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Efficacy of socket grafting for alveolar ridge preservation: a randomized clinical trial

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EFFICACY OF SOCKET GRAFTING FOR ALVEOLAR RIDGE PRESERVATION:

A RANDOMIZED CLINICAL TRIAL

by

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CERTIFICATE OF APPROVAL

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ABSTRACT

Objectives:

Tooth extraction initiates a cascade of events that often leads to local anatomic changes in the alveolar ridge. Ridge preservation is a surgical approach aimed at minimizing hard and soft tissue volume loss. There have been contradicting reports on the efficacy of socket grafting for alveolar ridge preservation. Interestingly, there is a paucity of adequately powered randomized controlled clinical trials. The purpose of this study was to assess the effect of the application of a socket grafting technique on alveolar ridge dimensional changes following tooth extraction.

Methods:

Healthy patients requiring the extraction of one single-rooted tooth on either arch, from second premolar to second premolar, excluding mandibular incisors, and who met the eligibility criteria were recruited. Patients were then randomly assigned to either the control group, consisting of tooth extraction alone, or the experimental group, which consisted of extraction and simultaneous ridge preservation using an allograft bone material to fill the socket and a dense polytetrafluoroethylene membrane (dPTFE) to seal it. Cone beam computed tomography (CBCT) was obtained immediately prior to extraction (baseline) and at 14 weeks. Linear measurements with the use of a tooth-supported stent were obtained immediately after extraction (baseline) and at 14 weeks. Linear and volumetric measurements were made using data obtained from the CBCTs. Masked, calibrated examiners performed all radiographic measurements. Measurements obtained included buccal keratinized tissue width, buccal and lingual plate height and width, alveolar ridge horizontal width (CBCT); and alveolar ridge volume changes.

Digital planning of dental implants was performed in the ideal restorative location and need for additional grafting was virtually determined. The primary outcome of interest was volumetric reduction of the alveolar ridge at 14 weeks. Linear mixed model statistical analyses were used to compare the mean change in the measurements between the grafted and control groups.

Results:

A total of 59 subjects were recruited, of which 53 patients (27 control and 26 experimental) completed the study. No statistically significant difference was found between the two groups at baseline for any of the parameters analyzed. At the 14 week follow-up appointment there was an average loss in height of the buccal plate of 1.17 mm and 0.61 mm for the control (CG) and experimental (ARP) groups, respectively, showing statistical significance ($p=0.012$). The lingual plate height was reduced 0.7 mm in CG and 0.47 mm in ARP with no statistical significance (0.075). A linear loss in the buccal-lingual dimension of the alveolar ridge was noted radiographically in both groups, 1.68mm in CG and 1.07mm in ARP, which demonstrated a statistical significant difference between them ($p=0.023$). Volumetric analysis demonstrated a mean volume loss of 15.83% in the CG showing statistical significance from the 8.36% loss shown in the ARP group. This difference demonstrates a clinical significance when virtual planning of implant placement in the ideal restorative location revealed the need for additional grafting at 13/27 or 48% of CG and 3/26 or 11% of ARP sites. Additionally, a very robust, statistically significant correlation was noted between buccal bone plate width and reduction of alveolar bone volume after 14 weeks of healing ($p< 0.0001$). A multivariate regression analysis revealed that within the control group a buccal plate

<1mm lead to >10% volumetric reduction, while the same reduction in the graft group was only seen when the buccal plate was less that 0.6mm.

Conclusions:

In this study, a novel volumetric analysis of alveolar ridge reduction after tooth extraction was performed, which demonstrated that socket grafting for alveolar ridge preservation does provide a therapeutic benefit. This finding was associated to a decreased probability of requiring additional grafting at the implant site. The thickness of the buccal plate at the time of extraction appears to be a valuable factor to predict the amount of resorption that will take place, meaning that more resorption should be expected, as the buccal plate gets progressively thinner.

PUBLIC ABSTRACT

Tooth extraction is a common procedure in dental practices. When a tooth is extracted the alveolar ridge undergoes dimensional changes reducing the tissues at the site where the tooth once existed. These changes can make it difficult for dentists to create esthetically pleasing tooth replacements, and possibly hinder the opportunity to have a dental implant. For this reason a bone graft can be performed into the tooth socket to help maintain the dimensions of the alveolar tissues. This is a technique called socket grafting for alveolar ridge preservation.

The purpose of this study was to assess the effect of the application of socket grafting on alveolar ridge dimensional changes following tooth extraction. A novel volumetric analysis of alveolar ridge reduction after tooth extraction was performed, which demonstrated that socket grafting for alveolar ridge preservation does provide a therapeutic benefit. This finding was associated with a decreased probability of requiring additional bone grafting at the implant site. The thickness of the buccal plate at the time of tooth extraction appears to be a valuable factor to predict the amount of dimensional loss of the alveolar ridge that will take place, meaning that more loss should be expected as the buccal plate gets progressively thinner.

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CHAPTER 1. INTRODUCTION

1.1. Anatomy of the Periodontium

The periodontium is defined as the tissues supporting and investing the tooth; this comprises gingival tissues, root cementum, periodontal ligament, bundle bone, and alveolar bone (Sharon R. Bannister 2001). The gingival tissues of the periodontium are composed of sulcular epithelium, long junctional epithelium, and connective tissue attachment. Gargiulo found the average dimensions of the periodontal attachment apparatus to be 0.69mm in sulcus depth, 0.97mm of epithelial attachment and 1.07mm of connective tissue attachment (Gargiulo, Wentz et al. 1961). Vacek et al. found the mean dimensions of the gingival attachment to be 1.34mm for sulcus depth, 1.14mm of epithelial attachment and 0.77mm for connective tissue attachment in a sample of 171 human sections (Vacek, Gher et al. 1994). A more recent clinical study by Tristao et al. based upon extractions en bloc used a slightly different methodology. The authors measured from the gingival margin to the apical extent of the junctional epithelium (1.58mm), which would include the sulcus depth and epithelial attachment looked at in the previous articles. They then measured the distance from the base of the epithelial attachment to the height of the alveolar bone crest (connective tissue attachment), which was 1.18 mm (Tristao, Barboza et al. 2014). It is important to know that there is some variation, not only between individuals, but also within individuals from site to site.

Sulcular epithelium differs from that of gingival epithelium because it is non-keratinized. However, with a strict regimen of oral hygiene and antibiotics in monkeys it has been shown that the sulcular epithelium can become keratinized (Kristoffersen, Caffesse et al. 1983). The base of the gingival sulcus gives rise to the junctional epithelium.

The junctional epithelium plays a crucial role, as this is where the internal periodontal tissues (i.e. connective tissue attachment, alveolar bone, cementum, periodontal ligament) are

sealed off from the oral environment, which is critical in maintaining the long-term health of these structures (Hormia, Owaribe et al. 2001). It is unique in that it is derived from the reduced enamel epithelium as a tooth erupts. It is a non-differentiated, stratified squamous epithelium with high cell turnover rate (Nanci and Bosshardt 2006). However, a separate histological study performed on 6 humans found that the junctional epithelium was a simple stratified epithelium. They also found that when these harvested cells were cultured *in vitro* the junctional epithelial cells had twice as long of an incubation period as the oral gingival cells, at which point they underwent rapid recession. The author linked the *in vitro* findings to the clinical behavior shown by the fact that the junctional epithelial cells, when introduced with a new environment, may take longer to adapt. After adaptation they can rapidly proliferate and reach contact inhibition in a relatively short period (Jiang, Yu et al. 2014). A hemidesmosomal attachment allows for the superficial layer of the junctional epithelium to attach to the tooth's surface (Hormia, Owaribe et al. 2001). Below the junctional epithelium is the connective tissue.

The connective tissue contains a dense network of collagen fiber bundles that make up for 50-60% of the connective tissue volume. These fibers not only anchor the connective tissue to the tooth, but the gingiva-bone, tooth-tooth and tooth-alveolar-crest, as well. The connective tissue also provides a matrix for rigidity and biomechanical resistance of the gingiva (Schroeder and Listgarten 1997). The periodontium also includes keratinized mucosa and alveolar bone that will be discussed in the following section.

1.2. Basic Concepts of Keratinized Mucosa and Alveolar Bone

The keratinized mucosa is composed of dense collagen rich connective tissue beneath the keratinizing epithelium. It has been shown to be stiffer and more resistant to mechanical stresses than non-keratinized oral mucosa (Goktas, Dmytryk et al. 2011).

The keratinized mucosa has received much attention regarding how much apico-coronal width is necessary in order to maintain a state of health in periodontal and peri-implant soft tissues. It has been shown that in areas with less than 2mm of keratinized mucosa inflammation persisted and suppuration prevalence was increased. This led to the suggestion that a minimum of 2mm keratinized mucosa was necessary to maintain health (Lang and Loe 1972). Subsequent studies have debunked this thought by showing that with adequate plaque control a minimum of 2 mm of keratinized mucosa is not necessary (Kennedy, Bird et al. 1985, Wennstrom 1987).

The alveolar bone develops in conjunction with the eruption of teeth and provides the bony housing of the tooth. It is connected to the tooth through the periodontal ligament, which has Sharpey's (collagen) fibers that insert into the inner aspect of the alveolus. This area of insertion is known as the alveolar bone proper or bundle bone. The bundle bone receives vascular supply from the periodontal ligament, which is severed when a tooth is extracted. This compromises the blood supply and also eliminates the masticatory strain that was once present on the bundle bone. A cascade of biological events is then triggered which leads typically results in local anatomic changes (Van der Weijden, Dell'Acqua et al. 2009). This will be further discussed in the extraction socket wound healing section.

1.3. Tooth Extraction

1.3.1. Prevalence of Edentulism

The percent of edentulous people among the US population has declined over the last century with each generation (Slade, Akinkugbe et al. 2014). However, there continues to be substantial growth in the U.S. coupled with longer life expectancy. The fastest growing population is the 65+ age group and they are expected to be 20% of the population or 54 million people 65+ by the year 2020. Considering 26% of the population 65+ is edentulous there will be 14 million edentulous people in this age group in by 2020 (Felton, Cooper et al. 2011). Thus we can see

that the 10% decline in edentulism experienced over the past 30 years will be more than offset by the 79% increase in the adult population older than 65 years (Douglass, Shih et al. 2002).

1.3.2. Indications for Dental Extraction and Frequency

Dental extraction is indicated when a tooth cannot be restored or maintained in acceptable conditions of health, function or esthetics. Data collected from 165 dental practitioners in Ontario Canada including 6134 patients found that 11.6% of the patients had 1 or more teeth extracted (Murray, Clarke et al. 1997).

The two most common reasons for tooth extraction include periodontal disease and dental caries. Untreated dental caries remains the most prevalent health condition across the globe. There is evidence that there is a shift of untreated dental caries from children to adults with a peak at age 25 (Kassebaum, Bernabe et al. 2015). This increase in adult dental caries is likely to lead to the indication of additional dental replacement procedures. A common procedure used to replace teeth is the use of dental implants to support fixed or removable prostheses. When treatment planning the restorative dental replacement it is important to understand the consequences derived from tooth extraction.

One must consider the patient's quality of life. Tooth loss has a direct impact on a person's quality of life. It impairs their ability to communicate, masticate, and in some instances socialize (Brennan, Spencer et al. 2008, Gerritsen, Allen et al. 2010).

1.4. Extraction Socket Wound Healing

The absence of a tooth in its natural position triggers a cascade of biologic events, which typically results in a significant loss in alveolar ridge volume (Jahangiri, Devlin et al. 1998, Van der Weijden, Dell'Acqua et al. 2009). This can pose a problem for the surgeon placing dental implants, as well as the restorative dentist. Adequate bone volume is critical for proper dental implant placement as well as for achieving sustainable and satisfactory functional and esthetic

outcomes. Esthetic considerations can be extremely important when planning to replace teeth in the anterior zone, primarily the premaxilla.

1.4.1. Soft Tissue

Immediately after tooth extraction a blood clot forms, this is then replaced by granulation tissue within the first 1-3 days. By day 4, connective tissue is seen as well as epithelial down growth. Epithelial fusion over the extraction socket was noted at days 24-35, approximately 1 month (Amler 1969).

1.4.2. Hard Tissue

Upon extraction the alveolar bone undergoes remodeling. Cardaropoli et al. used the canine model to study the sequence of biologic events that the resorptive process entails (Cardaropoli, Araujo et al. 2003). Similar to Amler and collaborators, they found that the initial blood clot is formed and then replaced by granulation tissue. Over the next 1-2 weeks an organized connective tissue matrix replaces the granulation tissue. At 4 weeks initial bone matrix, woven bone, was observed. Mature lamellar bone was observed between days 120-180. The authors noted that healing started in the apical portions of the socket and moved coronal. This may be due to the closer proximity of the bony walls. However, this study only looked at mesio-distal sections of the healing sockets. This was a great study to build upon Amler's previous study because it allowed for complete sections including the alveolar walls of the socket whereas Amler was only able to take central sections of the healing socket.

