT's were reimported back into 3D Slicer. As the 3D models were produced on aligned CBCT scans no further registration was necessary. Using the 'Easy Clip' module, common regions of interest (ROI) were defined using the mesial and distal surfaces of the adjacent teeth and the long axis of the socket to define the mesial and distal reference planes (Figure 8: green and yellow planes), while an apical reference plane was set at an orientation 90 degrees to the long axis of the removed tooth, and positioned at the most apical extent of the socket (Figure 8: blue plane). The coronal plane of the ROI was defined as the height of the pre-operative ridge, and the buccal and palatal extent included the entire buccal and palatal profile of the alveolus. The models were subsequently clipped in this position and the ends were automatically filled, producing a closed model. Using the 'Models' module, the volume of each model was recorded as the total bone volume.

Next a central plane (Figure 8: red plane) was defined utilizing the center of the adjacent teeth and the long axis of the socket as reference points, and the models were cut in half, producing a buccal and palatal portion. Using the 'Models' module, the volume of each model was subsequently recorded.

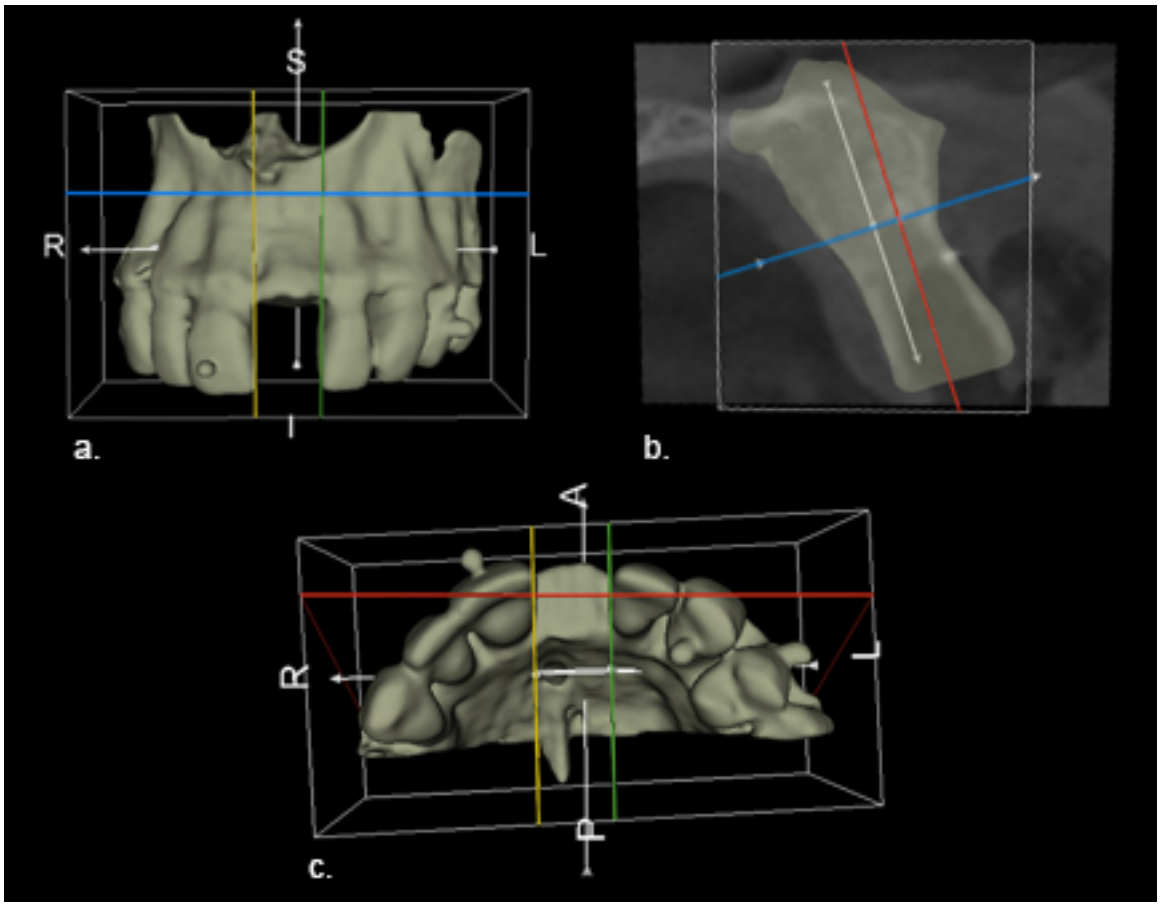


Figure 8: ROI definition: (a). facial view, (b). sagittal view with overlaid CBCT indicating apical extent of socket, (c). coronal view indicating position of central plane. Green and yellow planes indicate mesial and distal ROI boundaries, red indicates buccal palatal division boundary, and blue indicated apical boundary.

A color map to aid in visualization of the contour changes was produced with the pre-operative model as the reference model. This was achieved by using the 'Model to Model Distance' and the 'Shape Population Viewer' modules, utilizing a common color map and scale.

Secondary outcome variables

Volumetric Soft tissue changes

Pre-and post-operative stone models were scanned with the 3Shape D810 model scanner and exported as a .stl files. The pre-operative stl file was imported into 'MeshMixer' software (137). The gingival margin was selected and the points above the gingival margin (i.e. the tooth) were deleted and the hole subsequently filled using the shape preserving fill function, producing the 'ideal' soft tissue volume. The file was saved as a .stl file.

The pre-and post-operative .stl files were then imported back into 3D Slicer and the post-operative model was registered to the per-operative model using the fiducial marker registration function in the 'CMF Surface Registration' module. Up to 10 points were placed on cusp tips, grooves, incisal corners etc. The transform was then hardened to produce a new post-operative model aligned to the pre-operative model.

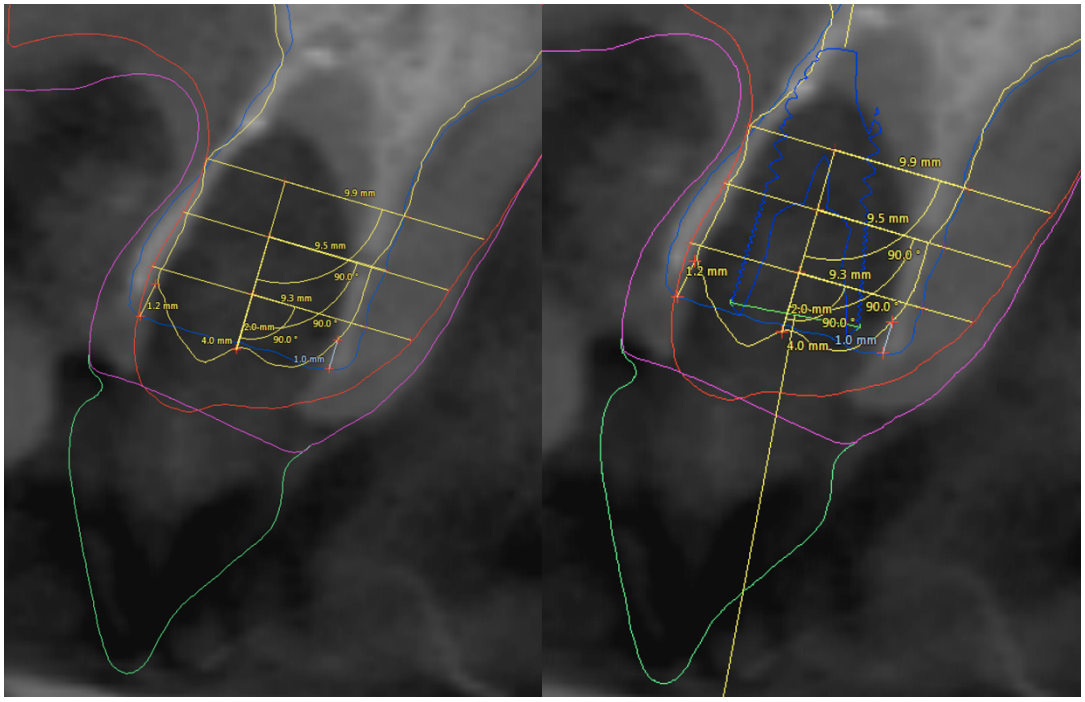
A common region of interest was defined in a similar fashion as in the osseous 3d models, however the apical extent was defined as a plane that was perpendicular to the other planes at the most apical extent of the recorded soft tissue profile. The 3D models were then divided into buccal and lingual halves in a similar process as in the osseous models. Only the buccal half was used for volume change analysis due to differences in palatal vault heights. Using the 'Models' module, the volume of each model was subsequently recorded.

A color map to visualize the contour changes was produced with the pre-operative model as the reference model, using the 'Model to Model Distance' and the 'Shape Population Viewer' modules, utilizing a common color map and scale.

Linear Bone and Soft Tissue Changes.

The pre-operative CBCT was imported into CoDiagnostix™ (Dental Wings, Montreal Canada) software. Next, the pre-and post-operative bone and soft tissue models were imported and aligned using the model registration module utilizing tooth anatomy and radiologic stent fiducial markers as registration points.

A central reference plane was defined using the long axis of the tooth/socket. A point was placed at 2mm, 4mm, and 6mm from the ideal bone crest height on this reference plane. Using the angle measurement function, an intersecting plane at each of these measurement points was placed at 90 degrees to the central reference plane (Figure 9a). The pre-and post-operative linear dimensions of the bone and soft tissue were recorded at 2mm and 4mm. The thickness of the buccal plate was recorded at 2mm, 4mm and 6mm from the original buccal plate height.

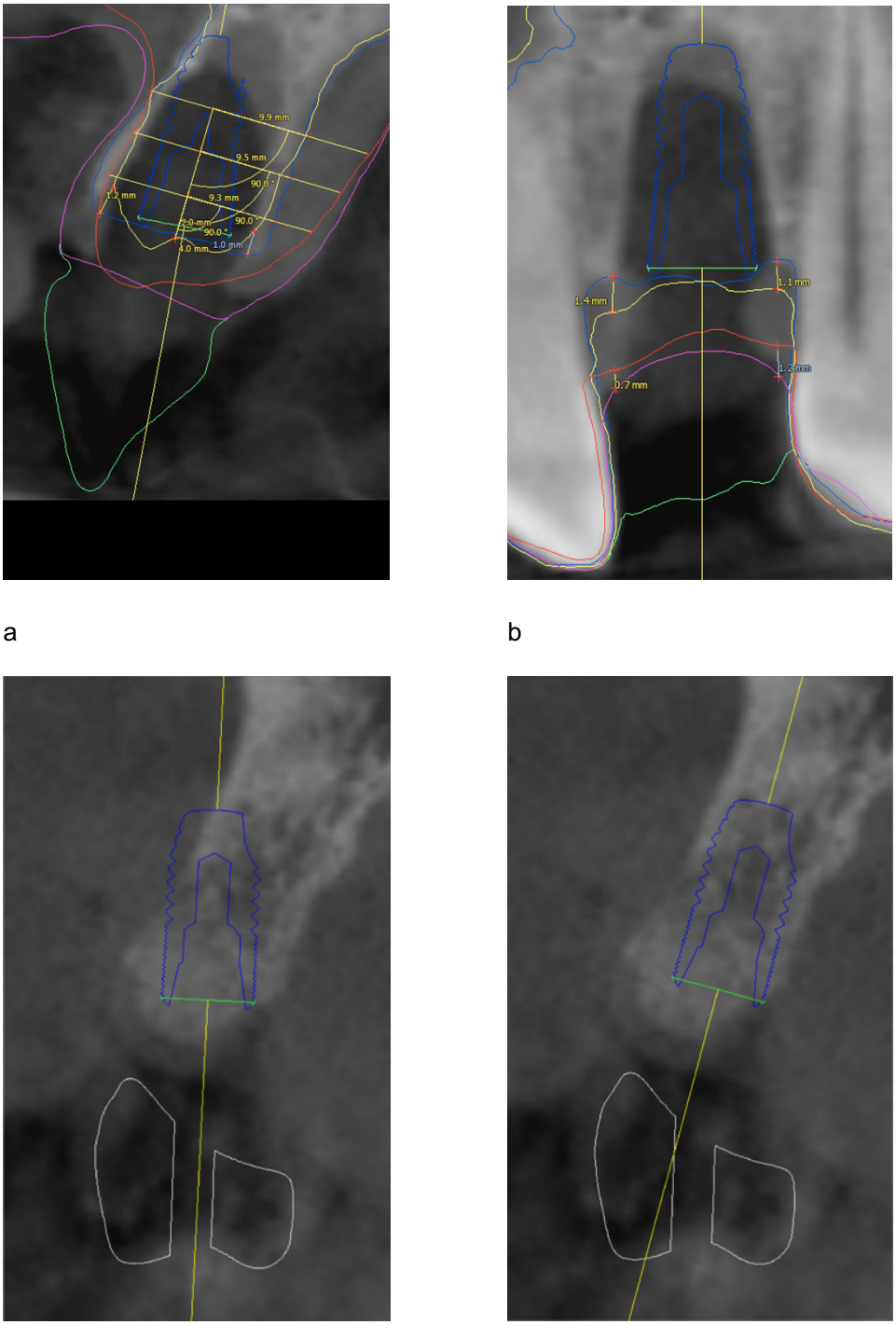


a. b.

Figure 9: Positions of (a) linear measurements and (b) implant positioning. Green = pre-op soft tissue with tooth, Pink= pre-operative soft tissue with tooth removed, Red = post operative soft tissue, Blue = pre-operative bone, Yellow = post-operative bone.

In the same CBCT slice, the change in vertical bone and soft tissue height was measured utilizing the overlaid pre-and post-operative bone and soft tissue models. Mid buccal and mid palatal measurements were taken from the most coronal point in the pre-and post-operative bone levels, along the plane of the initial bony plate (Figure 10). Mesial and distal height changes were obtained by utilizing the 90-degree tangential slice from the buccal-palatal slice, in the center of the ridge. Mesial and distal sites of measurement were defined as the most mesial and distal walls of the socket as seen in the preoperative CBCT. A linear measurement between the pre-and

post-operative bone and soft tissue levels was taken from the most coronal and apical point in this position (Figure 10).



a b

c d

Figure 10: Vertical measurements. (a) mid buccal and mid palatal and (b) mesial and distal measurement positions. Green = pre-operative soft tissue with tooth, Pink= pre-operative soft tissue with tooth removed, Red = post-operative soft tissue,

Blue = pre-operative bone, Yellow = post-operative bone. (c) implant position for screw retained and (d) cement retained.

Digital implant placement and need for additional grafting

Astra EV 4.2mm x 9mm straight implants were identified as the ideal implant size and length for the central incisor and premolar regions, while an Astra EV 3.6mm x 9mm straight implants were utilized in the maxillary lateral incisor position. Implants were digitally placed in the ideal prosthetic position for a screw retained restoration as determined by the preoperative tooth position (Figure 9c). The site was judged to need additional grafting if the implant surface was exposed outside of the bony housing or had less than 1mm of bone remaining between the implant and the buccal plate. The implant was then positioned to allow for maximum utilization of the residual bone volume, while still allowing for placement of a cement retained restoration (Figure 9d).

Measurement Error Calculations.

To determine the error in initial CBCT alignment, the initial postoperative scan and corresponding bone model segmented in the same position from one subject was imported into 3D Slicer 4.6. The same scan and model were reimported, rotated and resampled at this new orientation, creating two misaligned images. Using the 'Landmark Registration' module the two scans were aligned using an affine registration, using landmarks as listed prior. The transform was hardened, transform coordinates saved, and the now aligned scans saved as a .nrrd file. Using the 'Transform Module', the same transform coordinates were applied to the rotated model and hardened, producing a model in the same spatial orientation as the CBCT transform. Next, using the 'Model to Model Distance' function a new .vtk model was

produced, giving the absolute (Hausdorff) distance offset between the two models (error in CBCT registration/alignment). The ‘Mesh Statistics’ module was then used to export these results. The same protocol was used utilizing the pre-and post-operative scans of an individual to ascertain the alignment error of CBCT scans taken at different time points.

Registration error of the soft tissue models was calculated in a similar fashion, where the same model in different orientations from one patient was imported and aligned using the ‘CMF Surface Registration’ module, and an absolute difference was calculated using the ‘model to model distance’ and ‘mesh statistics’ module.

Error in segmentation was calculated by segmenting the same CBCT scan of two patient’s multiple times on different days using ITK Snap, using the same procedure described in the segmentation process. The files were exported as .vtk files and imported into 3D Slicer 4.6. As all models were already in the same spatial orientation, they were all cropped in the same ROI using the ‘Easy Clip’ module. The volumes were calculated using the ‘Models’ module. The average volume difference (mm^3) and average (%) difference were calculated, indicating the amount of error in the segmentation process.

Linear measurement errors were calculated by repeating the linear measurements in the same patient 3 times, and the average difference in measurements calculated and recorded.

To ensure an accurate representation of volume calculated by the software, a fixed volume steel cube of fixed dimensions was measured three times with a digital calliper to obtain a true volume. The cube was then placed on a flat base and scanned

using the 3 Shape D810 optical scanner and the stl file imported into 3d Slicer. Following this the base was removed using the 'easy clip' module, and the volume calculated using the 'models' module. A comparison was then made to the actual true volume calculated.

Statistical analysis

All data was inputted into SPSS software (SPSS Ver. 22, IBM). Mean, standard deviations and 95% confidence intervals were computed for all continuous variables. For all subsequent statistical analysis, a p-value set at 0.05 was considered statistically significant.

The variance in baseline variables age and buccal plate thickness in each group was first compared using a homogeneity of variance test. Subsequently each group was compared using a one-way ANOVA, and if required post-hoc Bonferroni correction or Tamhane's T2 multiple comparisons tests were applied. Baseline variables gender and tooth type were assessed using a Fisher's Exact test.

Change in total, buccal and palatal bone and soft tissue volume, along with the linear changes in height and width of the soft tissue was first compared using a homogeneity of variance test. Subsequently each group was compared using a one-way ANOVA, and if required post-hoc Bonferroni correction or Tamhane's T2 multiple comparisons tests were applied. To compare the combined results of all grafting groups to the control group, an independent samples t-test was undertaken.

To assess the differences in need for additional grafting, a Fisher's exact test was performed.

The relationship between the average buccal plate thickness with total and buccal bone volume loss and soft tissue volume loss was assessed using Pearson's correlation.

RESULTS

Baseline characteristics

12 patients were enrolled and completed the study from April 2016 until March 2017. Reasons for extraction included endodontic reasons such as cracked tooth (2/12), dental caries (4/12), fractured tooth (6/12). Baseline demographic and preoperative data is listed in Table 1. Due to the small sample size and large standard deviations, each group was not statistically different to each other in regards to age, gender, tooth type, and mean buccal plate thickness (Table 1).

	Allograft	Alloplast	Xenograft	Control	All Patients	p-value
Number of teeth	3	3	3	3	12	
Mean Age (years)	47.3 ± 4.5	63 ± 6.9	50 ± 14.9	58.3 ± 17.2	54.7 ± 12.2	0.412
Gender						0.836
Male	2	3	1	2	8	
Female	1	0	2	1	4	
Tooth Type						0.836
Incisor	1	0	1	1	3	
Canine	0	0	0	1	1	
Premolar	2	3	2	1	8	
Mean Buccal Plate Thickness (mm ± sd)						
2mm	0.9 ± 0.2	2.6 ± 1.7	1.5 ± 1.1	0.6 ± 0.1	1.4 ± 1.0	0.158
4mm	1.0 ± 0.2	1.6 ± 0.9	0.7 ± 0.2	0.5 ± 0.1	0.9 ± 0.6	0.086
6mm	0.9 ± 0.3	2.0 ± 1.1	1.1 ± 0.5	0.6 ± 0.1	1.2 ± 0.7	0.132

Table 1: baseline characteristics

Measurement/Registration Error

Absolute error in CBCT alignment/registration and soft tissue model registration are listed in Table 2.

	Min (mm)	Max (mm)	Mean ± S.D(mm)
CBCT registration error (same image)	0.000	0.149	0.041 ± 0.030
CBCT registration error (pre-to post image)	0.000	1.011	0.077 ± 0.100
Soft tissue registration error (same model)	0.000	0.130	0.040 ± 0.029

Table 2: Absolute error in alignment/registration in mm

The average error built into the alignment process was 0.041mm. When a pre- and post-operative scan are superimposed, the error value increases to 0.077mm, which in comparison to the voxel size of 0.3mm is minimal, but highlights the minor differences seen in consecutive CBCT scans at different time points, despite the area of assessment not changing.

Segmentation Error

The pre-and post-operative CBCT's of two patients was segmented at least 3 times each. The range of error in segmentation in mm^3 and percentage change of the average volume is listed in table 3.