A subsequent study then evaluated structural changes in the alveolar ridge following tooth extraction (Araujo and Lindhe 2005). This study again used the canine model, but made bucco-lingual sections of the healing sockets, which allowed for assessment of the buccal and lingual plates. They noted intense resorption of the buccal plate within the first 8 weeks after extraction while the lingual plate did not show the same marked resorption. This resorption

resulted in substantial loss of the vertical and horizontal dimensions of the alveolar ridge, primarily on the buccal aspect. A possible explanation for this resorptive pattern is that the facial plate is generally thinner than the lingual plate. Often this is just the buccal cortical plate fused directly to the bundle bone directly adjacent to the bundle bone receiving blood supply, this blood supply is disrupted upon extraction leaving the buccal plate without a nutrient supply.

The same pattern has also been shown in humans (Cawood and Howell 1988, Schropp, Wenzel et al. 2003). Schropp et al. looked at single tooth extractions of either pre-molars or molars. They found an average 50% loss in alveolar ridge width over a twelve-month healing period, peaking in the first 3-6 months of healing (Schropp, Wenzel et al. 2003).

1.5. Historical Evolution of Therapeutic Strategies to Preserve the Alveolar Ridge

Ridge preservation was initially introduced as root retention under a removable prosthesis, which would allow for maintenance of the alveolar ridge giving greater support and retention to the prosthesis (Osburn 1974, Donahue 1980). This method may not be practical due to deep caries, root fracture, or the desire to place a dental implant in that site.

Alveolar ridge preservation then emerged as an alternative to root submergence. This procedure included filling the fresh extraction socket with a biomaterial that would emulate the root retention effect. This ability to conserve the alveolar ridge is particularly important in cases where implant supported dental prosthesis are planned. Maintenance of the alveolar bone allows for proper placement of the dental implant, fulfilling both functional and esthetic requirements (Artzi and Nemcovsky 1998). There have been many different materials used for alveolar ridge preservation including, autologous bone, bone substitutes (allograft, xenograft and allografts), blood derived products, growth factors, sub-epithelial connective tissue grafts, free gingival grafts, resorbable and non-resorbable barrier membranes and different combinations of these products (Darby, Chen et al. 2009). Darby also found that all the different techniques used

seemed to be effective in limiting the resorption of the alveolar ridge in a horizontal and vertical direction, but did not completely prevent it (Darby, Chen et al. 2009).

1.6. Current Evidence on Alveolar Ridge Preservation via Socket Grafting

The application of a bone substitute into the fresh extraction socket, known as socket grafting, has become the most popular technique for alveolar ridge preservation. There are numerous publications regarding the use of socket grafting. These report on clinical, radiographic, and histologic outcomes.

The amount of buccolingual ridge resorption after tooth extraction has been reported to range between 17 and 60%, with approximately 1 mm of average loss in ridge height (Lekovic, Kenney et al. 1997, Yilmaz, Efeoglu et al. 1998, Iasella, Greenwell et al. 2003, Schropp, Wenzel et al. 2003, Barone, Aldini et al. 2008)

The Osteology Consensus group conference reported that, after extraction, the average ridge width loss was 3.8mm and average ridge height loss was 1.24mm (Hammerle, Araujo et al. 2012, Tan, Wong et al. 2012).

Avila-Ortiz et al.in a more recent systematic review and meta analysis based upon randomized clinical trials found that there was a 1.89mm benefit (less loss) in buccolingual direction when alveolar ridge preservation was performed vs. extraction alone. This same meta-analysis also found a 2.07 mm difference in the buccal plate height, benefiting alveolar ridge preservation (Avila-Ortiz, Elangovan et al. 2014). These findings were consistent with a previous systematic review, which found buccolingual dimension changes being 1.83mm greater in the control group than those receiving alveolar ridge preservation (Vignoletti, Matesanz et al. 2012). The common report includes ridge preservation using socket grafting as a beneficial procedure in reducing the resorptive process, but does not entirely prevent it.

With the improved technology in the cone-beam computed tomography arena it is now plausible to perform dimensional analysis in a linear fashion as has been reported on previously without the need for flap reflection at the time of tooth extraction, and a more accurate analysis of the volumetric changes of the extraction sites. Chappuis et al. used CBCT to make linear measurements and reported that in the maxillary anteriors (29 central incisors, 8 laterals, and 2 canines) a thin buccal plate, <1mm, resulted in a median vertical bone loss of the facial plate to be 7.5mm vs. those with a thick wall, >1mm, which only showed 1.1mm (Chappuis, Engel et al. 2013). In a randomized controlled clinical pilot study comparing three different ridge preservation techniques vs. a control (extraction and collagen plug) Avila-Ortiz et al. used CBCTs to perform a 3 dimensional, volumetric analysis over a 16-week healing period. They discovered that three of the groups demonstrated similar volumetric changes, (Extraction and collagen plug, 3%: extraction and socket graft with allograft and PTFE membrane, 7%: and extraction with socket grafting and a collagen membrane that was then covered by a PTFE membrane5%). However, it was the group that had socket grafting in combination with buccal overbuilding and a PTFE membrane that saw the largest volumetric reduction, 16%. It must be noted that the initial CBCT was made immediately after surgical treatment and thus the greater volumetric change in this group was largely due to resorption of the graft material that was used to overbuild the buccal aspect (Avila-Ortiz, Rodriguez et al. 2014).

Araujo et al. used CBCT data to analyze alveolar ridge changes in maxillary incisors, canines and pre-molars. They found that the area of the alveolar process was significantly reduced by 25% in the control group (extraction without further treatment). However, the test group (Socket grafting with Bio-Oss Collagen and a free-gingival graft) showed only a 3% reduction in the area of the alveolar ridge (Araujo, da Silva et al. 2015). Although they used a 3-

dimensional radiograph for analysis, they still used 2-dimensional measurements to quantify their results.

It is apparent that the alveolar ridge preservation literature is lacking a good randomized clinical trial with proper patient population to satisfy a well-constructed power analysis, and three-dimensional data investigation. Hence, we designed a randomized clinical trial to address the shortcomings of previous studies and to contribute to the knowledge base in this topic.

CHAPTER 2. HYPOTHESIS AND SPECIFIC AIMS

It was hypothesized that socket grafting for alveolar ridge preservation will be more effective in maintaining alveolar ridge volume as compared to tooth extraction alone.

The primary aim of this study was to volumetrically assess using CBCT data whether the use of a ridge preservation technique significantly minimizes alveolar ridge resorption following tooth extraction, and what influence certain topographic parameters have on the volumetric outcomes.

Secondary aims include analysis of baseline clinical measurements and their influence on ridge alterations after extraction with or without alveolar ridge preservation. This study also aimed to assess whether alveolar ridge preservation played a role in the need for additional bone grafting at the time of implant placement. Furthermore, patient centered outcomes such as wound healing index, patient satisfaction and patient discomfort following surgical therapy were determined.

CHAPTER 3. MATERIAL AND METHODS

3.1. Pre-screening

The clinical component of this study was conducted in the Graduate Periodontics clinic at the University of Iowa College of Dentistry and Dental clinics from August 2013 to October 2014. The University of Iowa Institutional Review Board approval was obtained in March 2013.

Patients needing a dental extraction of a maxillary premolar, canine, incisor or a mandibular premolar or canine were recruited. All patients were then prescreened by phone. Those patients that met the initial eligibility criteria and were interested in the study were invited to participate in a clinical screening.

This study has been registered at clinicaltrials.gov under code NCT01794806.

3.2. Clinical Screening

At the clinical screening all patients were informed in detail of the purpose and timeline of the study (Fig. A1). All eligible subjects were required to read and sign a consent form, which included an explanation of possible risks and rewards of both treatment possibilities (extraction with or alveolar ridge preservation procedure). Patients were also given ample time for questions and answers, as necessary.

Patients between 18 and 75 years of age, requiring a single-rooted tooth extraction excluding lower incisors were eligible for the study. All patients must be able and willing to follow instructions pertaining to the treatment. All patients must have read, understood and signed the informed consent document.

The exclusion criteria contained: any reported allergy or hypersensitivity to any of the materials to be used in the study. Any patients with severe hematologic disorders such as hemophilia or leukemia as well as any active or infectious or metabolic bone diseases that may compromise healing were excluded. Any patients with liver or kidney failure were excluded along those undergoing cancer treatment or a history of radiation treatment. Any subject who had smoked within the last 6 months was excluded as well as any uncontrolled diabetic (HbA1c>7.5). Any patients that were on concomitant medications, such as antibiotics, that may affect the outcome of the study were excluded. Any patients that were pregnant or planning to get pregnant were excluded as well.

Following initial screening procedures each patient underwent a site-specific intra-oral and radiographic exam. If a recent peri-apical radiograph (<1-year) was not available a new one was made at the screening appointment to properly assess eligibility. Candidates exhibiting clinical or radiographic signs of active periodontal disease were excluded from the study, but invited to receive comprehensive care at the College of Dentistry.

3.3. Groups and Randomization

Following enrollment, patients were randomly assigned to one of two treatment modalities, using a computer-generated randomization list. Group 1 (control) consisted of minimally invasive tooth extraction with no further treatment. Subjects in group 2 (experimental) were treated with a minimally invasive tooth extraction followed by socket grafting for alveolar ridge preservation using a combination allograft containing a mixture of FDBA and DFDBA (enCore, Osteogenics Biomedical Inc., Lubbock, TX), dPTFE barrier (Cytoplast TXT-200 Singles, Osteogenics Biomedical Inc., Lubbock, TX) and PTFE suture (Cytoplast 5-0 suture, Osteogenics Biomedical Inc., Lubbock, TX).

The surgeon (MG) and the examiner performing the clinical measurements (GA) were unaware of the allocation group until directly prior to the baseline surgical appointment.

3.4. Baseline surgical appointment and post-operative care

Immediately prior to surgical intervention a cone beam computed tomography (CBCT) scan was obtained (i-CAT, Imaging Sciences International). Only the arch containing the tooth of interest was scanned to minimize the radiation exposure to the patient. The field of view was 6 cm, and the machine was fixed at 120 kVp and 18.66 mAs with 0.3 voxel size for all scans.

All surgical procedures were performed under local anesthesia. At the baseline surgical appointment, tooth extraction was performed in a minimally traumatic fashion using hand instruments with minimal trauma applied to the adjacent soft tissues and the alveolar bone (Figure A2).

After extraction, the sockets were gently curetted and clinical measurements were made. Clinical measurements made relative to a pre-fabricated stent included the width (apico-coronal) of the keratinized mucosa (Figure A3 and Figure A4). Clinical measurements made not relative to a stent included the thickness of the buccal and lingual gingiva at a level 2mm apical to the gingival margin; and buccal and lingual bony plate thickness. Measurements were made using a periodontal probe (UNC periodontal probe Hu-Friedy), (Figure 4).

Following clinical measurements those in the control group were excused. The experimental group proceeded to have the socket grafting procedure. This was performed by placing allograft material into the socket up to the level of the crestal bone, then 2-3mm sub-periosteal flaps were reflected buccal and lingually. A dPTFE membrane was placed over the graft material and under the buccal and lingual soft tissue. A horizontal cross mattress suture was placed to aid in maintaining the placement of the non-resorbable membrane (Figure A5).

Upon extraction of the tooth if a dehiscence of any of the bony socket walls was noted patients were then removed from the study and if part of the control group (no graft) patients were then offered the opportunity to have a ridge preservation procedure performed.

Patients received detailed verbal and written postoperative instructions. Prescriptions for 600mg tablets of Ibuprofen every 6-8 hours to be taken for the first 3 days, then as needed for pain for the remainder of the first week; 1 16oz. bottle of 0.12% Chlorhexidine gluconate to be used twice daily, and Amoxicillin 500mg to be taken three times daily for one week (Penicillin allergy patients were prescribed 300mg Clindamycin to be taken four times daily for one week).

3.5. Follow-up Appointments

3.5.1 One-week postoperative visit

At the one-week post-op sutures were removed and oral hygiene was reinforced. Patients in group-2 were shown how to use a cotton swab dipped in 0.12% Chlorhexidine aqueous solution to gently clean the membrane for the next three weeks. Plaque index of the adjacent teeth to the extraction site were assessed (Quigley and Hein 1962, Turesky, Gilmore et al. 1970)(Figure A6). Wound healing was assessed using a modified wound healing scale (Figure A7). The amount of exposed membrane was again measured for those in the graft group.

Prior to seeing the periodontist (GA or MG) the patients were asked to rate their discomfort following the surgical procedure on a 0-100 scale (Figure A8). One-week post-operative photos can be seen in Figure A9.

3.5.2 Four-week postoperative visit

The extraction sites were again assessed. Wound healing index and plaque indices of the adjacent teeth were evaluated. In the sites included in the experimental group, the exposed membrane was measured on those in group-2 and then it was removed using cotton forceps. Oral hygiene instructions were given verbally.