	Min	Max	Mean ± sd
Pre-op			
mm3	-2.72	2.43	0.00 ±1.81
%	-0.57	0.45	0.00 ±0.35
Post-op			
mm3	-1.71	2.94	0.00 ±1.58
%	-0.31	0.46	-0.02 ± 0.21

Table 3: Range and standard deviation of the difference in segmentation volume (segmentation error).

The error in segmentation in the preoperative images was not largely different to the post-operative images, suggesting that creating a line in each slice to 'fill in' the socket did not adversely affect the segmentation outcome. The error in segmentation was relatively small ranging from -2.72 to 2.94 mm^3, or -0.57 to 0.46% of the total volume. This suggests that the segmentation process utilized in this study cannot detect a difference of $3mm^3$ in magnitude.

Linear Measurement Error

The linear measurements were repeated three times in one patient and the average distance found. The deviations of each individual measurement to this average measurement was calculated, producing an average linear measurement error of 0.04mm. Despite this small difference, the software is not able to measure distances below a 0.10mm threshold, and so the linear measurement error would then theoretically lie between 0.04-0.10mm.

Volume Calculation Error

The physical dimensions of a metal cube (Figure 11) was measured with a digital calliper 3 times, and the dimensions averaged. The average dimensions were 12.70 x 12.70 x 12.71mm, giving a calculated volume of 2050.00mm^3. Following software manipulation of the .stl file, the calculated volume by the software was 2047.98mm^3. This represented an underestimation of the actual volume by 0.1%.

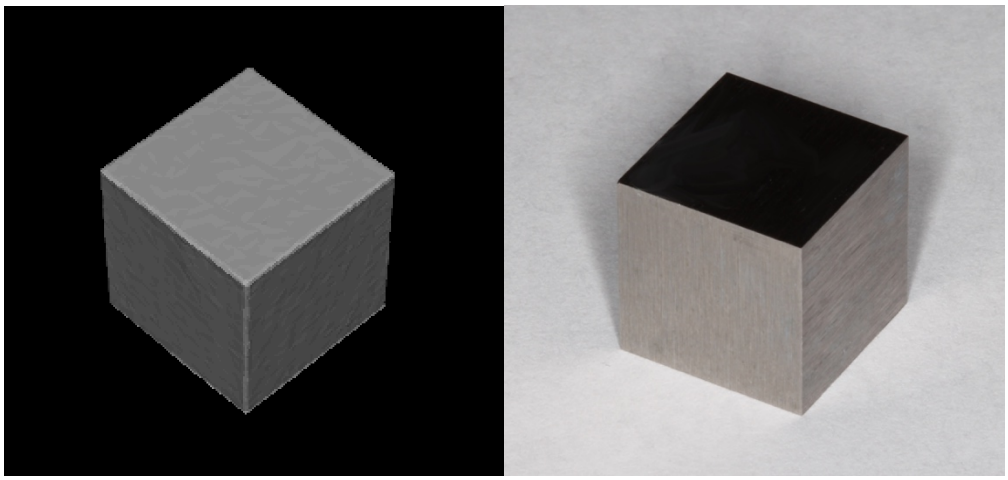


Figure 11: Metal cube used for volume calculation error – digital model of cube (left) and actual cube (right)

Change in Bone and Soft Tissue Volume

Placement of a graft post-extraction allowed retention of more bone volume, with the ungrafted control group losing 1.2x more bone (Table 4, 6, Figure 12). When comparing all treatment groups to each other, no difference in volumetric changes were seen, indicating that one graft did not perform better than another. When the ridge was divided into buccal and palatal portions (Table 5, 7), sites which were not grafted showed approximately 1.7x more buccal bone volume loss than the grafted groups (Figure 13). These results were not statistically significant. Grafted sites and ungrafted controls showed similar volume losses in the palatal portion. When a graft was not placed, 50% more soft tissue loss was seen than if it was grafted (table 8 and figure 14). These differences were not statistically significant. No statistical significance between the different grafting materials were identified.

	Change in Total Bone Volume (%)		
Group	Mean ± sd	95% CI	p-value
Grafted Sites	11.05 ± 4.39	7.68 – 14.43	0.444
Allograft	10.49 ± 5.93	-4.24-25.22	0.728
Alloplast	13.07 ± 5.41	-0.37-26.51	
Xenograft	9.60 ± 1.69	5.39-13.81	
Ungrafted Control	13.54 ± 5.73	-0.70-27.79	*

Table 4: Change (%) in Total Bone Volume

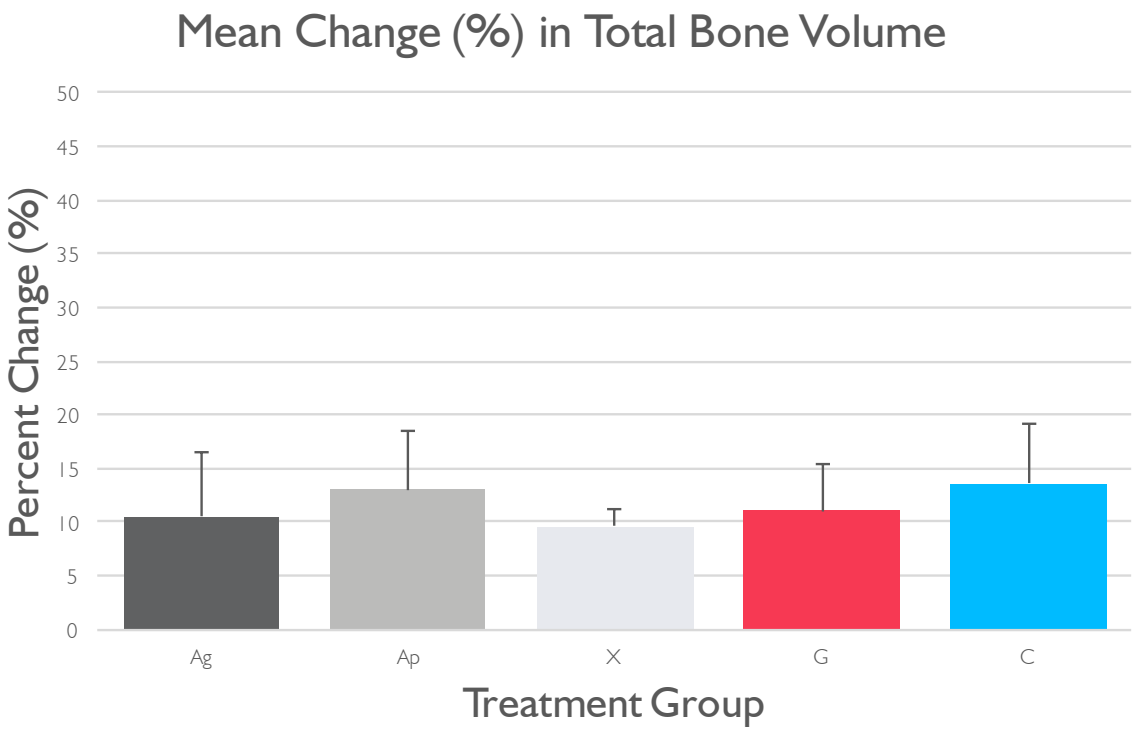


Figure 12: Mean change (% ± sd) in total bone volume

	Change in Buccal Bone Volume (%)			Change in Palatal Bone Volume (%)		
Group	Mean ± sd	95% CI (mm)	p-value	Mean ± sd	95% CI	p-value
Grafted Sites	16.65 ± 7.03	11.25-22.05	0.440	7.03 ± 4.13	3.85-10.20	0.501
Allograft	19.44 ± 11.83	-9.95-48.83	0.557	5.83 ± 3.64	-3.20-14.87	0.622
Alloplast	15.97 ± 6.19	0.59-31.35		9.24 ± 5.53	-4.50-22.99	
Xenograft	14.54 ± 0.69	12.83-16.26		6.00 ± 3.63	-3.03-15.03	
Ungrafted Control	28.58 ± 21.60	-25.07-82.24	*	5.23 ± 2.54	-1.08-11.54	*

Table 5: Change (%) in Buccal and Palatal bone volume

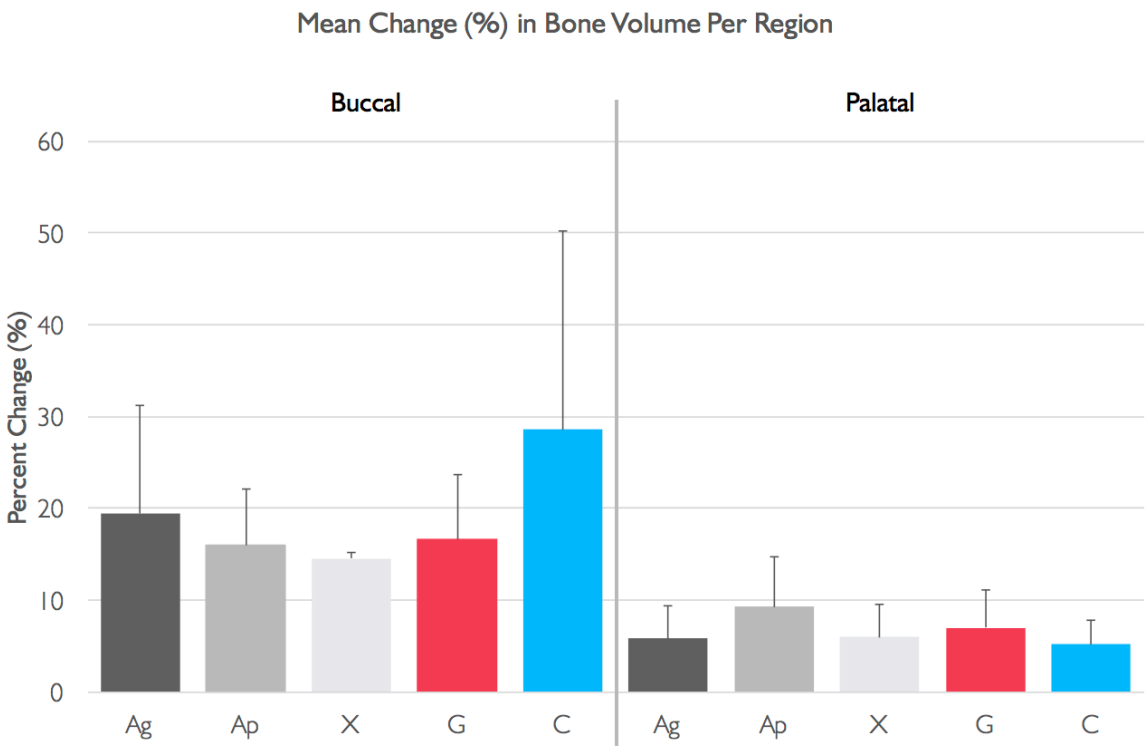


Figure 13: Mean change (% ± sd) in bone volume per region

	Change in Total Bone Volume (mm^3)		
Group	Mean ± sd	95% CI	
Grafted Sites	92.41 ± 45.88	57.15-127.68	0.598
Allograft	91.64 ± 51.97	-37.45-220.73	0.585
Alloplast	121.94± 53.36	-10.62-254.50	
Xenograft	63.65 ± 17.92	19.14-108.16	
Ungrafted Control	111.65 ± 75.07	-74.83-298.12	*

Table 6: Change (mm^3) in total bone volume

	Change in Buccal Bone Volume (mm^3)			Change in Palatal Bone Volume (mm^3)		
Group	Mean ± sd	95% CI	p-value	Mean ± sd	95% CI	p-value
Grafted Sites	54.71 ± 20.03	39.32-70.10	0.525	35.25 ± 25.43	15.70-54.79	0.383
Allograft	58.55 ± 30.76	-17.86-134.96	0.571	33.09 ± 21.54	-20.42-86.60	0.537
Alloplast	66.36 ± 4.41	55.41-77.31		48.21 ± 37.83	-45.77-142.19	
Xenograft	39.22 ± 7.26	21.17-57.26		24.43 ± 16.03	-15.38-64.25	
Ungrafted Control	90.49 ± 80.93	-110.55-291.52	*	21.16 ± 9.54	-2.54-44.87	*

Table 7: Change (mm^3) in Buccal and Palatal bone volume

	Change in Soft Tissue Volume (%)		
Group	Mean ± sd	95% CI	p-value
Grafted Sites	23.61 ± 7.45	17.88-29.34	0.076
Allograft	28.23 ± 11.20	0.39-56.07	0.273
Alloplast	21.21 ± 4.80	9.28-33.14	
Xenograft	21.38 ± 13.20	8.94-33.81	
Ungrafted Control	35.36 ± 13.20	2.57-68.14	*

Table 8: Change (%) in Soft tissue volume

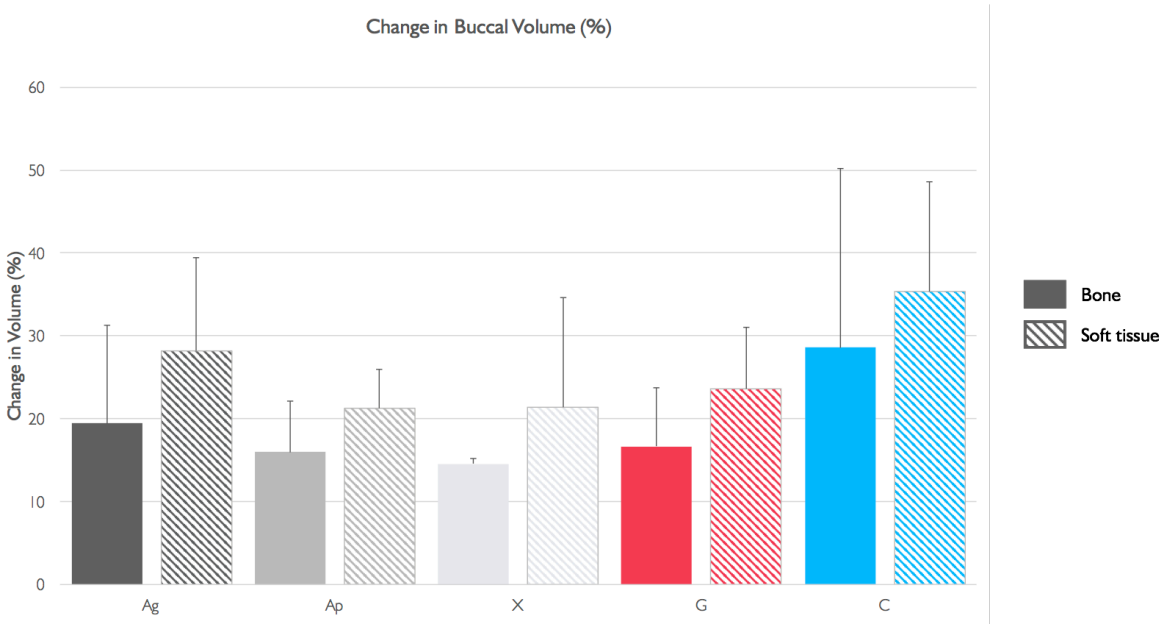


Figure 14: Mean change (% ± sd) in buccal bone vs buccal soft tissue volume

	Change in Soft Tissue Volume (mm^3)		
Group	Mean ± sd	95% CI	p-value
Grafted Sites	82.32 ± 28.61	60.32-104.31	0.072
Allograft	99.44 ± 48.93	-22.11-220.99	0.232
Alloplast	74.82 ± 4.00	64.89-84.76	
Xenograft	72.69 ± 14.22	37.37-108.01	
Ungrafted Control	121.73 ± 32.17	41.82-201.63	*

Table 9: Change (mm^3) in Soft Tissue Volume

Change in Bone and Soft Tissue Linear Dimensions

Sites in the ungrafted control group lost more bone and soft tissue width and height than when a graft was used. Ungrafted sites lost an additional 1.4x to 1.9x more bone width (Table 10 and Figure 15), and 1.3x to 1.5x more soft tissue thickness (Table 10 and Figure 15). These differences, however, were not statistically significant. No statistically significant differences seen between the different grafting materials were identified.

Change in Bone Ridge Width (mm)					
	Region	Group	Mean (± sd)	95% CI	p-value
Bone	2mm	**Grafted Sites**	1.23 ± 0.76	0.65-1.82	0.725
		Allograft	0.87 ± 0.98	-1.57-3.30	0.822
		Alloplast	1.20 ± 0.87	-0.97-3.37	
		Xenograft	1.63 ± 0.38	0.69-2.57	
		Ungrafted Control	1.73 ± 2.12	-3.54-7.00	*
	4mm	**Grafted Sites**	0.64 ± 0.63	0.16-1.13	0.613
		Allograft	1.03 ± 0.80	-0.96-3.03	0.219
		Alloplast	0.30 ± 0.56	-1.08-1.68	
		Xenograft	0.60 ± 0.46	-0.54-1.74	
		Ungrafted Control	1.23 ± 1.70	-3.00-5.47	*
Soft Tissue	2mm	**Grafted Sites**	0.66 ± 0.50	0.27-1.04	0.654
		Allograft	0.47 ± 0.47	-0.71-1.64	0.718
		Alloplast	0.53 ± 0.47	-0.64-1.71	
		Xenograft	0.97 ±0.59	-0.49-2.42	
		Ungrafted Control	1.00 ± 1.13	-1.80-3.80	*
	4mm	**Grafted Sites**	0.51 ± 0.35	0.22-0.80	0.862
		Allograft	0.40 ± 0.28	-2.14-2.94	0.975
		Alloplast	0.47 ± 0.21	-0.05-0.98	
		Xenograft	0.63 ±0.55	-0.73-2.00	
		Ungrafted Control	0.67 ± 1.34	-2.67-4.00	*

Table 10: Loss (mm) in Horizontal Linear bone and soft tissue width

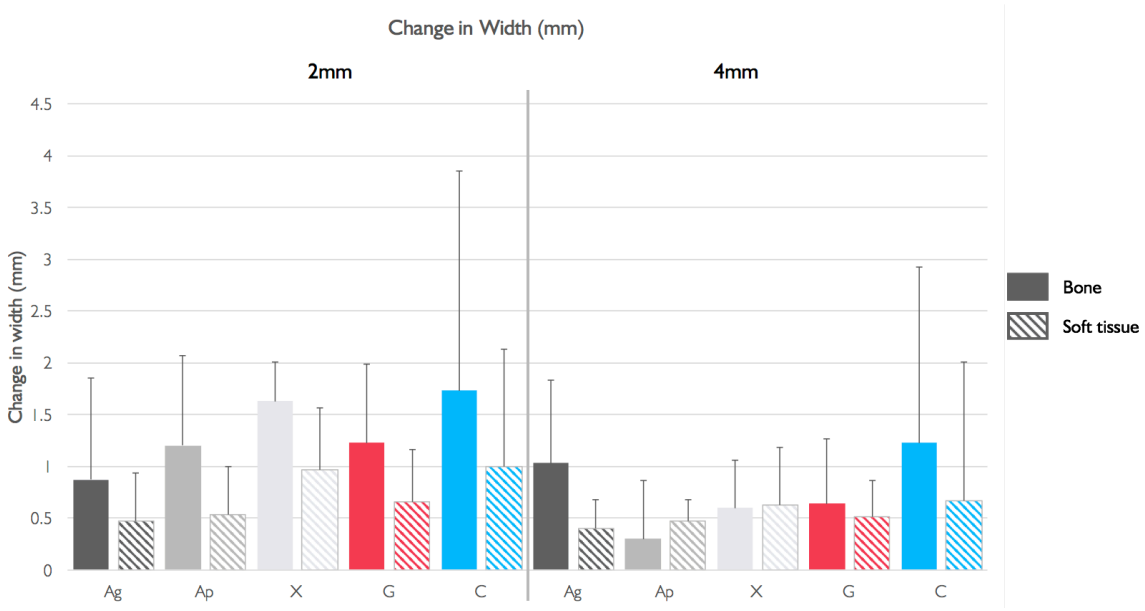


Figure 15: Mean change (mm ± sd) in linear bone and soft tissue width

Ungrafted control sites had 2.8x, 1.8x, and 1.8x more vertical bone height loss in the mid-buccal, mesial and distal regions respectively, than those which received grafting (Table 11, Figure 16,17). 1.0mm loss of palatal bone height in the grafted groups and 0.9mm loss of palatal bone height in the ungrafted control was seen. These results were not statistically significant. A similar scenario was seen in the soft tissue height changes, showing 2.1x, 1.4x, 1.5x and 1.3 x more loss in soft tissue height at the mid-buccal, mid-palatal, mesial and distal regions, respectively (Table 12, Figure 16,17). Again, these differences were not statistically significant. There were no statistically significant differences between the different bone grafting materials.