3.5.3 Fourteen-week post-operative visit

At fourteen weeks patients received a second CBCT prior to repeating clinical measurements. The same calibrated periodontist (GA) that had performed all clinical measurements throughout the study was present to perform final measurements. The measurement stent was placed and measurements made in relation to the stent included width apico-coronal of the keratinized mucosa (Figure A10). Patients were locally anesthetized to allow for piercing of the soft tissue to measure soft tissue thickness on the mid-buccal and lingual aspects. Patients were again asked what their overall satisfaction level was with the treatment that was rendered; this was on a 0-100 scale with 100 being complete satisfaction. The patients were asked to draw a line that corresponded with their satisfaction just as they did for their discomfort (Figure A8). Patients also reported on their overall discomfort level that they experienced throughout the study (Figure A8).

Patients were told what the current condition of their alveolar ridge was, as it pertained to restoring the edentulous site. Those seeking tooth replacement were scheduled in the appropriate clinic and further surgical and restorative treatment was completed outside of this study.

3.6 Radiographic Evaluation

A freelance, blinded examiner performed the three-dimensional radiographic evaluations (OMF Solutions, Atlanta, GA). CBCT scan digital imaging and communication in medicine (DICOM) files were opened with the computer program Simplant 16 Pro by Materialise (Dentsply Implants, Waltham, MA). This program allows for the selection of a volume of interest (VOI) that permits the separation of the soft tissues from the alveolar bone using constant thresholds. Thus, the volumetric analysis of this study was performed on the alveolar bone alone to potentiate its clinical significance, since dental implant planning is primarily made on the basis of available alveolar bone. The six boundaries of the VOI were a plane parallel to the crestal

bone, a plane parallel to the apex of the adjacent roots, the most external plane of the facial and lingual bony plates and an extension in both the mesial and distal direction including approximately 2-3 mm of the adjacent teeth, used as structures of reference, as illustrated in figure A11. The same segmented portion of the alveolus (VOI) was delineated at baseline and 14 weeks. The total volume in cubic mm (mm^3) of these 3-dimensional images was then quantified using Simplant View v.15.0. The blinded examiner was then able to calculate the percentual loss of volume that occurred over the 14 weeks. This was done by subtraction analysis and expressed in terms of percentage loss (Figure A11).

A separate blinded examiner (MR) used the CBCT data to make bucco-lingual ridge width measurements in the same location at baseline and 14 weeks using the Invivo v.5.3 software (Anatomage, San Jose, CA). These measurements were accomplished by using a specific anatomic landmark on the adjacent teeth, such as the cemento-enamel junction or crown margins, in order to identify the same mid-buccal and mid-lingual site to measure between (Figure A12). A similar method was used to determine the height of the lingual and facial plates at baseline and 14 weeks. Using the CEJs of the adjacent teeth a reference line was made, then a measurement from that line was made to the respective buccal or lingual crestal bone (Figure A13).

This examiner then used the same software to digitally plan implant placement in an ideal restorative location at each of the edentulous sites. Bone level implants with a diameter of 4.0 mm and a length of 9.0 mm were chosen as the standard implants for all sites, except for maxillary lateral incisors where 3.5mm diameter and 9mm length implants were used (Figure A13). Additional grafting at time of placement was deemed to be necessary if any part of the implant body was outside of the bony housing (Figure A14).

3.7 Power Analysis

Percentage change in horizontal ridge width from baseline to 16 weeks for each of the two treatment groups (experimental and control) was an outcome of interest in this study. 3D volumetric changes in residual ridge from baseline to 14 weeks were assessed as well. Since this is a novel approach to ridge assessment, sample size calculations focused on providing adequate power for the well-established linear width outcome.

In a previous study (Iasella, Greenwell et al. 2003) the change in horizontal ridge width variable for each group was normally distributed with standard deviations 2.3mm for the control group and 0.9mm for the ridge preservation group. If the true difference between the experimental and control mean decrease at 16 weeks is 1.4mm, we will need to study 26 experimental subjects and 26 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 80%. The Type I error probability associated with this test of this null hypothesis is 0.05.

3.8 Data Analyses

Data analyses were performed with descriptive statistics for the volumetric analyses as well as the baseline and linear measurements. A p-value of $< .05$ was considered statistically significant. Mean values and standard deviations were calculated for each of the quantities assessed in the 2 groups. Differences between the two groups were then calculated with the Wilcoxon rank-sum test. Linear mixed model analysis was used to compare mean change in the radiographic measurements between the grafted and control groups. The fixed effects in the mixed model included treatment group (control, graft), time (baseline, 14-weeks), and treatment-time interaction, with the test for treatment-time interaction effect corresponding to the test comparing mean change between the grafted group and the control group. In addition, based on the fitted

model, test of mean contrast was performed to test for change over time within each group, and also compare between the groups at each time. P-values for these tests have been adjusted using Bonferroni's method, i.e. adjusted p-value=2 (unadjusted p-value) for testing for change within each group; and for comparing between graft and control at each time. Linear regression analyses was performed to determine the effect of baseline parameters (buccal and lingual plate thickness, buccal and lingual gingiva thickness and the baseline width of keratinized mucosa) on the final volumetric outcome of the alveolar ridge. In addition to this a Pearson correlation was performed to assess the correlation of soft tissue parameters (thickness and width apico-coronal) with the underlying buccal plate thickness. A multivariate logistic regression analysis was performed to determine buccal plate thickness thresholds regarding the volumetric reduction of the edentulous site post extraction.

CHAPTER 4. RESULTS

4.1. Study Population

Fifty-nine (59) patients were initially recruited and randomly distributed between both treatment groups. A total of 53 patients (22 males and 31 females overall; 14 males and 13 females in the control group and 9 males and 17 females in the test group completed the study and, therefore, their data were included in the analyses. Of the 6 patients who did not finish the study, 1 was lost to follow-up, 1 was dismissed as she reported that she was actively trying to get pregnant, and 4 were excluded at the time of extraction due to morphologic differences in the extraction socket such as a dehiscence in the buccal wall. This study met the power analysis criteria of 26 patients in each group (control: 27, test: 26).

4.2. Baseline Parameters

Subjects had a mean age of 57.84±11.99 years old (control: 57.24±11.82 and test: 58.46 ±12.37). The body mass index (BMI) of each patient was calculated, the mean overall BMI was 30.59±7.17 (control: 32.02±7.52, test: 29.17±6.65) (Table B1).

Baseline clinical parameters included keratinized gingiva in relation to a stent (control: 3.81±1.27, test: 4.31±1.69), mean thickness of the buccal bone or buccal plate (control: 0.61±0.31, test: 0.98±0.35), mean lingual bone or lingual plate thickness (control: 1.00±0.36, test: 0.87±0.24). The mean baseline buccal soft tissue thickness (control: 0.49mm±0.2mm, test: 0.43±0.13), and lingual soft tissue thickness (control: 0.83mm±0.33, test: 0.84±0.36) (Table B2). The sites included in the study were, maxillary central incisors (5), maxillary lateral incisors (10), maxillary canines (4), maxillary pre-molars (24) and mandibular pre-molars (9). The breakdown of the sites treated within each group is listed on table 3 (Table B3). There was no significant difference noted between the two groups for any of the baseline clinical parameters recorded.

4.3. Patient Reported Outcomes

Patient discomfort level reported at each time point revealed the patients within the test group were the same or slightly higher, with no clinical or statistical differences between the two groups (Table B4). Patient's satisfaction regarding the overall treatment when asked immediately following the 14-week appointment, which required local anesthesia for clinical measurements, was very high for both groups (control: 95.52±9.56, test: 92.54±13.78) with no significant difference between groups.

4.4. Linear Clinical and Radiographic Evaluations

Baseline linear ridge width measurements from the CBCT revealed mean bucco-lingual width of the alveolar ridge at the extraction site to be 9.26±1.4mm and 9.36±2.34mm for the control and test respectively.

After 14 weeks of healing there was a significant increase in soft tissue thickness within both groups as well as a significant decrease in both the width of the ridge and volume of the alveolar ridge (Table B5). The control group exhibited a radiographic bone loss of 1.68mm in the bucco-lingual width of the alveolar bone, but a gain of 1.1mm in buccal soft tissue as well as 1.2mm in the lingual soft tissue. The graft group saw similar gains in soft tissue although a smaller decrease in the alveolar bone width, 1.07mm (Table B6).

A height reduction of the facial plate was noted in both groups (median values, control: 1.17mm and test 0.61), which was statistically significant within each group ($p<0.0001$) and between groups ($p+0.012$). A similar median loss was noted with the lingual plate (control: 0.7mm and test: 0.47mm). This change saw a statistical significance within each group ($p<0.001$), but not between groups (0.075) (Table B7).

Radiographic evaluation of the alveolar ridge after extraction showed a significant mean decrease in the ridge width of 1.68mm and 1.07mm in the control and graft groups respectively.

This was not only statistically significant within each group, but was also statistically significant between groups. The clinical significance of this may be dependent upon planned restorative treatment (Table B8).

Healing was assessed at each follow-up appointment (Figure A6). The groups exhibited similar healing indexes at all follow-up times (Table B9).

4.5. Volumetric Changes

A reduction in ridge volume was noted in both groups. The magnitude of change was of 15.83% and 8.36% in the control and graft groups, respectively. This reduction in the control group is significantly more than that of the graft group $p<0.0001$ (Table B10). The clinical significance of this is shown in the results of the digital implant placement in the ideal restorative location. This showed that 13/27 (48%) of the control patients needed additional grafting at the time of placement while in the test group just 3/26 (11%) of the patients required additional grafting at the time of placement.

At 14 weeks, analysis of the volumetric changes revealed that the control group had nearly double the volumetric reduction as that seen in the experimental group, 15.83% reduction vs. 8.36% respectively.

The virtual implant placement revealed that nearly half of the control group (13/27, 48%) needed additional grafting while socket grafting at time of extraction did not totally eliminate the possibility for the need of additional grafting it did significantly reduce the possibility (3/26, 11%) of additional grafting.

When analyzing the significance of baseline clinical measurements with the ridge volume reduction the one variable that showed a statistical significance with in helping predict increased volumetric loss was the thickness of the buccal plate at the time of extraction (Table B11). This

significance was perceived in both the control and graft groups. However, the effect is increased in the control group (Figure A15).

Multivariate logistic regression was performed to determine at what point of buccal bone thickness a clinician might expect more than 10% of volumetric loss. It was found that within the control group a buccal plate of >1mm was necessary to avoid the 10% reduction and just a buccal plate thickness of just 0.6 mm was necessary for those having received socket grafting at the time of extraction. This was at a specificity value of 90% and sensitivity of 87% (Table B12).

CHAPTER 5. DISCUSSION

The primary aim of this randomized clinical trial was to assess whether the use of a ridge preservation technique significantly minimizes alveolar ridge resorption following tooth extraction on the basis on radiographic and clinical parameters. Secondarily, we aimed at assessing whether the influence of certain clinical parameters, such as initial buccal plate width, have an influence on the dimensional ridge changes associated to each therapy. The technique used for alveolar ridge preservation in this study was socket grafting with a combination (FDBA+DFDBA) allograft covered with a non-resorbable (dPTFE) membrane, which is a commonly used ridge preservation technique (Darby, Chen et al. 2009).

Many studies have shown that the use of a barrier membrane is beneficial, whether it be an absorbable or non-absorbable membrane as was used in this study (Ten Heggeler, Slot et al. 2011). Early studies showed some concern with the exposure of non-resorbable membranes leading to complications and unpredictable results (Simion, Baldoni et al. 1994, Lekovic, Kenney et al. 1997). However, more recent studies have shown predictable results with minimal or no adverse events when using these membranes, provided appropriate case selection and postoperative care are included into the equation of patient care (Fotek, Neiva et al. 2009, Avila-Ortiz, Rodriguez et al. 2014). Within the realm of alveolar ridge preservation many different socket-sealing strategies have been used (collagen plug, collagen membrane, free gingival graft, and PTFE membranes) with or without graft material, all showing similar superior results when used in combination with graft material (Iasella, Greenwell et al. 2003, Mahesh, Salama et al. 2012, Thalmair, Fickl et al. 2013, Avila-Ortiz, Rodriguez et al. 2014). With this in mind, for this study a non-resorbable dPTFE membrane was selected as the membrane of choice. This also allowed for the clinicians to ensure stability of the exposed membrane for at least the first week of healing at which time the suture helping hold the membrane in place was removed. It is also

interesting to note that within the present study there were not any healing abnormalities in either group. The similar wound healing indices noted at the post-operative appointments confirmed this.

Patient-reported outcomes revealed no difference in discomfort between the two groups. Level of discomfort was never reported to be above 13 on a 0-100 scale by a patient in either group. Final overall satisfaction level was above 90 on a 0-100 scale in both groups, which is reflective of a high level of patient satisfaction throughout the study conduction.

To the authors' knowledge this is only the second study in which volumetric measurements of the bony compartment have been made to assess the outcomes of socket grafting for alveolar ridge preservation, after the study published by Avila-Ortiz and collaborators (Avila-Ortiz, Rodriguez et al. 2014). Chappuis et al. used a similar technique, but only extraction sites without grafting were included in their study (Chappuis, Engel et al. 2013). The observed volumetric reduction was almost twice as much in the control group when compared to the experimental group (15.83% and 8.36% for control and test groups respectively), which appears to be in line with previous studies that have focused on linear measurements (Vignoletti, Matesanz et al. 2012, Avila-Ortiz, Elangovan et al. 2014). Yet, direct comparisons between volumetric and linear data should be interpreted with caution. For example, Cardaropoli et al. reported a 15% loss of ridge volume when alveolar ridge preservation was performed. This reporting, however, is based on posterior multi-rooted teeth and calculated off of linear ridge width changes (Cardaropoli and Cardaropoli 2008).