		Change in Bone height (mm)		
Region	**Group**	**Mean ± sd**	**95% CI**	**p-value**
Buccal	**Grafted Sites**	1.26 ± 0.74	0.68-1.83	0.078
	Allograft	1.23 ± 1.04	-1.35-3.82	0.431
	Alloplast	1.10 ± 0.38	-1.38-3.58	
	Xenograft	1.43 ± 0.21	0.92-1.95	
	Ungrafted Control	3.50 ± 3.58	-5.39-12.39	*
Palatal	**Grafted Sites**	1.00 ± 0.41	0.68-1.31	0.795
	Allograft	1.00 ± 0.40	0.01-1.99	0.994
	Alloplast	0.97 ± 0.45	-0.15-2.09	
	Xenograft	1.03 ± 0.55	-0.33-2.40	
	Ungrafted Control	0.90 ± 0.95	-1.47-3.27	*
Mesial	**Grafted Sites**	1.01 ± 0.91	0.31-1.71	0.248
	Allograft	1.47 ± 0.55	0.10-2.83	0.460
	Alloplast	1.07 ± 0.70	-0.68-2.81	
	Xenograft	0.50 ± 1.34	-2.84-3.84	
	Ungrafted Control	1.80 ± 1.15	-1.06-4.66	*
Distal	**Grafted Sites**	1.01 ± 0.91	0.31-1.71	0.248
	Allograft	1.47 ± 0.55	0.10-2.83	0.460
	Alloplast	1.07 ± 0.70	-0.68-2.81	
	Xenograft	0.50 ± 1.35	-2.84-3.84	
	Ungrafted Control	1.80 ± 1.15	-1.06-4.66	*

Table 11: Change (mm) in bone height

		Change in Soft tissue height (mm)			
Region	**Group**	**Mean ± sd**	**95% CI**	**p-value**	
Buccal	**Grafted Sites**	1.74 ± 0.70	1.21-2.28	0.321	
	Allograft	1.60 ± 1.15	-1.26-4.46	0.034*	0.073
	Alloplast	2.07 ± 0.38	1.13-3.01		0.214
	Xenograft	1.57 ± 0.49	0.34-2.79		0.670
	Ungrafted Control	3.73 ± 0.95	1.37-6.09	*	
Palatal	**Grafted Sites**	1.10 ± 0.49	0.72-1.48	0.202	
	Allograft	1.20 ± 0.36	0.30-2.10	0.643	
	Alloplast	1.00 ± 0.36	0.10-1.90		
	Xenograft	1.10 ± 0.82	-0.93-3.13		
	Ungrafted Control	1.53 ± 0.42	0.50-2.57	*	
Mesial	**Grafted Sites**	0.89 ± 0.78	0.29-1.49	0.153	
	Allograft	1.30 ± 1.04	-1.29-3.89	0.293	
	Alloplast	1.03 ± 0.55	-0.33-2.40		
	Xenograft	0.33 ± 0.55	-1.03-1.70		
	Ungrafted Control	1.30 ± 0.00		*	
Distal	**Grafted Sites**	1.16 ± 0.86	0.49-1.82	0.260	
	Allograft	1.53 ± 1.00	-0.95-4.02	0.695	
	Alloplast	0.93 ± 0.76	-0.95-2.81		
	Xenograft	1.00 ± 1.04	-1.59-3.59		
	Ungrafted Control	1.57 ± 0.32	0.77-2.36	*	

Table 12: Change (mm) in soft tissue height

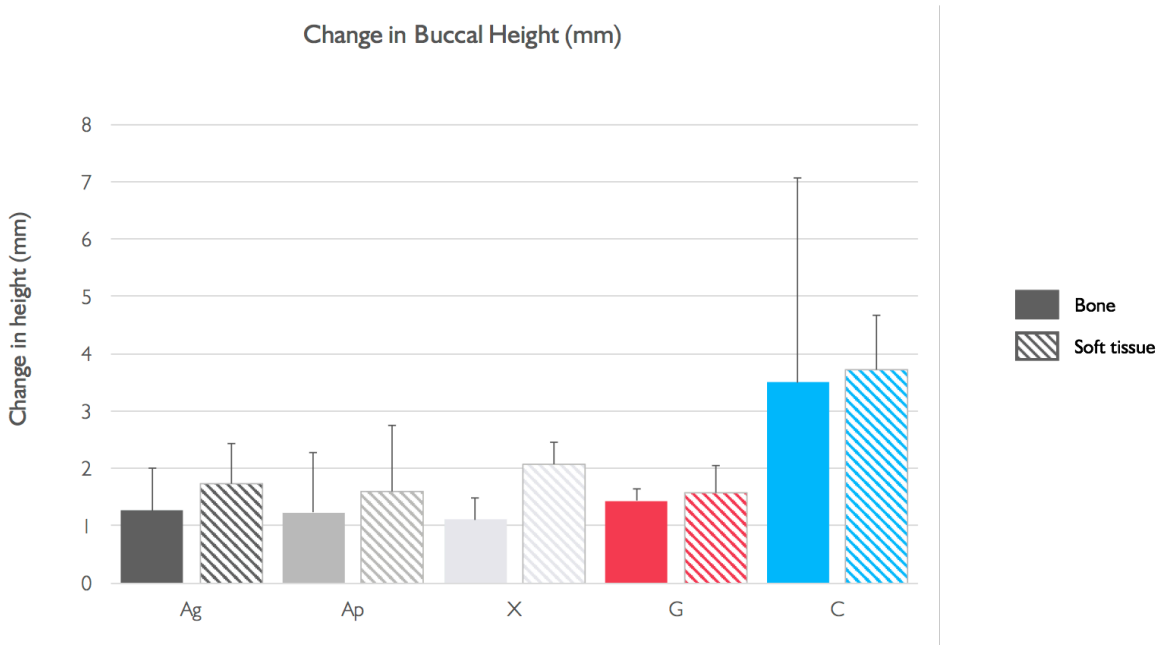


Figure 16: Mean change (mm ± sd) in linear mid buccal bone and soft tissue height

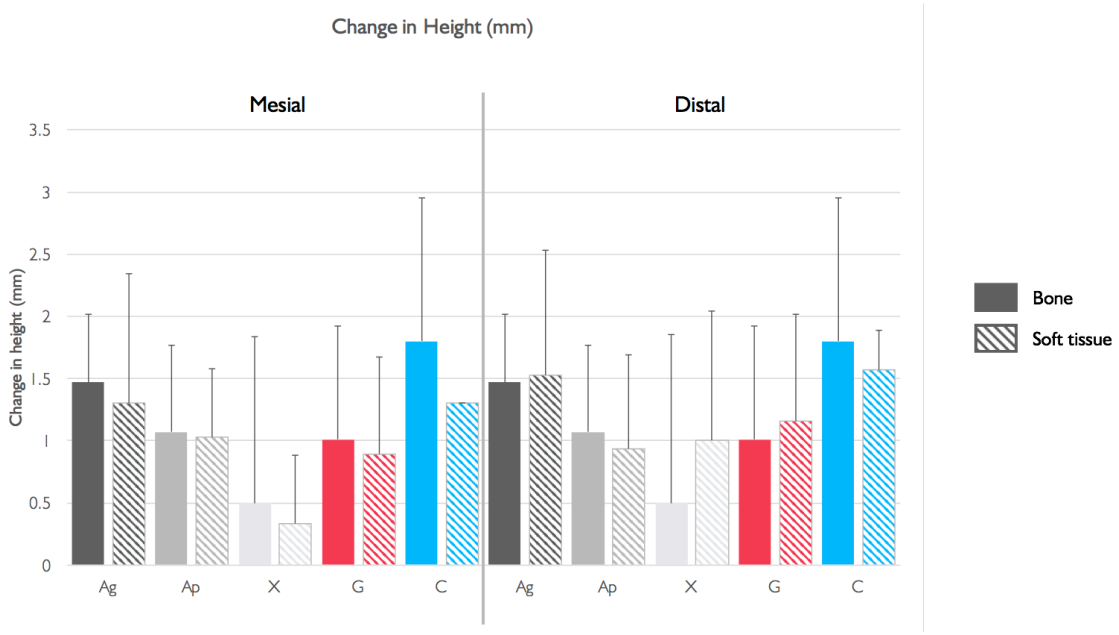


Figure 17: Mean change (mm ± sd) in linear mesial and distal bone and soft tissue height

Bone and Soft Tissue Loss Color Maps

Visualization of the spatial linear changes using a color map can be seen in Figure 18. All groups produced similar amounts of bone and soft tissue loss, occurring in the coronal most aspect of the ridge, except for one control group case, which lost a considerable amount of facial bone and soft tissue loss down to a level near the apex of the tooth. While more severe soft tissue loss was frequently identified in the ungrafted control group, the results were not statistically significant.