Additionally, it is important to consider that the total VOI has a direct influence on the final percentual difference, since in larger VOI the estimated volumetric reduction may be diluted. That is the main reason why in our sample only single rooted teeth, that were anatomically comparable, were included. Furthermore, the well-defined VOI boundaries (apico-

coronally, bucco-lingually and mesio-distally) also contributed to the quality of the collected data, which allowed for reliable comparisons between different samples.

Thalmair et al. used dental casts made from pre-surgical impressions and impressions made at 4 months post-surgery. They had 4 different groups composed of 1: xenograft in socket with free-gingival graft, 2: free-gingival graft only, 3: xenograft only and 4: extraction with no further treatment (control). They found less volume loss in the groups with free-gingival grafting (mean loss within each group- 1: 19.92 cubic mm, 2: 24.89 cubic mm, 3: 32.89 cubic mm and 4: 41.41 cubic mm) (Thalmair, Fickl et al. 2013).

A separate study was conducted in a similar manner in which impressions were made of both grafted and non-grafted extraction sites at baseline, 2, 4, 6, 8 and 12 weeks post extraction. These were then digitized and analyzed. Their findings showed that at 12 weeks there was significantly more resorption at the buccal aspect when compared to the lingual in both groups. Their findings also showed that although there was more resorption in the control group at 4 weeks post extraction when compared to the grafted sockets, at 12 weeks the total resorption was similar between the two groups (Flugge, Nelson et al. 2015).

Considering the findings of the present study in which there was soft tissue thickening, while the alveolar bone was resorbed, it can be inferred that volumetric analyses on dental casts, which include the soft tissue, may not be a reliable method to assess the loss of the underlying bone, since they are likely to underestimate the true extent of bone loss, and should be used as a complement to exclusive bone assessments. In addition it must be noted that 3mm thick free-gingival grafts were used in two of the groups within the Thalmair study, which may have significantly increased the thickness of the crestal tissue leading to even more skewing of the data.

It is also interesting to note that although there was significant thickening in a bucco-lingual direction of the buccal and lingual soft tissue in our sample, there was minimal change in the apico-coronal width of the keratinized mucosa. Also, it was found that there was not a significant effect of the baseline soft tissue parameters (bucco-lingual thickness or apico-coronal width) on the dimensional ridge changes observed.

Other studies have used CBCT data to assess linear changes seen in the resorptive process of the bone (Clozza, Biasotto et al. 2012, Chappuis, Engel et al. 2013). In addition to their clinical findings regarding alveolar bone resorption, these studies have found that reconstructed 3 dimensional data from CBCTs is reproducible and reliable. As aforementioned, to the authors' knowledge the only study which assessed volumetric bone reduction with or without alveolar ridge preservation was a pilot randomized clinical trial in which they found no differences between ridge preservation techniques in terms of bone volume loss (Avila-Ortiz, Rodriguez et al. 2014). This study brought to light the need for a larger randomized clinical trial with volumetric analysis to assess the efficacy of alveolar ridge preservation.

In our study we used DICOM data from CBCT scans obtained at baseline and 14-weeks after tooth extraction to achieve a volumetric evaluation. The 14-week healing time was selected as the end-point for this study based upon biologic reasoning, as well as what is commonly performed by clinicians throughout the world, to assess the site prior to implant placement or other corrective/restorative therapy. Biologically, the 14 weeks is based upon healing patterns of extraction sockets. At 14 weeks we would expect a calcified mature lamellar bone matrix to be present (Amler 1969, Evian, Rosenberg et al. 1982). This allows for proper analysis radiographically and in addition the bone is mature and ready for the placement of the dental implant. Also, it is common practice for clinicians to wait 16 weeks (4 months) after a ridge preservation procedure for implant placement. This being the common practice, it is also routine

for the clinician to see their patients 1-2 weeks prior to the surgical procedure to evaluate the surgical site, for a dental implant a CBCT would be made at this appointment to evaluate the edentulous site, approximately 14-weeks.

Interestingly, the 7.47% difference noted at 14 weeks in volumetric reduction between the two groups has pronounced clinical importance. The importance of this morphologic change is shown in the ability to place dental implants in the ideal restorative location without the need for additional grafting. In the current study it was determined that 48% of the control patients needing additional grafting and just 11% of the graft group needing the same. This finding is similar to that of Barone et al. that found a need for additional grafting at non ridge preservation sites to be 46.4% of implants placed compared to just 7.1% needing additional grafting in sites where ridge preservation was performed (Barone, Ricci et al. 2013). These results, however, are not aligned with the previously mentioned pilot randomized clinical trial performed by Avila-Ortiz et al. in which they found that all patients (20 subjects) in each of the 4 groups in their study were able to have implants placed following the study, although some of them had to receive simultaneous bone grafting at the time of implant placement. Also, their study was a pilot and thus had just 5 patients within each group. It must also be noted that in the present study there was very strict eligibility criteria, which may have attributed to the homogenization of the data. Also, the surgical technique used in this study was very meticulous causing a minimal amount of trauma to the adjacent tissues. Last, one must understand the measurement techniques used within this study were very precise. A calibrated, blinded examiner made digital measurements on the CBCT images. These measurements are accurate to $1/10^{th}$ of a millimeter versus clinical measurements, such as those made with a periodontal probe, which are generally regarded to be less accurate (Hefti 1997).

A set of local topographical features of the alveolar socket (keratinized mucosa width, soft tissue thickness on the buccal and lingual, buccal and lingual plate thickness and buccal and lingual plate height), all of which were measured at baseline, were factored in to assess possible correlations with the amount of volumetric reduction noted after 14 weeks. Although there was not a significant correlation noted between any of the soft tissue parameters or the lingual plate thickness on the volumetric outcomes of the bony ridge, there was one baseline parameter that did show a significant correlation. The variable that showed a statistical significance in predicting increased volumetric loss was baseline buccal plate thickness (Table 9). This significance was perceived in both the control and graft groups. However, the effect was more exacerbated in the control group (control: $p< 0.0001$ and graft: $p< 00001$ control vs graft: $p<0.0001$) (Figure 13).

In a clinical study, Cardaropoli et al. specifically analyzed the buccal plate thickness, and its correlation with the final resorptive outcome. They found a strong negative correlation between initial buccal bone thickness and alveolar bone loss ($r= -7.52$), while the same was not seen within the graft group ($r= 0.055$). They conclude that the ridge preservation procedure compensated for the presence of thin buccal plates (Cardaropoli, Tamagnone et al. 2014).

Within this study we found that within the control group those with a buccal plate <1mm lost more than 10% of the of the alveolar ridge volume at the site of the extraction. While in the control group a buccal plate thickness of just 0.6mm was the point at which a 10% reduction was seen. This is significant because 10% loss of an average extraction socket is a 1-2 mm dimensional change, which has been shown to have a significant effect on the placement of dental implants within the realm of this study. This finding is in line with the findings of Chappuis et al.

Chappuis et al. evaluated the validity of using buccal plate thickness as a predictor for future volumetric bone loss. They found severe resorption in those with thin wall phenotypes (<1mm), showing a median 7.5mm or 62.3% loss in buccal bone height and 0.8mm or 10.5% horizontal bone loss. This compared to a median of 1.1mm or 9.1% of buccal bone height loss and 0mm of horizontal bone loss when the buccal plate was thicker than 1mm. These results were compiled from CBCT data at baseline and 8 weeks on maxillary anterior teeth after extraction with no further treatment (Chappuis, Engel et al. 2013). Our results are not as dramatic, however they are in agreement with Chappuis and collaborators' observations in that buccal bone thickness at the time of extraction does play a significant role on the amount of resorption one might expect following extraction. Our results expanded upon this showing that this is also true in those receiving socket grafting for alveolar ridge preservation, since a similar, although attenuated; volumetric reduction response was seen in grafted sites with thinner buccal plates at baseline.

Another interesting finding of the present study was that the mean difference in alveolar ridge width change at the 14-week follow-up between the two groups was 0.61mm, favoring the graft group. This was statistically significant. This is much less than the difference reported in a previous study by Iasella et al. who performed a randomized clinical trial similar to this study but with 24 patients and use of collagen membrane over FDBA for the test group. They found that socket grafting for ridge preservation led to a 1.6mm benefit in bucco-lingual ridge dimension and 2.2mm difference in height with a gain in height having been recorded in their test group (Iasella, Greenwell et al. 2003). In a classic study by Schropp et al. they found a 50% reduction in the alveolar ridge width at the extraction site over a twelve-month period with 2/3 of that coming within the first 3 months (Schropp, Wenzel et al. 2003). Our study saw significant changes in the buccal plate height within both the control and experimental groups ($p < 0.0001$).

A significant difference was also noted in the change between the two groups (p=0.012) with the control losing nearly twice as much height (1.17mm) in the buccal plate as the experimental sites (0.61mm).

The results reported in recent systematic reviews are in agreement with the findings of our study in that alveolar ridge preservation via socket grafting contributes to minimize alveolar ridge dimensional loss after tooth extraction. However, the magnitude of the effect differed for certain parameters. Avila-Ortiz et al found a 1.89mm benefit in bucco-lingual width when using socket grafting for alveolar ridge preservation and 1.18mm benefit in mid-buccal height (Avila-Ortiz, Elangovan et al. 2014).

Although some of the linear measurements were not as pronounced within this study it is imperative to understand that the ridge preservation group out performed the control group in every alveolar bone measurement analyzed. The lack of significance in many of the linear measurements may be due to the previously mentioned criteria: 1. A stringent eligibility criterion was used for this study, 2. Meticulous and careful extracton technique that was performed, and 3. Methodology in which measurements were made upon CBCT by a blinded calibrated examiner. These may justify the observed outcomes, which are inline with the existing literature, but with lower mean values.

CHAPTER 6. CONCLUSIONS

In this study, a novel volumetric analysis was performed, which demonstrated that socket grafting for alveolar ridge preservation provides a beneficial effect by preserving the alveolar volume. This leads to a decreased probability of requiring additional grafting at the implant site. Attention to the thickness of the buccal plate at the time of extraction may help the clinician predict the amount of resorption to take place. According to this study, if the thickness of the buccal plate is less than 1mm and ridge preservation is not performed then one might expect >10% reduction of the alveolar ridge at the extraction site. More resorption should be expected, as the buccal plate gets increasingly thinner.

APPENDIX A - FIGURES

Figure A1. – Study Timeline

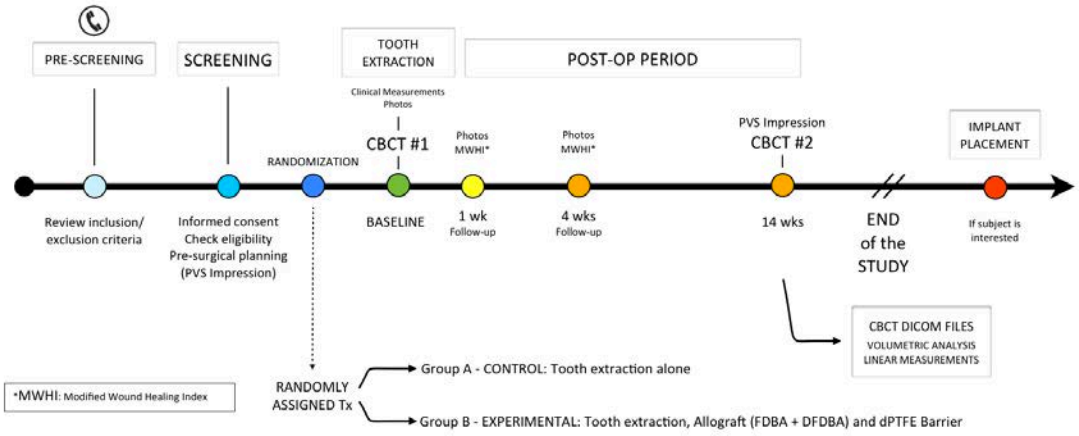
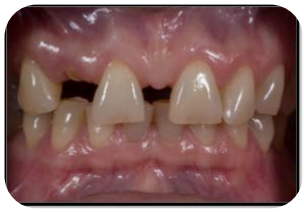
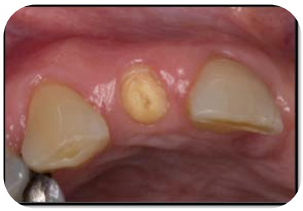


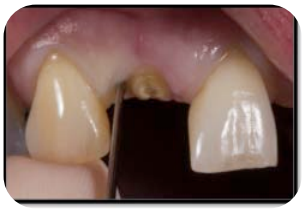
Figure A2. – Baseline Surgery



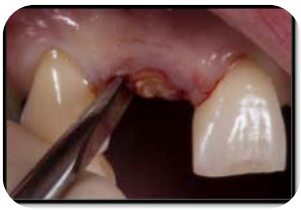
Patient presents with fractured #7 at the gingival margin