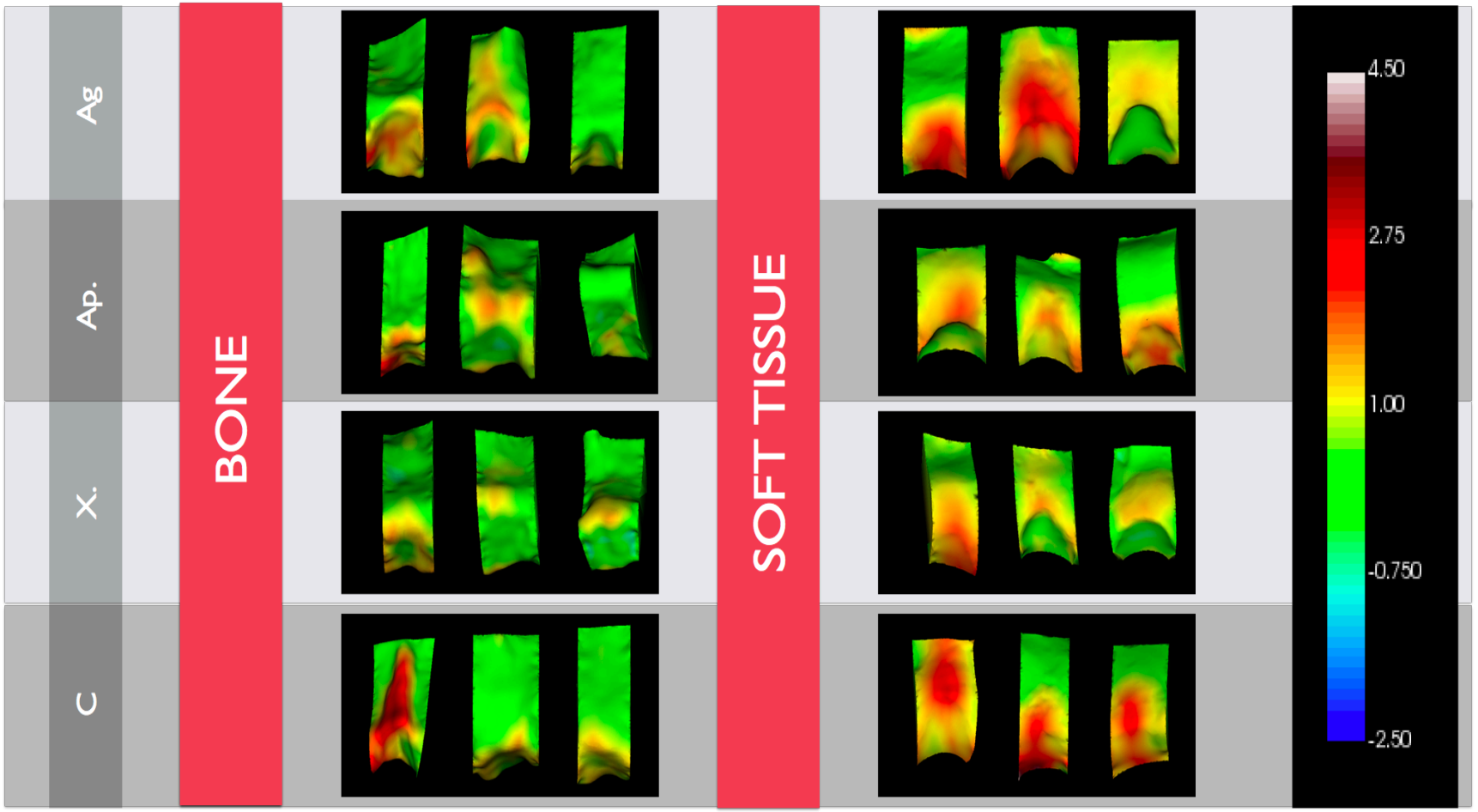


Figure 18: Color maps displaying the spatial linear change (mm) in bone and soft tissue contour in each treatment group. Areas in red represent bone loss

Correlation of Buccal Plate Thickness to Post-Operative Healing Outcomes

The influence of the average buccal plate thickness on the total and buccal bone volume loss, and soft tissue volume loss was assessed using a Pearson correlation (Table 13). When the control group was assessed, a strong negative correlation between initial average buccal plate thickness and volume loss was identified, i.e. the thinner the buccal plate thickness, the more volume loss seen. However, when a graft was introduced, there was a weak negative correlation, suggesting that the addition of a graft counteracted this negative effect of a thin buccal plate. Due to the small sample size in the study the results are not statistically significant.

Correlation of Average Buccal Plate Thickness to Volume loss (%)

	Pearson Correlation	p-value
All grafts		
Average Buccal plate thickness vs Total Bone Volume Loss (%)	**-0.091**	0.816
Average Buccal plate thickness vs Buccal Bone Volume Loss (%)	-0.353	0.352
Average Buccal plate thickness vs Soft Tissue Volume Loss (%)	-0.272	0.478
Control		
Average Buccal plate thickness vs Total Bone Volume Loss (%)	**-0.906**	0.279
Average Buccal plate thickness vs Buccal Bone Volume Loss (%)	-0.957	0.163
Average Buccal plate thickness vs Soft Tissue Volume Loss (%)	-0.943	0.217

Table 13: Correlation of initial average buccal plate thickness to healing outcomes at 3 months

Ability to Place a Dental Implant and Need for Additional Augmentation

Overall, only 3 out of 12 cases hypothetically required additional grafting at the time of implant placement if the restoration was to be screw retained. Of these cases, 1 was in the control group, 1 in the alloplast group, and 1 in the xenograft group (Figure 19). Of the cases needing grafting, the case from the control group required significant grafting due to exposure of the majority of the facial surface of the implant, while the two in the xenograft and alloplast group required only minor grafting in the apical area. Standard 4.2mm x 9mm (or 3.6mm x 9mm in lateral incisor region) Astra EV implants were able to be placed in all cases despite the need for additional grafting.

Comparing the control group to all groups individually ($p=0.418$), and to all grafting groups combined ($p=0.543$), the need for additional grafting at time of implant placement was not statistically different between groups, indicating that sites which did or did not receive a graft were able to have an implant placed at the 3-month time period without the need for additional grafting.

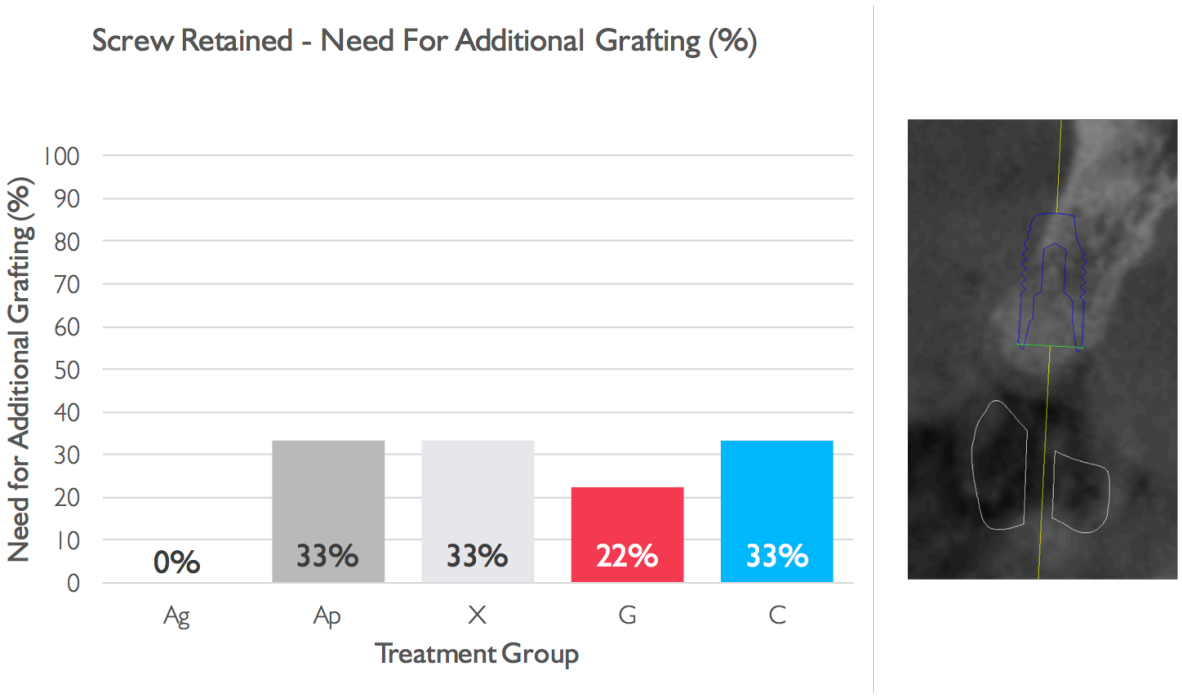


Figure 19: Percentage of subjects needing additional grafting at time of implant placement if placed for a screw retained restoration

If the implants were positioned to take advantage of the residual bone volume, allowing a cement retained restoration, only 1 subject in the control group required additional grafting at time of implant placement (Figure 20). Again, this control group subject required major grafting. Statistical analysis comparing all groups to each other ($p=0.192$) showed no statistical differences in the need for additional grating between all groups, while the combined grafting group was statistically less likely to need additional grafting when compared to the control group ($p=<0.001$). This indicated that if a site was not grafted, placement of an implant in a restorable yet non-screw retained position was 33% more likely to require a graft than when a site was grafted.

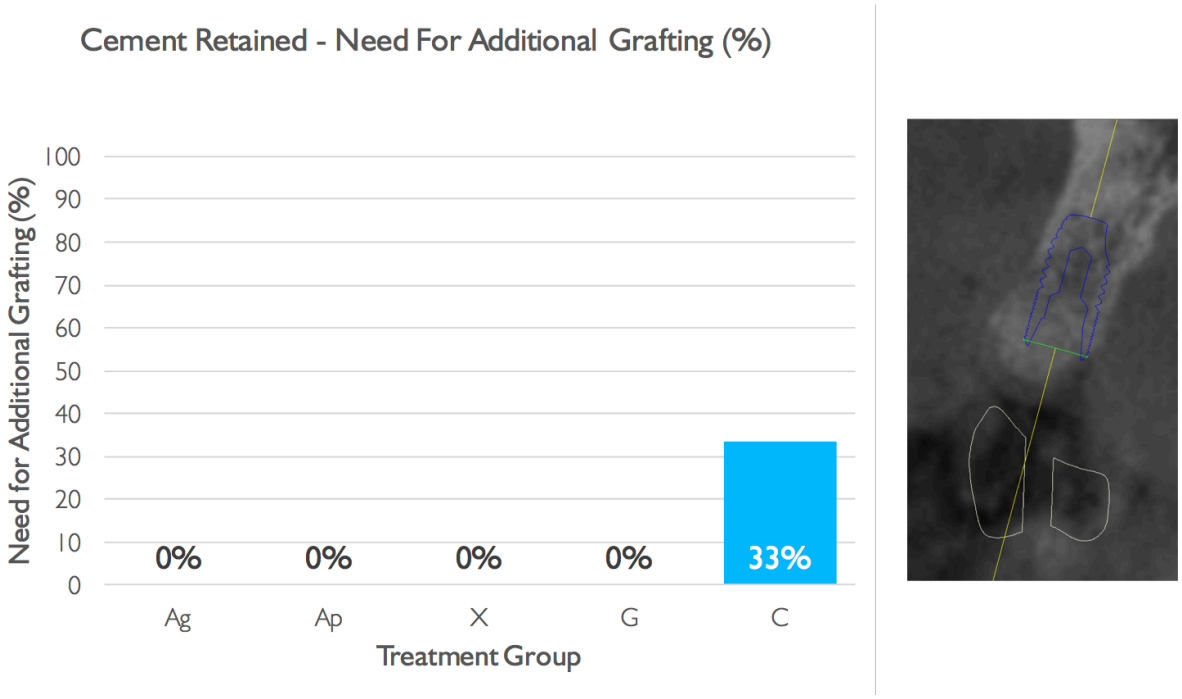


Figure 20: Percentage of subjects needing additional grafting at time of implant placement if placed for a cement retained restoration

DISCUSSION

Loss of buccal bone and soft tissue volume can complicate future implant placement, necessitating additional more involved and costly grafting procedures to produce a satisfactory esthetic outcome. While a non-grafted socket can and has been shown to heal uneventfully, providing a satisfactory ridge for future implant placement, the predictability of achieving this outcome is called into question. Nevins *et al.* attempted to see if they could predict if a non-grafted socket healed with a positive outcome, however they found that they could not predict the path of healing, and found that when a site was not grafted, 71% showed ridge dimensional loss of more than 20%, which could complicate future implant placement (64). In daily clinical practice, we strive for not only success but predictable success, and Nevins and others (including this study) have shown that undertaking in a ridge preservation procedure can more predictably result in a more positive healing outcome.