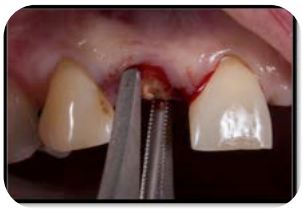
Occlussal view of fractured #7



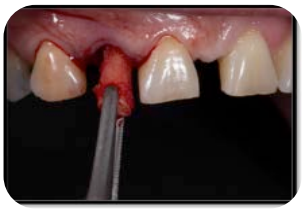
Periotome used to release the dento-gingival fibers



Elevation achieved with a straight elevator

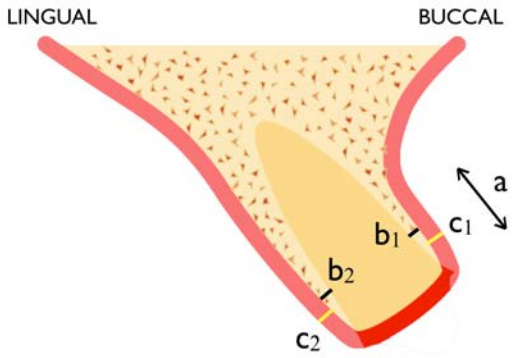


Forceps placed under the gingiva and onto the root surface



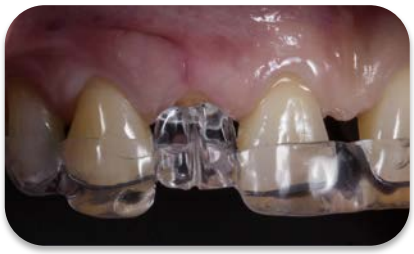
Tooth #7 extracted

Figure A3. – Baseline Measurements Diagram

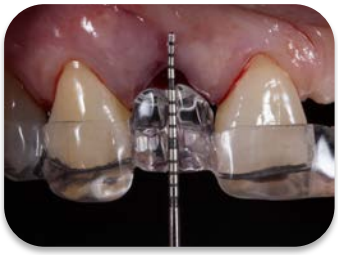


a - Width of buccal KG (using a stent)
b_1 - Buccal plate thickness 1 mm apical from the bone crest
b_2 - Lingual plate thickness 1 mm apical from the bone crest
c_1 - Buccal gingiva thickness 2 mm apical from the gingival margin
c_2 - Lingual gingiva thickness 2 mm apical from the gingival margin

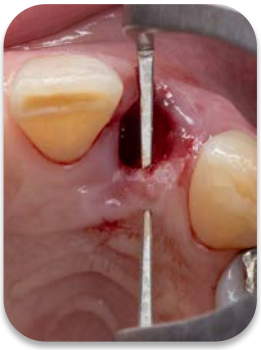
Figure A4. – Clinical Measurements at Baseline



Stent placed after extraction

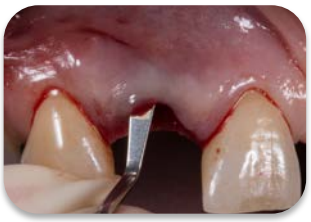


Apico-coronal width of the keratinized mucosa relative to the stent

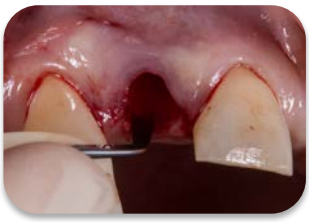


Palatal plate thickness

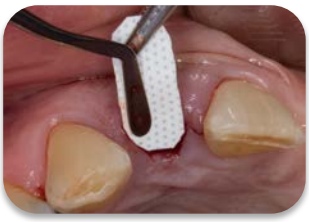
Figure A5. – Socket Grafting Procedure



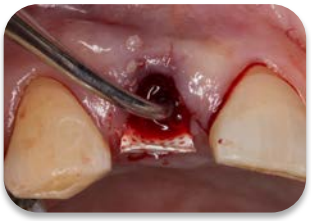
Elevation of the buccal sub-periosteal flap



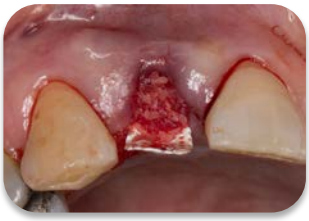
Elevation of the palatal sub-periosteal flap



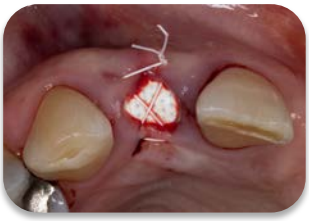
PTFE membrane being placed



PTFE membrane placed under palatal soft tissue



Allograft material placed in the socket



PTFE membrane placed over graft material and under buccal soft tissue, and sutured in place

Figure A6. – Modified Wound Healing Index

Modified Wound Healing Scale (Mod-CWHS)	
1	Uneventful wound healing with no gingival edema, erythema, suppuration, discomfort or barrier exposure
2	Uneventful wound healing with slight gingival edema, erythema, or discomfort but no suppuration
3	Poor wound healing with significant gingival edema, erythema, discomfort, loss of barrier or any suppuration

Figure A7. – Plaque Index

PLAQUE INDEX (Quigley Hein – Modified By Turesky et al. 1970)											
0 No plaque		**1** Cervical plaque flecks		**2** Thin layer, <1 mm		**3** >1mm, but <1/3		**4** >1/3, but <2/3		**5** > 2/3 covered	
B	**L**	**B**	**L**	**B**	**L**	**B**	**L**	**B**	**L**	**B**	**L**

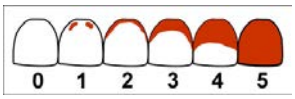
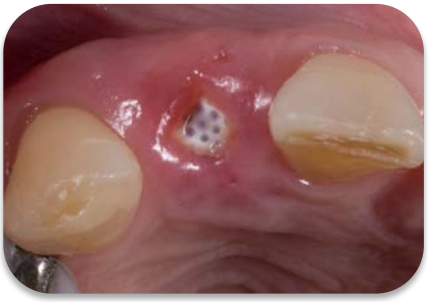


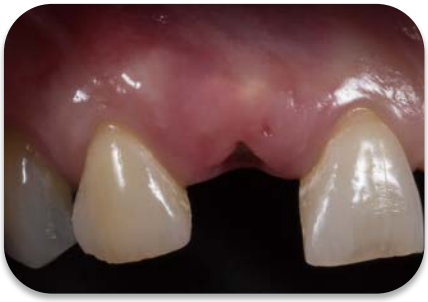
Figure A8. – Scale used for patient reported discomfort

DISCOMFORT
Less ---------- More

Figure A9. – 1-Week Follow-up

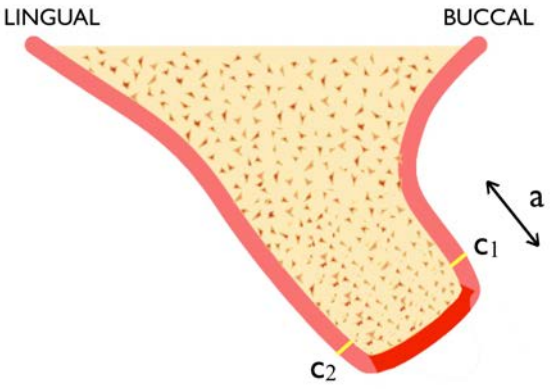


One week post-op with a wound healing index of 2

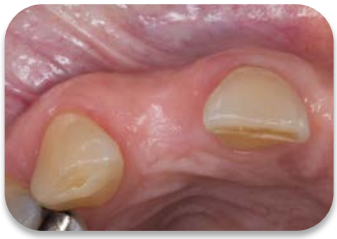


Facial view at 1 week after suture removal

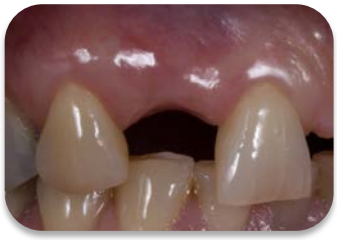
Figure A10. - 14-week follow-up measurements



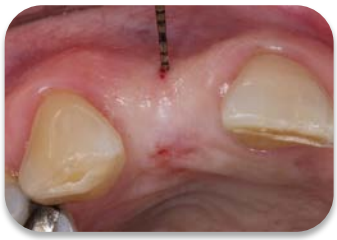
a - Width of buccal KG (using a stent)
c_1 - Buccal gingiva thickness 2 mm apical from the gingival margin
c_2 - Lingual gingiva thickness 2 mm apical from the gingival margin



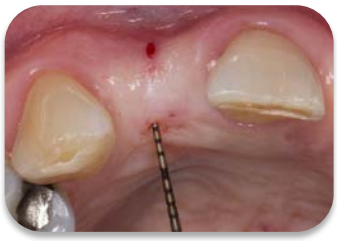
Occlusal view at 14-weeks- site #7, test group



Facial view at 14-weeks- site #7, test group

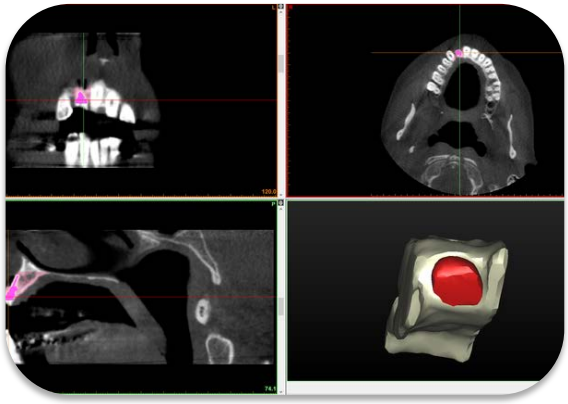


Periodontal probe piercing through the soft tissue to measure buccal keratinized mucosa thickness

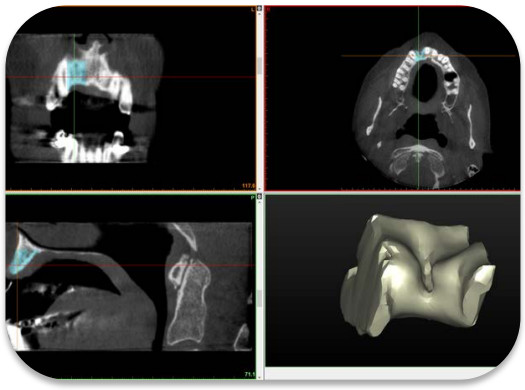


Periodontal probe piercing through the soft tissue to measure palatal gingiva thickness

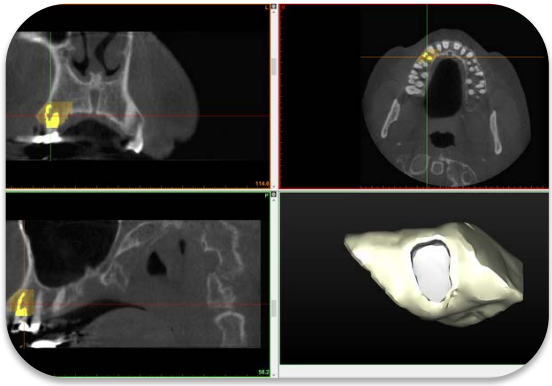
Figure A11. - Diagram showing the selection of the VOI on the CBCT on a control and test subject.



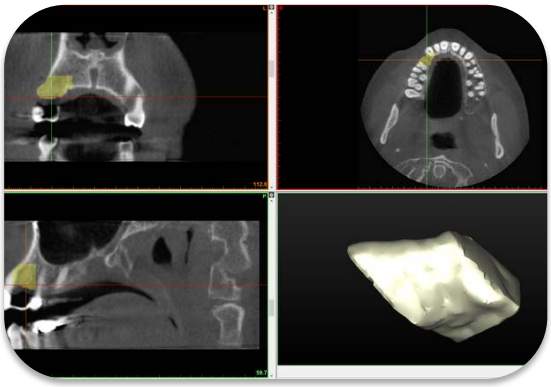
Selection of the VOI in a control case at baseline visit



Selection of the VOI in a control case at 14 weeks.