Tissue Volume Change

The results of this current study suggest that use of a membrane alone with no underlying bone graft resulted in an additional 12% more bone and soft tissue volume loss and 2x more vertical bone and soft tissue height loss, compared to grafted sites. Secondly, the choice of grafting material did not affect the final outcome, suggesting

that all grafting products perform similar. These results highlight the beneficial effect of a graft material on the maintenance of the wound space, along with additional clot stability during the early healing phases of the extraction socket. The additional support offered by the grafting material ultimately led to a reduction in the amount of ridge volume loss. These results were not significant, with the small sample size affecting the statistical outcome. The overall results, however, are in agreeance with the results of Brkovic *et al.* and Fickl *et al.* who also highlighted the importance of a graft in preventing wound collapse (82, 86), reducing the volume of alveolar ridge reduction post-extraction.

Following the 3-month healing period, a total volume loss of 92.41 mm^3 (11.05%) was seen in the grafting group. This was notably different to what was seen by Barone *et al.* who saw a reduction of 244 mm^3 and 349mm^3 when a collagenated porcine or cortical porcine graft respectively were used (63). However, Agbaje *et al.* found that the mean socket volume of maxillary and mandibular incisors, canines and premolars was approximately 225 mm^3 when measured via CBCT and validated by physical measurement on a dry skull (138). These differences between studies may be due to differing measurement methods.

Sbordone *et al.* also evaluated bone volume loss with or without a ridge preservation procedure, in the premolar and molar regions (65). After 6 months of healing, the grafted group experienced 72mm^3 or 9.9% bone volume loss, compared to 274mm^3 or 34.8% bone volume loss in the no graft group. These results are more in concordance with the current study, where a 92.41mm^3 bone volume loss (11.05%) occurred following ridge preservation. This highlights the positive effect a ridge

preservation has on limiting alveolar ridge volume reduction. When a graft was not used in the current study, the volume loss was smaller (111.65mm^3 and 13.54%) than the no graft group in the Sbordone study. This could suggest a positive but small effect of the membrane on healing, which has also been suggested in a histological study by Pellegrini (57).

Bone only makes up one half of the optimal esthetics equation, with the soft tissue making up the other. Thalmair *et al*. evaluated the loss in the buccal soft tissue volume after 4 months of healing, following use of a xenograft and FGG, FGG alone, xenograft alone and spontaneous healing alone (71). In the xenograft and FGG group, an average volume loss of 19.92 $\pm$ 3.77mm^3 was seen; the FGG alone produced 24.89 $\pm$ 7.68mm^3 loss in volume; graft alone 32.89 $\pm$ 6.96mm^3 volume loss; and the spontaneous healing alone lost 41.41 $\pm$ 15.96mm^3 in volume. The amount of soft tissue loss identified by Thalmair was smaller than what was observed in the current study (average soft tissue loss in all graft groups 23.61% and 82.32mm^3 loss in volume; 121.73mm^3 and 35.36% in the no graft group). This difference could be due to a difference in ROI. The ROI identified by Thalmair included a band of tissue facial of the socket up to the muco-gingival junction, to the center of the papilla in a mesial and distal dimension, and did not include interproximal tissue. This region is considerably smaller than what was used in the current study which included soft tissue up to the root of the adjacent teeth, the entire facial portion of the papilla, and to the depth of the vestibule that was recorded. A larger ROI might capture more change and provide additional details on buccal soft tissue changes. The current study also produced what was called an ideal soft tissue volume, attempting to produce an

ideal esthetic soft tissue profile for comparison, as based off the original tooth and gingival contour. This may also explain the difference seen in soft tissue loss between the two studies.

Linear Tissue Change

Historically, ridge preservation studies have only assessed linear dimensional changes post extraction. At 2mm and 4mm, horizontal reductions of 1.23mm and 0.64mm were seen in the grafted groups, and 1.73mm and 1.23mm in the control group, the differences not reaching statistical significance. The magnitude of change seen in the grafted groups was similar to what was seen by Barone *et al.* (1.8-2.5mm) (63) and Pang *et al.* (1.11 ±0.13mm) (69), however substantially greater ridge width reductions (4.5mm) were identified by Barone in ungrafted control sites (41) (Table 14). Differences in surgical technique, the use of a barrier membrane, and low subject numbers in the current study can account for these differences.

	Grafted	**Nongrafted**
Current Study	1.23mm	1.73mm
Barone *et al.*	2.50mm	4.50mm
Pang *et al.*	1.11mm	
Caardaropoli *et al.*	0.71mm	4.04mm

Table 14: Comparison of Horizontal Bone Loss (mm)

Cardaropoli *et al.* utilized a DBBM and porcine collagen grafting material, assessing the linear dimensional change after 4 months of healing (29) (Table 14).

The control group lost an additional 3.3mm in ridge width when compared to the treatment group, amounting to a 7.23 $\pm$ 9.24% reduction in the grafted group, and 40.15 $\pm$ 8.29% in the control group. A systematic review by Avila-Ortiz *et al.* (87) found that not grafting resulted in only 1.95mm more ridge width reduction. Both studies presented linear dimensional changes considerably larger than what was seen in the current study, where in all groups that were grafted, only an additional 0.5mm were lost in the control group (when measured at the 2mm ridge height position), amounting to 13.5% lost in the treatment and 21.3% in the control group. The differences between groups however were not significant, and was highly influenced by the small sample size. Emphasis should be placed on the large standard deviation in the control group which suggests that with a larger number of subjects a similar magnitude of difference would be seen.

When a site was not grafted 2.24mm, 0.1mm, 0.79mm, and 0.79mm more bone height loss in the mid buccal, palatal, mesial and distal regions respectively was seen, representing double the amount of bone loss seen than if the site was grafted. Similarly, Barone *et al.* found an additional 2.9mm, 2.6mm, 0.2mm, and 0.1mm of vertical bone height when no grafting was performed, at the mid-buccal, palatal, mesial and distal sites respectively, however the magnitude of bone loss was higher (41) (Table 15). A similar pattern of soft tissue height loss was seen in the current study (1.99mm, 0.43mm, 0.41mm, 0.41mm), where more soft tissue height was lost when an area was not grafted, although these changes were smaller than the amount of bone lost, suggesting a minor increase in soft tissue thickness/compensation for bone loss, which was also demonstrated by Tan *et al.* (18) and Chappuis *et al.* (139).

Chappuis showed that subjects with a buccal plate less than 1mm in diameter saw 1.6mm of mid buccal vertical tissue height loss compared to 7.5mm in bone height and 0.8mm in horizontal bone loss and 1mm in horizontal soft tissue loss, while thick phenotypes lost only 1.4mm of soft tissue height compared to 1.1mm of bone, and 1mm of horizontal soft tissue thickness loss. The differences between the phenotypes was not significant, indicating that the thickness of the thin phenotypes increased following extraction. In fact, the thin bone phenotypes saw a soft tissue thickness increase of 4.8mm (7-fold increase), while the thick phenotype remained stable at 0.7mm, with minimal change over an 8-week healing period. They also indicated that 51% of the total dimensional soft tissue changes occurred within the first 2 weeks of healing.

	Buccal	**Palatal**	**Mesial**	**Distal**
Current Study	2.24mm	0.10mm	0.79mm	0.79mm
Barone *et al.*	2.90mm	2.60mm	0.20mm	0.10mm

Table 15: Comparison of Vertical Bone Loss (mm)

Chappuis *et al*. assessed the linear changes of anterior extraction sockets after 8 weeks of healing with no grafting, and found that overall 5.2mm of vertical bone loss occurred on the buccal aspect of the socket when a graft was not used. Correlations to the initial buccal plate thickness showed that a thin buccal plate (<1mm) allowed 7.5mm or 62.3% of vertical bone loss (140), while a thick wall phenotype (>1mm), showed only 1.1mm or 9.1%. Only 0.5mm of vertical bone loss was seen at the

interproximal sites. The Chappuis study illustrated that the central portion of the socket experienced the majority of the dimensional changes, a finding confirmed in this project, and highlighted the important role of buccal plate thickness on influencing bone remodeling. Cardaropoli *et al.* also highlighted this strong negative relationship (r=-0.752) between the buccal plate thickness and bone loss (29). They too, found that post-extraction socket grafting compensated for post-extraction alveolar ridge resorption, irrespective of initial buccal plate thickness. The mean buccal plate thicknesses in their study was 1.2mm, while Chappuis *et al.* had a mean buccal plate thickness of 0.8mm, both similar to what was seen in the current study. Similar to the current study, both studies demonstrated a strong negative correlation between the initial buccal plate thickness and bone loss (volume).

Graft Material Selection

When a graft was placed within the socket the negative effect of a thin buccal plate is reduced. Utilizing the principles of guided bone regeneration, placement of a graft maintains the would space, provides additional clot stability and imparts osteoconductive properties to the wound site, ultimately preventing soft tissue collapse into the wound as demonstrated by Chappuis (139), and maintaining alveolar bone width. Material selection does not seem to impact on the outcome of ridge preservation at 3 months, providing similar space maintaining abilities in the initial stages of healing. Atieh *et al.* came to similar conclusions in their recent systematic review which included 8 RCTs, comparing multiple techniques and materials. They stated that all materials and techniques produced a statistically significant reduction in ridge width and height loss compared to extraction alone, however there was no

difference seen between them (97). Contrary to this review and the current study, Jambhekar *et al.* suggested in their systematic review of 32 RCTs, that allografts and xenografts preserved ridge dimensions more adequately than alloplasts (103), however no meta-analysis was performed, and so the significance of these differences is not clear.