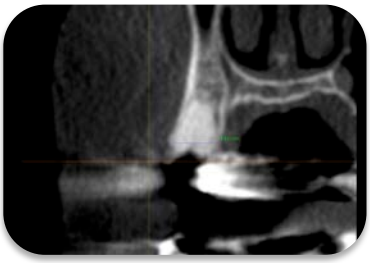


Selection of the VOI in a test case at the baseline visit

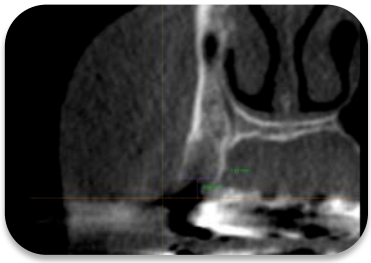


Selection of the VOI in a test case at 14 weeks

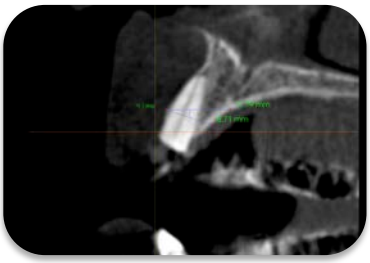
Figure A12.- Linear ridge width dimension on CBCT



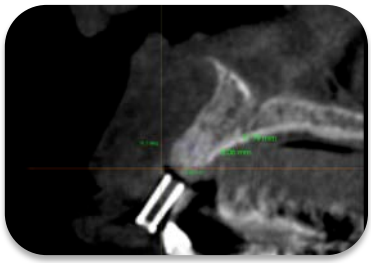
Baseline ridge width measurement in a control patient with the buccal and lingual walls perpendicular to the adjacent CEJs



14-week ridge width measurement in a control patient with the buccal and lingual walls perpendicular to the adjacent CEJs

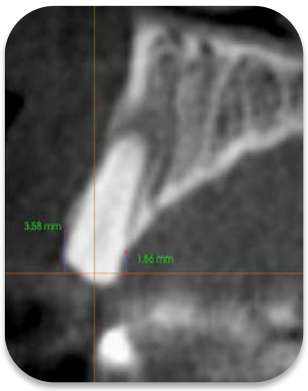


Baseline ridge width measurement in a test patient with the buccal and lingual walls not perpendicular to the adjacent CEJs so a repeatable bisecting angle was created

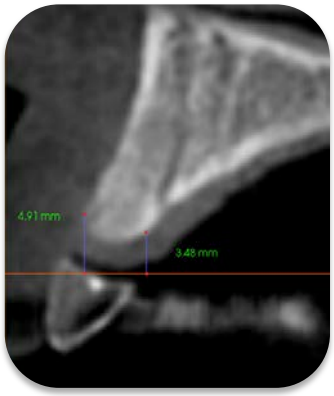


14-week ridge width measurement in a test patient with the buccal and lingual walls not perpendicular to the adjacent CEJs. The angle was repeated and ridge width measured

Figure A13. – Buccal and lingual crestal height on CBCT

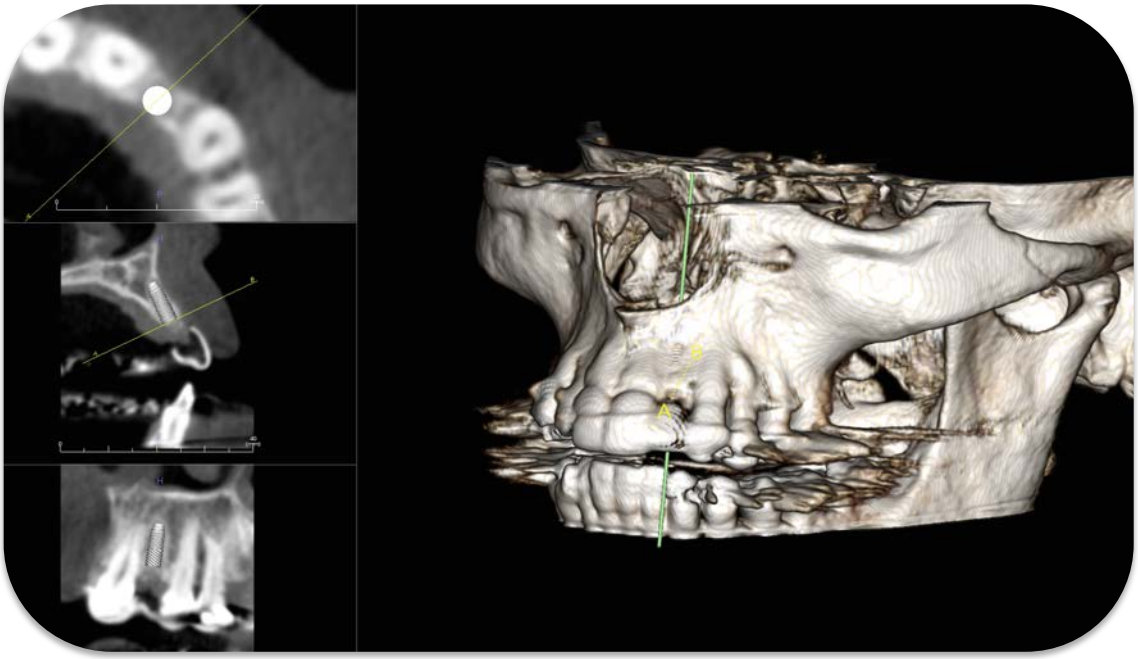


Baseline buccal and lingual crest height measurement



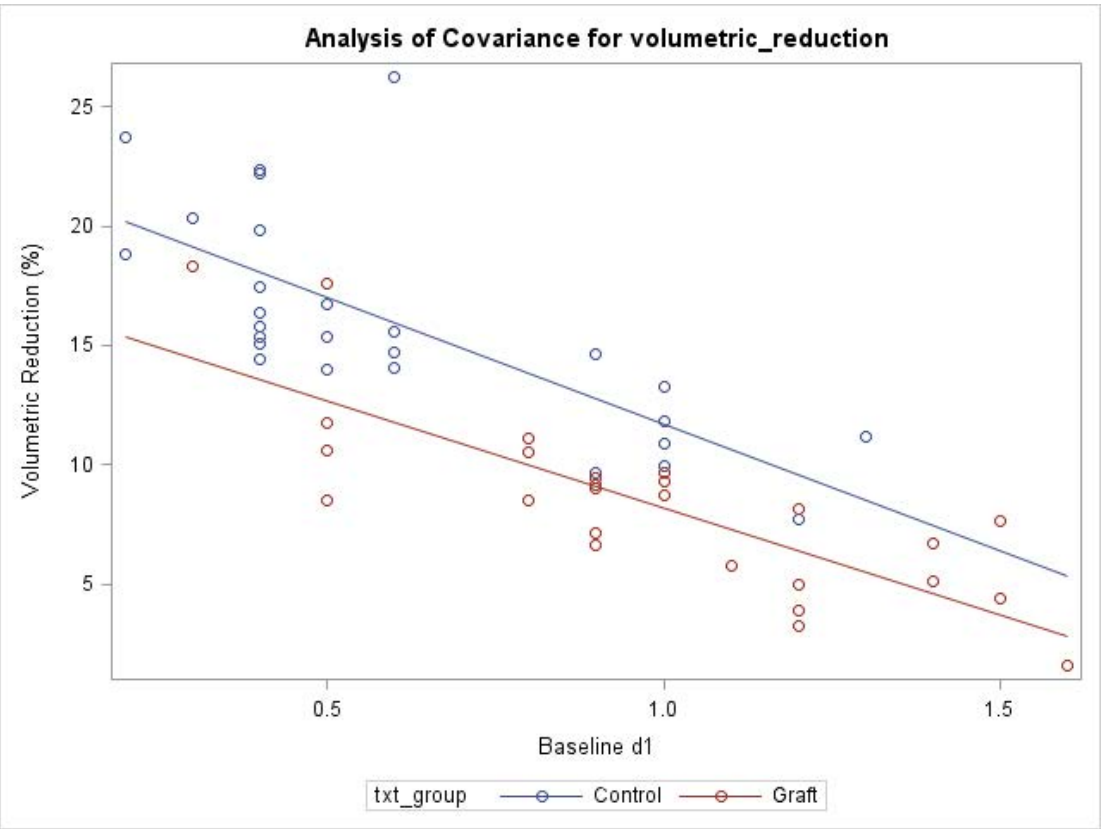
14-week buccal and lingual crest height measurement

Figure A14. – Digital placement of 3.5mm diameter x 9mm length implant



Virtual placement of #10, a 3.5 x9mm implant, in ideal restorative location with apical perforation and the need for additional grafting

Figure A15. - Baseline buccal bone thickness (mm) plotted with % volumetric reduction at 14-weeks.



APPENDIX B - TABLES

Table B1. – Baseline Patient Based Parameters

Baseline Parameter	Control	Graft
Age	57.24±11.82	58.46 ±12.37
Gender	F-14 M-13	F-17 M-9
BMI	Control- 32.02±7.52	Graft- 29.17±6.65

Table B2. – Baseline clinical measurements (all expressed in mm)

Baseline Clinical Parameters	**Control**	**Graft**
Keratinized Mucosa	3.81±1.27	4.31±1.69
Buccal Bone Thickness	0.61±0.31	0.98±0.35
Lingual Bone Thickness	1.00±0.36	0.87±0.24
Buccal Gingival Thickness	0.49±0.2	0.43±0.13
Lingual Gingival Thickness	0.83±0.33	0.84±0.36
Baseline Bucco-Lingual Width	9.26±1.4	9.36±2.34

Table B3. – Extraction sites

	Control	**Test**
Maxillary Central Incisors	3	2
Maxillary Lateral Incisors	5	5
Maxillary Canines	2	2
Mandibular Canines	0	1
Maxillary Pre-Molars	13	11
Mandibular Pre-Molars	4	5

Table B4. – Patient Reported Discomfort

Discomfort- Median (IQR)	**Control**	**Graft**	**Graft vs. Control p-value**
Week-1	6 (0-10	6 (1-13)	p=0.419
Week-4	0 (0-3)	2 (0-3)	p=0.531
Overall at Week-14	3 (0-13)	5 (1-11)	p=0.383

Table B5. – Change in soft and hard tissue thickness associated with ridge width change

	Control Median (IQR)	**Graft Median (IQR)**
Change in B-L Ridge Width	-1.68 (95% CI: -2.10, -1.26)	-1.07 (95% CI: -1.49, -0.64)
Change in Buccal Soft Tissue Thickness	1.1 (0.6-1.9)	1.2 (0.8-1.5)
Change in Lingual Soft Tissue Thickness	1.2 (0.7-1.5)	1.1 (0.9-1.5)

Table B6. – Clinical measurements at baseline and 14-week follow-up

Variable	**Time**	**Graft**	**Control**	**Graft vs. Control Wilcoxon rank-sum test p-value**
		Median (IQR)	**Median (IQR)**	
Buccal Gingiva Thickness	Baseline	0.4 (0.3-0.5)	0.5 (0.4-0.5)	0.5
	Week 14	1.5 (1-2)	1.5 (1-2)	>0.99
	Change Test: change=0	1.2 (0.8-1.5) p<0.0001	1.1 (0.6-1.9) p<0.0001	0.78
Lingual Gingiva Thickness	Baseline	0.8 (0.5-1.0)	0.8 (0.5-1.1)	>0.99
	Week 14	2.0 (2.0-2.0)	2.0 (1.5-2.5)	>0.99
	Change Test: change=0	1.1 (0.9-1.5) p<0.0001	1.2 (0.7-1.5) p<0.0001	0.759
Apico-Coronal Width of Keratinized Mucosa	Baseline	4.31 (0.28)	3.81 (0.27)	0.415
	Week 14	4.19 (0.28)	3.68 (0.27)	0.389
	Change Test: change=0	-0.12 (95% CI: -0.64, 0.41) p>0.99	-0.13 (95% CI: -0.65, 0.39) p>0.99	0.965

Table B7. – Radiographic height of the buccal and lingual plates

Variable	Time	Graft	Control	Graft vs. Control Wilcoxon rank-sum test
		Median (IQR)	**Median (IQR)**	**p-value**
Facial Plate Height	Baseline	2.33 (0.93-3.50)	3.03 (1.98-3.73)	0.595
	Week 14	3.38 (2.56-4.50)	4.20 (3.26-6.28)	0.094
	Change Test: change=0 (Wilcoxon signed-rank)	0.61 (0.46-0.94) p<0.0001	1.17 (0.70-2.10) p<0.0001	0.012
Lingual Plate Height	Baseline	1.82 (1.25-2.33)	1.40 (0.93-3.03)	>0.99
	Week 14	2.80 (1.70-3.02)	2.80 (1.86-3.70)	0.535
	Change Test: change=0	0.47 (0.23-0.94) p<0.0001	0.70 (0.46-1.40) p<0.0001	0.075

Table B8. – Radiographic ridge width changes

Variable	Time	Graft	Control	Graft vs. Control p-value
		Mean (SE)	**Mean (SE)**	
Buccolingual ridge width	Baseline	9.36 (0.38)	9.26 (0.37)	>0.99
	Week 14	8.29 (0.45)	7.58 (0.44)	0.517
	Change Test: change=0	-1.07 (95% CI: -1.49, -0.64) p<0.0001	-1.68 (95% CI: -2.10, -1.26) p<0.0001	0.023

Table B9. – Wound healing indices at follow-up appointments

	Control Mean ± SD	**Graft Mean ± SD**
1-Week	2.04 ± 0.44	2.04 ± 0.2
4-Weeks	1.33 ± 0.55	1.77 ± 0.43
14-Weeks	1 ± 0	1 ± 0

Table B10. – Volumetric ridge reduction in cubic mm

Variable	**Graft (n=26)**	**Control (n=27)**	**Graft vs. Control p-value**
Volumetric reduction % Mean (SD)	8.36 (3.81)	15.83 (4.48)	t-test <0.0001

Table B11. – Correlation of baseline clinical variables with ridge volume reduction

Variable	**Graft**			**Control**			**Same slope (Graft and Control)**		
	slope	**95% CI**	**p-value**	**slope**	**95% CI**	**p-value**	**slope**	**95% CI**	**p-value**
Buccal Plate Thickness	-8.82	-12.11, -5.73	<0.0001	-10.59	-14.11, -7.08	<0.0001	-9.68	-12.02, -7.33	<0.0001
Lingual Plate Thickness	-1.94	-9.00, 5.12	0.583	0.75	-3.86, 5.36	0.746	-0.06	-3.89, 3.78	0.968
Buccal Gingiva Thickness	-3,75	-16.90, 9.40	0.570	-0.33	-8.85, 8.18	0.938	-1.34	-8.43, 7.75	0.705
Lingual Gingiva Thickness	-1.60	-6.26, 3.06	0.494	3.63	-1.26, 8.51	0.142	0.89	-2.52, 4.31	0.602
Width of Buccal KG	-0.56	-1.55, 0.44	0.269	-0.05	-1.26, 1.25	0.940	-0.37	-1.15, 0.42	0.352

Table B12. – Classification for the outcome <10% volumetric reduction

Prob Level	Correct		Incorrect		Percentages				
	Event	Non-Event	Event	Non-Event	Correct	Sensitivity	Specificity	FALSE POS	FALSE NEG
0	23	0	30	0	43.4	100	0	56.6	.
0.02	23	19	11	0	79.2	100	63.3	32.4	0
0.04	23	19	11	0	79.2	100	63.3	32.4	0
0.06	23	19	11	0	79.2	100	63.3	32.4	0
0.08	23	20	10	0	81.1	100	66.7	30.3	0
0.1	22	20	10	1	79.2	95.7	66.7	31.3	4.8
0.12	21	20	10	2	77.4	91.3	66.7	32.3	9.1
0.14	21	20	10	2	77.4	91.3	66.7	32.3	9.1
0.16	21	20	10	2	77.4	91.3	66.7	32.3	9.1
0.18	21	21	9	2	79.2	91.3	70	30	8.7
0.2	20	21	9	3	77.4	87	70	31	12.5
0.22	20	21	9	3	77.4	87	70	31	12.5
0.24	20	21	9	3	77.4	87	70	31	12.5
0.26	20	24	6	3	83	87	80	23.1	11.1
0.28	20	24	6	3	83	87	80	23.1	11.1
0.3	20	24	6	3	83	87	80	23.1	11.1
0.32	20	24	6	3	83	87	80	23.1	11.1
0.34	20	27	3	3	88.7	87	90	13	10
0.36	20	27	3	3	88.7	87	90	13	10
0.38	20	27	3	3	88.7	87	90	13	10
0.4	20	27	3	3	88.7	87	90	13	10
0.42	20	27	3	3	88.7	87	90	13	10
0.44	20	27	3	3	88.7	87	90	13	10
0.46	20	27	3	3	88.7	87	90	13	10
0.48	20	27	3	3	88.7	87	90	13	10
0.5	20	27	3	3	88.7	87	90	13	10
0.52	20	27	3	3	88.7	87	90	13	10
0.54	20	27	3	3	88.7	87	90	13	10
0.56	19	27	3	4	86.8	82.6	90	13.6	12.9
0.58	19	27	3	4	86.8	82.6	90	13.6	12.9
0.6	19	27	3	4	86.8	82.6	90	13.6	12.9
0.62	19	27	3	4	86.8	82.6	90	13.6	12.9
0.64	19	27	3	4	86.8	82.6	90	13.6	12.9
0.66	19	27	3	4	86.8	82.6	90	13.6	12.9
0.68	19	27	3	4	86.8	82.6	90	13.6	12.9
0.7	18	27	3	5	84.9	78.3	90	14.3	15.6
0.72	18	27	3	5	84.9	78.3	90	14.3	15.6
0.74	18	27	3	5	84.9	78.3	90	14.3	15.6
0.76	18	27	3	5	84.9	78.3	90	14.3	15.6
0.78	18	27	3	5	84.9	78.3	90	14.3	15.6
0.8	18	29	1	5	88.7	78.3	96.7	5.3	14.7
0.82	18	29	1	5	88.7	78.3	96.7	5.3	14.7
0.84	13	29	1	10	79.2	56.5	96.7	7.1	25.6
0.86	13	29	1	10	79.2	56.5	96.7	7.1	25.6
0.88	13	29	1	10	79.2	56.5	96.7	7.1	25.6
0.9	13	29	1	10	79.2	56.5	96.7	7.1	25.6
0.92	10	30	0	13	75.5	43.5	100	0	30.2
0.94	10	30	0	13	75.5	43.5	100	0	30.2
0.96	10	30	0	13	75.5	43.5	100	0	30.2
0.98	9	30	0	14	73.6	39.1	100	0	31.8
1	0	30	0	23	56.6	0	100	.	43.4

APPENDIX C – ADDITIONAL FORMS

INFORMED CONSENT DOCUMENT

Project Title: **Efficacy of Socket Grafting for Alveolar Ridge Preservation: A Randomized Controlled Clinical Trial**

Principal Investigator: **Dr. Gustavo Avila Ortiz**

Research Team Contact: **Dr. Gustavo Avila-Ortiz 319-335-7232**
Dr. Mitchell Gubler 435-669-6157
Ms. Lauren Thomann 319-335-7377

This consent form describes the research study to help you decide if you want to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits entailed, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask a member of the research team for more information.
- You should discuss your participation with anyone you choose, such as family or friends.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you to participate in this research study because you are a candidate for tooth extraction and implant placement.
The purpose of this research study is to determine if a grafting technique can significantly contribute to prevent bone loss and enhance gum esthetics after tooth extraction.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 60 people are expected to take part in this study at the University of Iowa. Subjects will be distributed between two treatment groups: test and control. The control group receives no bone grafting treatment. It will randomly be determined which of the subjects will receive the test treatment and which will receive the control treatment.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, you can expect to spend 4-6 months involved in it. This participation consists of a minimum of 5 visits (including this visit) averaging about 2 hours per visit, but some may range from 1-4 hrs.

WHAT WILL HAPPEN DURING THIS STUDY?

Screening visit
After reading and signing this informed consent form, you will complete a detailed medical and dental history form. It will be reviewed with you to ensure you can safely participate in the study. You will also have an oral exam to determine if you qualify for the study. You will also have digital dental x-rays of the area for tooth extraction, which is standard of care. You will also have dental impressions (molds of your teeth), which are made in order to design and fabricate make a guide to record some of the research measurements. This visit will last about 2-3 hours.

Baseline visit
In less than 8 weeks after the screening visit, you will have the tooth extraction, which will be similar to an extraction performed for patients who are not enrolled in the study. Prior to this visit, you will be randomly assigned to one of two groups:

1. Control group receives the extraction, but no grafting.
2. Small bone graft pieces in the socket plus a barrier membrane.

After numbing the area, the extraction will be performed and the tooth socket will be cleaned which is similar to that done for patients who are not enrolled in the study. At this time measurements of the area will be taken. These measurements will not cause you any extra discomfort. If you belong to the group of patients planned to have socket grafting, you will receive it after tooth extraction. Neither of these procedures is experimental. In this case, a membrane will be placed over the socket to serve as a protective barrier and enable bone to grow. This area will then be sutured (with one stitch) and allowed to heal. You will be given prescriptions for an antibiotic, a pain reliever and a mouth rinse. You will also receive home care instructions before you leave. After the surgical procedure, a dental scan (CBCT) will be taken for research measurements. This visit will last about 2 ½-3 hours.

Post operative follow up visits
You will return to the clinic at 1 week, 4 weeks and 14 weeks after tooth extraction for follow up, which is standard care. You will have an oral exam and the researchers will monitor how well you are healing.
These visits will last ½ to 1 hour.

Audio Recording/Video Recording/Photographs
One aspect of this study involves making intraoral photographs of the tooth/site. These are made for documentation purposes and may be taken at each study visit. You will not be identified in any of the photographs taken in this study.
[ ] Yes [ ] No I give you permission to make photographs of me during this study.

Follow-up Study
The CBCT made at 14 weeks after tooth extraction will be used to determine implant placement of the following research study. If after healing it appears that you will be

eligible for implant placement without additional bone grafting you may be contacted for another study that will follow this study.
Being a part of this study does not obligate you to participate in any future studies. A separate informed consent form will be presented to you should you choose to participate in the continuation study.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Risks associated with tooth extraction

There are risks and discomfort due to tooth extractions for which you will receive separate routine information.

Risks associated with X-rays

There is no discomfort related to the x-rays. Specific risks with radiation are unknown, and could happen many years after the x-ray was performed. The amount of radiation used for one intraoral film is relatively low; approximately equal to the amount of radiation you receive naturally from background radiation in 2 weeks while living in this part of the country. The amount of radiation used for one cone beam scan (digital x-rays) is approximately 12 times more than an intraoral film. Even though the radiation dose is low, you should **not participate** in the study if you are or think you might be pregnant. Female subjects must be postmenopausal for at least 2 years, surgically sterilized, or utilize effective birth control. Wearing a lead apron will minimize these risks.

Risk associated with grafting materials

The therapies included in this study have been documented and published before, in association with satisfactory clinical outcomes. However there is a possibility that the bone does not show evidence of healing on you. If the bone shows no evidence of healing, you may be treated with any additional therapy recommended by your surgeon.

Although the experimental material is tested for sterility and there is no reported case in dental literature of infection from the grafting material to be used in this study, as with the use of any bone graft material, there is the possibility of infection from its use. If you are allergic to any of the elements contained in the grafting materials, you may experience a low blood pressure (hypotension) or in severe cases you could experience difficulty breathing (anaphylaxis). As it occurs with any research study, there may be additional risks that are unknown or unexpected.

WHAT ARE THE BENEFITS OF THIS STUDY?

We don’t know if you will benefit from being in this study.
However, we hope that, in the future, other people will benefit from this study because we may be able to decrease the number of procedures and time between tooth extraction and implant placement.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

The study will cover the costs for your x-rays, CBCT scans, surgery and exams. If tooth replacement is desired, after tooth extraction and prior to implant restoration, a device can be prepared for you, but you will be charged (although a reduced fee) $80. Insurance companies often deny many if not all of these treatments.

WILL I BE PAID FOR PARTICIPATING?

Yes, you will receive three payments of $20 each at baseline and 4 weeks and 14 weeks after it.

WHO IS FUNDING THIS STUDY?

Osteogenics Biomedical is funding this research study. This means that the University of Iowa is receiving payments from Osteogenics Biomedical to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from Osteogenics Biomedical for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

- If you are injured or become ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.
- The University of Iowa does not plan to provide free medical care or payment for treatment of any complication, illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.
- If you experience a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

WILL YOU KEEP MY NAME ON FILE TO GIVE TO OTHERS?

We will keep information about you in a special kind of computer listing called a registry. A registry keeps information about you on file so that *other* researchers, not involved in this particular study, may contact you in the future about whether you are interested in being in *different* research studies. The registry will contain information such as your name, address, age, and selected medical information such as diagnosis and treatment. We will keep the information in this registry secure in locked cabinets behind a locked door. You may request that your personal information be removed from this file at any time by contacting:

Gustavo Avila-Ortiz, DDS, MS, PhD
Mailing Address: University of Iowa College of Dentistry, 801 Newton Rd. Iowa City, IA 52240
Phone: **319-335-7232**
Email: gustavo-avila@uiowa.edu

[ ] Yes [ ] No I give you permission to put my name and personal information in a registry so that other researchers can contact me in the future about different research studies.

WHAT ABOUT CONFIDENTIALITY?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Federal government regulatory agencies,
- U.S. Food and Drug Administration and the sponsor, Osteogenics Biomedical.
- People who use the registry
- Auditing departments of the University of Iowa
- The University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

In the future, Osteogenics Biomedical may continue to use some information that is collected as part of this study. For example, Osteogenics Biomedical may combine information from this study with the results of other studies to re-analyze the safety and effectiveness of the study grafting material, to evaluate other products or therapies, to develop a better understanding of a disease, or to improve the design of future research studies. Osteogenics Biomedical may also share information from the study with regulatory agencies in foreign countries.

To help protect your confidentiality, we will Subjects enrolled will have their privacy protected throughout the research study. ID codes will be assigned to each subject, and no personal identifiers will be used for the ID code. The protected health information (PHI) gathered for the study will be limited to PHI that affects the subject's inclusion/exclusion criteria and ongoing participation in the study. No other PHI will be collected. Only members of the research team will have access to each subject's study information. Records will be kept in locked cabinets within locked offices and password protected computers. Only 3 individuals will have access to these records: Ms. Lauren Thomann, Dr. Gustavo Avila and Dr. Mitch Gubler.

If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

“A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.”

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I Decide to Drop Out of the Study?

If you choose, you may leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

If you decide to leave the study early, we will ask you to contact one of the contact persons listed. It may be recommended that you return for post-operative appointments but not within the study.