While material selection may not affect the gross anatomy following healing, histological healing differences may influence future implant placement. The histological differences seen between different graft materials between 3 and 7 months was analysed by De Risi *et al.* (104). 38 studies were included in this systematic review, utilizing allografts (mineralized and demineralized), xenografts, alloplasts, along with no grafting control groups. Up to a 7-month healing period, the amount of new bone formation between all groups was no different, and suggested that an implant could be placed at an earlier time point, 3 months, due to the stable histological characteristics. Although not statistically significant, a trend for more bone formation in the alloplast group, and less connective tissue in the allograft and alloplast groups was seen. Not surprisingly the alloplasts and xenografts showed the highest amount of residual grafting particles at 7 months, both approximately 37%, however this would largely depend on the specific material used and its resorption profile.

DBBM has been shown to have a slow resorption rate over time (141), and hence could influence the amount of space available for new bone and CT formation, although the significance of this is not clear. The question to be asked is how much vital bone is needed to support a dental implant during the initial healing, how does the presence of residual grafting particles influence primary stability and long term

implant osseointegration? Grafting with DBBM commonly results in a high residual particle content (47), however systematic reviews have shown that residual particles are rarely in contact with the implant surface. Higher volumes of vital bone have been seen in sites which do not receive a graft, however similar implant survival outcomes have been noted in those sites grafted and not grafted, suggesting that the presence of residual particles and lower amounts of vital bone do not negatively affect osseointegration (27, 40).

Some graft materials have additional osteoinductive properties, where bone formation can be induced through the release of growth factors. Demineralized allografts are one such product, in which the demineralization process allows the bioavailability of BMP's stored within the bone structure, potentiating bone formation. In the current study, osteoinduction through the release of BMP's in the allograft group did not seem to impart any benefit to the ridge when assessing dimensional change. This is also reflected in the work of Wood and Mealey, who showed that use of a demineralized human allograft produced no difference in final ridge width than if a mineralized graft was used, although the osteoinductivity of the source bone used in the study was low and could have affected the outcome (61). This is an important issue, as it has been shown that the amount of BMP release from human sourced allografts is variable, and dependent on the donor source (142-144). Human recombinant BMP-2 is now available, which allows for a consistent release profile of BMP-2, accelerating bone formation (145).

Osseointegration is a delicate interplay between initial primary stability, new bone formation, and long-term bone remodelling to establish and maintain integration. Residual graft particles may impart some effect of primary stability and could be advantageous, however excessive number of residual particles or overcondensation of graft particles, could obstruct the ingrowth of new bone. A mineralized:demineralized mix may provide an advantage, where the mineralized portions would be more slowly resorbed away, providing long term scaffolding and ridge maintenance, while the demineralized portion is more quickly resorbed, allowing for the ingrowth of new bone, and the possible release of osteoinductive growth factors. Borg and Mealey compared the effects of mineralized allograft and a 70:30 mineralized:demineralized allograft mix in ridge preservation procedures, finding that the combination graft group had 36.16% vital bone compared to 24.69% in the mineralized only group. They also found a lower mean percentage of residual graft particles (18.24 vs 27.04%) in the combination graft group(146). This combination of grafting materials may then produce a more ideal bone for osseointegration if an implant was placed at an earlier time period. Over time however this advantage may dissipate, with other grafting materials producing similar histologic outcomes (104).

Additional Grafting Needs

The need for additional grafting following ridge preservation procedures is not completely negated as ridge preservation procedures do not prevent all bone remodelling post-extraction (25). This study found that depending on the desired crown abutment connection (screw vs cement retained), ridge preservation reduces the possible need for additional grafting procedures. Those that were not grafted more

commonly required more extensive grafting at or prior to implant placement than those that received a ridge preservation procedure (minor grafting). This is echoed in other studies, reporting that those sites which were not grafted were between 2.5x and 14.5x more likely to need additional grafting (30, 40, 70, 112). This grafting not only included horizontal augmentation but vertical augmentation, including subantral sinus augmentation (30). These additional procedures can be costly for the patient, and providing a ridge preservation procedure can offer more predictable control over the healing and need for additional extensive grafting procedures.

Study Design

The three month follow-up time point was chosen in this study, as it represents a common time frame when implants are placed following extraction and ridge preservation, with similar survival rates seen than if it was placed at 6 months (117). It is also expected that the majority of the bone remodelling would have occurred as shown by Schropp *et al.* who demonstrated that 2/3 of the bone loss occurred within the first 3 months (17). Future histological changes in the bone after 3 months may be minimal (104), and so placement of a dental implant at 3 months is a viable option. Placement of an implant before this time period however, risks further recession post implant placement and adverse esthetic outcomes (117).

CBCT was used as the method of choice due to its non-invasive means for assessment of osseous changes. Studies by Ganguly *et al.,* Kim *et al.*, Timock *et al.* and Veyre-goulet *et al.* have shown that the accuracy of measurements made on CBCT scans are comparable to direct measurement made surgically and on embalmed and dried skulls (128, 129, 131, 147), with only a 1% difference in

measurements (148). However, when assessing volumetric changes, CBCT data can be affected by numerous factors such as scatter, orientational alignment, and challenges in delineating soft tissue from bone undergoing remodeling. Together, these aspects can produce errors in segmentation and alignment, reducing the 'threshold' in change that is able to be seen between treatment groups. This could have affected the ability of the current study to visualize any differences in preservation outcomes when comparing the different materials. If there were minor changes which were below the threshold of error, they would not be able to be visualized. The ultimate clinical relevance of these minor changes however, would come into question.

In the current study, open source software was used to register CBCT and soft tissue optical scan models. The use of 3D Slicer resulted in great accuracy with relatively small errors found in the registration process, ranging from a mean of 0.04 – 0.07mm for both bone and soft tissue. These results are on par with what was found by Kang *et al.* who used commercially available engineering software. They found that the average error when using different registration methods (bone surface registration, cusp tip, bony landmarks etc.) was 0.070 ± 0.707mm (149). The current study showed an error range of 0.040 ± 0.029 and 0.077 ± 0.100mm when soft tissue and CBCT images were registered respectively, representing a subvoxel level of accuracy. This suggest that use of an open source software like 3D Slicer was able to register images as accurate as commercially available CAD CAM engineering software.

Segmentation of the CBCT resulted in maximum absolute error of 2.72mm^3 or 0.57%. Windisch *et al.* evaluated the reproducibility and accuracy of volumetric measurements of an optical scanner and the true volume of a geometric complex form specimen (150). After repeated measures they found a difference of 1.5% between test and control groups, amounting to a difference of 2.5mm^3 or less. They accepted that these differences were minimal and that the accuracy of the 3D optical system was excellent. Given these results were produced using an optical scanner (which does not suffer from scatter artifacts, interference with soft tissue, etc.) and the true physical volume of the source was known, the error in segmentation of the current study was excellent, with the absolute difference in error being 2.72mm^3 or 0.57% of the average volume calculated.

The linear measurement error in a 3D volume compared to the true dimension has been shown in numerous other studies to be between 0.13 $\pm$ 0.09mm and 0.29 $\pm$ 0.20mm (151, 152), and the measurement error in this study is within these boundaries. However, the current study utilized linear measurements by registering and overlaying the pre-and post-operative segmented bone models on the pre-operative CBCT image. Using the segmentations as measurement points may introduce inaccuracies obtained through the segmentation process. Loubele *et al.* compared the differences in linear measurements when measuring from segmentation boundaries in both medical grade CT and 3 different CBCT machines (153). Similar to the current study, segmentation was completed utilizing a global threshold automatic segmentation process, however we also used manual segmentation to ‘tidy up’ the segmentation. With medical grade CT considered more

dimensionally similar to the true dimensions, the CBCT segmentations produced a statistically significant difference from the CT data varying between 0.05 ± 0.47mm to 1.2 ± 1.00mm, dependant on the CBCT machine used. It was also found that the mandible produced smaller differences between the imaging modalities than the maxilla, as well as anterior versus posterior segments, due to the regional differences in bone intensity, and lack of homogeneity in bone intensity levels.

In the current study, one global threshold for segmentation of all patients and images was chosen, and set at 400. This threshold choice could have affected the accuracy of the segmentations and hence the linear and volumetric measurements. Loubele *et al.* found that when an intensity of 276.8 was chosen, the maximum number of valid CBCT measurements peaked at 98%. When a higher intensity was used, differences between consecutive measurements was reduced, however the validity of these measurements was reduced by about 10%, indicating that the 400 threshold could yield an unreliable segmentation for about 10% of the bone surface (153). Other studies have suggested that individualized bone and patient thresholds may be a better approach (154, 155). This is relevant in the current study as a higher intensity level was used, along with an additional manual alteration in segmentation step which could reduce the true dimensional accuracy of the 3D models produced and hence the linear and volumetric assessments made. Despite this, error in volume as a result of segmentation was quite low at an absolute value of 3mm^3 or 0.5%. Considering that this was a comparison study between groups that underwent the same segmentation process, we do not think that this difference between the segmented dimensions to

the true dimensions plays a large role in the final outcome as all cases would incorporate the same inbuilt errors.

Ferrare *et al.* compared CBCT measurements to micro CT, which is purportedly more accurate (156). They found that CBCT underestimated the bone height by 0.3mm, while areas of thin bone may not be visualized on CBCT images (157), which could amount to areas of bone loss which are not actually clinically present. The reduction in image quality or accuracy produced by CBCT and CBCT analysis thus needs to be factored in when comparing this study's results to other studies utilizing differing measurement techniques.

The major limitation in the current study is the small sample size of 3 cases per group. Due to the low numbers, the ability of the current study to show any significant differences between the grafting groups is small. With higher enrollment numbers, more statistically robust data will be available. Despite this, global trends are seen and have been outlined between this study and others.

CONCLUSION

Within the limitations of this study, spontaneous extraction socket healing is unpredictable and may result in insufficient ridge dimensions, compromising long term implant placement and esthetics. A thin buccal plate shows a strong inverse relationship with subsequent ridge volume loss, however ridge preservation procedures counteract this effect by providing additional clot stability, and wound support, preventing soft tissue infiltration, and reducing the amount of bone and soft tissue loss, although these results were not statistically significant. Ridge preservation may reduce the need for additional major grafting, although minor grafting procedures may still be required at the time of dental implant placement. Graft material selection does not seem to affect ridge preservation outcomes, and as such the most economical product with desirable handling characteristics can be utilized.

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