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can Someone Else End my Participation in this Study?

Under certain circumstances, the researchers or Osteogenics Biomedical might decide to end your participation in this research study earlier than planned. This might happen because in our judgment it would not be safe for you to continue, because your condition has become worse, because you are or became pregnant, because funding for the research study has ended, because the sponsor has decided to stop the research, etc.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself or if you experience a research-related injury, please contact: Dr. Gustavo Avila-Ortiz - 319-335-7232; Dr. Mitchell Gubler – 435-669-6157 or Ms. Lauren Thomann 319-335-7377.

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://hso.research.uiowa.edu/. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Subject's Name (printed):

_____

Do not sign this form if today's date is on or after $STAMP_EXP_DT.

_____

_____

(Signature of Subject) (Date)

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____

(Signature of Person who Obtained Consent) (Date)

BIBLIOGRAPHY

Amler, M. H. (1969). "The time sequence of tissue regeneration in human extraction wounds." Oral Surg Oral Med Oral Pathol **27**(3): 309-318.

Araujo, M. G., J. C. da Silva, A. F. de Mendonca and J. Lindhe (2015). "Ridge alterations following grafting of fresh extraction sockets in man. A randomized clinical trial." Clin Oral Implants Res **26**(4): 407-412.

Araujo, M. G. and J. Lindhe (2005). "Dimensional ridge alterations following tooth extraction. An experimental study in the dog." J Clin Periodontol **32**(2): 212-218.

Artzi, Z. and C. E. Nemcovsky (1998). "The application of deproteinized bovine bone mineral for ridge preservation prior to implantation. Clinical and histological observations in a case report." J Periodontol **69**(9): 1062-1067.

Avila-Ortiz, G., S. Elangovan, K. W. Kramer, D. Blanchette and D. V. Dawson (2014). "Effect of alveolar ridge preservation after tooth extraction: a systematic review and meta-analysis." J Dent Res **93**(10): 950-958.

Avila-Ortiz, G., J. C. Rodriguez, I. Rudek, E. Benavides, H. Rios and H. L. Wang (2014). "Effectiveness of three different alveolar ridge preservation techniques: a pilot randomized controlled trial." Int J Periodontics Restorative Dent **34**(4): 509-521.

Barone, A., N. N. Aldini, M. Fini, R. Giardino, J. L. Calvo Guirado and U. Covani (2008). "Xenograft versus extraction alone for ridge preservation after tooth removal: a clinical and histomorphometric study." J Periodontol **79**(8): 1370-1377.

Barone, A., M. Ricci, P. Tonelli, S. Santini and U. Covani (2013). "Tissue changes of extraction sockets in humans: a comparison of spontaneous healing vs. ridge preservation with secondary soft tissue healing." Clin Oral Implants Res **24**(11): 1231-1237.

Brennan, D. S., A. J. Spencer and K. F. Roberts-Thomson (2008). "Tooth loss, chewing ability and quality of life." Qual Life Res **17**(2): 227-235.

Cardaropoli, D. and G. Cardaropoli (2008). "Preservation of the postextraction alveolar ridge: a clinical and histologic study." Int J Periodontics Restorative Dent **28**(5): 469-477.

Cardaropoli, D., L. Tamagnone, A. Roffredo and L. Gaveglio (2014). "Relationship between the buccal bone plate thickness and the healing of postextraction sockets with/without ridge preservation." Int J Periodontics Restorative Dent **34**(2): 211-217.

Cardaropoli, G., M. Araujo and J. Lindhe (2003). "Dynamics of bone tissue formation in tooth extraction sites. An experimental study in dogs." J Clin Periodontol **30**(9): 809-818.

Cawood, J. I. and R. A. Howell (1988). "A classification of the edentulous jaws." Int J Oral Maxillofac Surg **17**(4): 232-236.

Chappuis, V., O. Engel, M. Reyes, K. Shahim, L. P. Nolte and D. Buser (2013). "Ridge alterations post-extraction in the esthetic zone: a 3D analysis with CBCT." J Dent Res **92**(12 Suppl): 195s-201s.

Clozza, E., M. Biasotto, F. Cavalli, L. Moimas and R. Di Lenarda (2012). "Three-dimensional evaluation of bone changes following ridge preservation procedures." Int J Oral Maxillofac Implants **27**(4): 770-775.

Darby, I., S. T. Chen and D. Buser (2009). "Ridge preservation techniques for implant therapy." Int J Oral Maxillofac Implants **24 Suppl**: 260-271.

Donahue, T. J. (1980). "The case against the edentulous ridge--and an alternative." J Am Dent Assoc **101**(5): 781-784.

Douglass, C. W., A. Shih and L. Ostry (2002). "Will there be a need for complete dentures in the United States in 2020?" J Prosthet Dent **87**(1): 5-8.

Evian, C. I., E. S. Rosenberg, J. G. Coslet and H. Corn (1982). "The osteogenic activity of bone removed from healing extraction sockets in humans." J Periodontol **53**(2): 81-85.

Felton, D., L. Cooper, I. Duqum, G. Minsley, A. Guckes, S. Haug, P. Meredith, C. Solie, D. Avery and N. D. Chandler (2011). "Evidence-based guidelines for the care and maintenance of complete dentures: a publication of the American College of Prosthodontists." J Am Dent Assoc **142 Suppl 1**: 1s-20s.

Flugge, T., K. Nelson, C. Nack, A. Stricker and S. Nahles (2015). "2-Dimensional changes of the soft tissue profile of augmented and non-augmented human extraction sockets: a randomized pilot study." J Clin Periodontol **42**(4): 390-397.

Fotek, P. D., R. F. Neiva and H. L. Wang (2009). "Comparison of dermal matrix and polytetrafluoroethylene membrane for socket bone augmentation: a clinical and histologic study." J Periodontol **80**(5): 776-785.

Gargiulo, A. W., F. M. Wentz and B. Orban (1961). "Dimensions and relations of the dentogingival junction in humans." Journal of Periodontology **32**(3): 261-267.

Gerritsen, A. E., P. F. Allen, D. J. Witter, E. M. Bronkhorst and N. H. Creugers (2010). "Tooth loss and oral health-related quality of life: a systematic review and meta-analysis." Health Qual Life Outcomes **8**: 126.

Goktas, S., J. J. Dmytryk and P. S. McFetridge (2011). "Biomechanical behavior of oral soft tissues." J Periodontol **82**(8): 1178-1186.

Hammerle, C. H., M. G. Araujo and M. Simion (2012). "Evidence-based knowledge on the biology and treatment of extraction sockets." Clin Oral Implants Res **23 Suppl 5**: 80-82.

Hefti, A. F. (1997). "Periodontal probing." Crit Rev Oral Biol Med **8**(3): 336-356.

Hormia, M., K. Owaribe and I. Virtanen (2001). "The dento-epithelial junction: cell adhesion by type I hemidesmosomes in the absence of a true basal lamina." J Periodontol **72**(6): 788-797.

Iasella, J. M., H. Greenwell, R. L. Miller, M. Hill, C. Drisko, A. A. Bohra and J. P. Scheetz (2003). "Ridge preservation with freeze-dried bone allograft and a collagen membrane compared to extraction alone for implant site development: a clinical and histologic study in humans." J Periodontol **74**(7): 990-999.

Jahangiri, L., H. Devlin, K. Ting and I. Nishimura (1998). "Current perspectives in residual ridge remodeling and its clinical implications: a review." J Prosthet Dent **80**(2): 224-237.

Jiang, Q., Y. Yu, H. Ruan, Y. Luo and X. Guo (2014). "Morphological and functional characteristics of human gingival junctional epithelium." BMC Oral Health **14**: 30.

Kassebaum, N. J., E. Bernabe, M. Dahiya, B. Bhandari, C. J. Murray and W. Marcenes (2015). "Global Burden of Untreated Caries: A Systematic Review and Metaregression." J Dent Res.

Kennedy, J. E., W. C. Bird, K. G. Palcanis and H. S. Dorfman (1985). "A longitudinal evaluation of varying widths of attached gingiva." J Clin Periodontol **12**(8): 667-675.

Kristoffersen, E. K., R. G. Caffesse, C. E. Nasjleti and T. O. Kristoffersen (1983). "Ultrastructural study of induced keratinization in sulcular gingival epithelium in rhesus monkeys." Acta Odontol Scand **41**(4): 227-240.

Lang, N. P. and H. Loe (1972). "The relationship between the width of keratinized gingiva and gingival health." J Periodontol **43**(10): 623-627.

Lekovic, V., E. B. Kenney, M. Weinlaender, T. Han, P. Klokkevold, M. Nedic and M. Orsini (1997). "A bone regenerative approach to alveolar ridge maintenance following tooth extraction. Report of 10 cases." J Periodontol **68**(6): 563-570.

Mahesh, L., M. A. Salama, G. M. Kurtzman and F. P. Joachim (2012). "Socket grafting with calcium phosphosilicate alloplast putty: a histomorphometric evaluation." Compend Contin Educ Dent **33**(8): e109-115.

Murray, H., M. Clarke, D. Locker and E. J. Kay (1997). "Reasons for tooth extractions in dental practices in Ontario, Canada according to tooth type." Int Dent J **47**(1): 3-8.

Nanci, A. and D. D. Bosshardt (2006). "Structure of periodontal tissues in health and disease." Periodontol 2000 **40**: 11-28.

Osburn, R. C. (1974). "Preservation of the alveolar ridge: a simplified technique for retaining teeth beneath removable appliances." J Indiana State Dent Assoc **53**(1): 8-11.

Quigley, G. A. and J. W. Hein (1962). "Comparative cleansing efficiency of manual and power brushing." J Am Dent Assoc **65**: 26-29.

Schroeder, H. E. and M. A. Listgarten (1997). "The gingival tissues: the architecture of periodontal protection." Periodontol 2000 **13**: 91-120.

Schropp, L., A. Wenzel, L. Kostopoulos and T. Karring (2003). "Bone healing and soft tissue contour changes following single-tooth extraction: a clinical and radiographic 12-month prospective study." Int J Periodontics Restorative Dent **23**(4): 313-323.

Sharon R. Bannister, D. R. D., James B. Barnes, Frederick C. Bisch, Casey M. Campbell, Margaret Hill, Robert A. Faiella, Cristina Cunha Villar, and S. Jerome Zackin. (2001). Glossary of Periodontal Terms. Glossary of Periodontal Terms AAP. AAP. AAP Connect.

Simion, M., M. Baldoni, P. Rossi and D. Zaffe (1994). "A comparative study of the effectiveness of e-PTFE membranes with and without early exposure during the healing period." Int J Periodontics Restorative Dent **14**(2): 166-180.

Slade, G. D., A. A. Akinkugbe and A. E. Sanders (2014). "Projections of U.S. Edentulism prevalence following 5 decades of decline." J Dent Res **93**(10): 959-965.

Tan, W. L., T. L. Wong, M. C. Wong and N. P. Lang (2012). "A systematic review of post-extractional alveolar hard and soft tissue dimensional changes in humans." Clin Oral Implants Res **23 Suppl 5**: 1-21.

Ten Heggeler, J. M., D. E. Slot and G. A. Van der Weijden (2011). "Effect of socket preservation therapies following tooth extraction in non-molar regions in humans: a systematic review." Clin Oral Implants Res **22**(8): 779-788.

Thalmair, T., S. Fickl, D. Schneider, M. Hinze and H. Wachtel (2013). "Dimensional alterations of extraction sites after different alveolar ridge preservation techniques - a volumetric study." J Clin Periodontol **40**(7): 721-727.

Tristao, G. C., C. A. Barboza, Jr., D. M. Rodrigues and E. P. Barboza (2014). "Supracrestal gingival tissue measurement in normal periodontium: a human histometric study." Int J Periodontics Restorative Dent **34**(1): 97-102.

Turesky, S., N. D. Gilmore and I. Glickman (1970). "Reduced plaque formation by the chloromethyl analogue of victamine C." J Periodontol **41**(1): 41-43.

Vacek, J. S., M. E. Gher, D. A. Assad, A. C. Richardson and L. I. Giambarresi (1994). "The dimensions of the human dentogingival junction." Int J Periodontics Restorative Dent **14**(2): 154-165.

Van der Weijden, F., F. Dell'Acqua and D. E. Slot (2009). "Alveolar bone dimensional changes of post-extraction sockets in humans: a systematic review." J Clin Periodontol **36**(12): 1048-1058.

Vignoletti, F., P. Matesanz, D. Rodrigo, E. Figuero, C. Martin and M. Sanz (2012). "Surgical protocols for ridge preservation after tooth extraction. A systematic review." Clin Oral Implants Res **23 Suppl 5**: 22-38.

Wennstrom, J. L. (1987). "Lack of association between width of attached gingiva and development of soft tissue recession. A 5-year longitudinal study." J Clin Periodontol **14**(3): 181-184.

Yilmaz, S., E. Efeoglu and A. R. Kilic (1998). "Alveolar ridge reconstruction and/or preservation using root form bioglass cones." J Clin Periodontol **25**(10): 832-839.