Tufts University School of Dental Medicine

Department of Periodontology

Clinical Analysis of Demineralized Freeze Dried Bone Allograft and Deproteinized Bovine Bone Mineral Bone Graft Materials in a Bilateral Sinus Augmentation

Submitted in partial fulfillment of requirements for the degree of

Masters of Science

Tufts University School of Dental Medicine 2011

Thesis submitted by Sarah Stipho DMD

Thesis Committee

Principal Investigator:

Terrence Griffin DMD
Department of Periodontology
Tufts University
School of Dental Medicine
One Kneeland Street
Boston, MA 02111
Telephone: (617)636-6531
Terrence.Griffin@tufts.edu

Co- Investigator:

Sarah Stipho DMD
Department of Periodontology
Tufts University
School of Dental Medicine
One Kneeland Street
Boston, MA 02111
Sarah.Stipho@tufts.edu

Co- Investigator:

Yong Hur DMD, MSc
Department of Periodontology
Tufts University
School of Dental Medicine
One Kneeland Street
Boston, MA 02111
Yong.Hur@tufts.edu

Co-Investigator:

Khalid Al-Hezaimi BDS, MSc
Department of Periodontology
Tufts University
School of Dental Medicine
75 Kneeland Street
Boston, MA 02111
Khalid.Alhezaimi@tufts.edu

Co- Investigator:

Paul Stark PhD
Division of Advanced and Graduate Education
Tufts University
School of Dental Medicine
One Kneeland Street
Boston, MA 02111
Telephone: (617)636-3753
Paul.Stark@tufts.edu

Acknowledgements

I'd like to thank the following in helping me complete this thesis:

Dr. Terrence Griffin, chairman

Dr. Yong Hur

Dr. Khalid Al-Hezaimi

Dr. Paul Stark

Department of Periodontology at TUSDM

My mother and father and sister.

Engineer Abdullah Bugshan, Research Chair for Growth Factors and Bone Regeneration, College of Dentistry, King Saud University, Riyadh, Saudi Arabia.

Micro CT grant number# PG-IS-00019GFBR

Table of contents

Abstract

Sinus augmentation is often necessary in areas of the posterior maxilla where extensive alveolar bone resorption has occurred leading to insufficient bone height for adequate implant placement. The purpose of this study was to compare and analyze bone height and regeneration of two different bone graft materials in a split-mouth design: a demineralized freeze dried bone allograft incorporated with bone morphogenetic proteins and growth factors, Accell Connexus®, from Keystone Dental (Burlington, MA), and a deproteinized bovine bone mineral bone graft, Bio-Oss® product from Osteohealth, (Shirley, NY), which currently has been the standard material of choice.

After obtaining informed consent and evaluating inclusion criteria, ten patients underwent a bilateral sinus augmentation procedure, with one side utilizing Accell Connexus® and the other side utilizing Bio-Oss® material. The piezoelectric system (Piezotome, Acteon, Paris, France) was used to perform the access for the sinus augmentation procedures to enable the grafting. After six months healing time, core biopsies were taken at the same location of implant placement and sent for analysis. Each patient underwent panoramic and CT radiographs to evaluate bone density, height and volume. Micro-CT analysis was performed for all core samples to evaluate degree of mineralization. No statistical significance was found in density or volume between the two materials. However, statistical significance was found for height changes with a p value of < 0.001.

Bone graft materials used in the pneumatized sinus are needed for the placement of implants. The use of bone morphogenetic proteins and growth factors in these graft materials may suggest enhancement of healing but the loss in height due to resorption presents some disadvantage in these areas requiring implant placement.

Objectives

The performance of this proposed project will advance in the field of sinus augmentation by expanding knowledge regarding characteristics of the different types of materials for these procedures. The parameters of this study were height changes, volume, density and degree of mineralization. These important aspects are evaluated when augmenting sites for implant installation procedures. Adequate height, density and volume of bone at the time of implant insertion are needed for stability of the future implant while the mineralization and regenerative turnover rate determine the type of materials that are best suited for osseointegration with the implant.

Introduction

The maxillary sinus is the largest of all the paranasal sinuses and starts to develop at twelve weeks. It grows rapidly with the facial skeleton and at twelve years of age, drops to the same level as the nasal floor. The maxillary sinus is pyramidal in shape with its base forming the lateral nasal wall and its apex extending towards the zygoma. The size of the maxillary sinus varies between individuals and the average volume is 15 ml. The walls of the maxillary sinus are thin and uneven and the cavity is lined by pseudostratified columnar epithelium which is known as the *Schneiderian membrane*. One or more septa are sometimes present and can divide the sinus into compartments[1].

The posterior maxilla commonly presents with limitations in alveolar bone height for implant placement. Loss of maxillary molar teeth leads to rapid loss of bone in the maxillary sinus floor and increases the maxillary sinus cavity causing a phenomenon known as sinus pneumatization; bone loss can extend to the alveolar process, leaving a thin wall of bone between the maxillary sinus and the oral cavity[2,3,4]. This may compromise the alveolar bone height thereby limiting the possibilities of future implant placement in the affected sites. The successful placement and integration of endosseous implants under such circumstances requires augmentation of the maxillary sinus floor. This procedure may help raise the alveolar bone height facilitating future implant placement in the compromised sites[5,6]. Misch *et al.* (1987) showed that a minimum of 10mm vertical bone height is usually required for predicable implant success[7]; in addition, the bone density in the posterior maxilla is often poor which may also lead to a diminished implant success rate[8].

The sinus lift procedure was conceived and introduced by Tatum in 1976 at the Birmingham, Alabama implant meeting. However, the first publication on this surgical technique was reported by Boyne and James in 1980[9] followed by Tatum later in 1986[2]. The sinus augmentation surgery is a procedure in which the sinus membrane is elevated such that space is created to place more bone and thereby gaining more height and volume for future implant placement. These sinus augmentation procedures have been performed for several years and successful results of sinus lift surgeries for the placement of implants have been well documented by several studies[10,11].

Elevating the sinus involves augmenting and grafting the floor of the maxillary sinus with bone graft material. The grafting materials, which are derived from or composed of tissue involved in the growth or repair of bone, could encourage bone formation or stimulate quicker bone growth in bone implant sites[12].

Requirements of an ideal graft material should fulfill the following criteria: (1) osteoinduction, (2) osteoconduction and (3) volume stability[13]. Osteoinduction is a process in which bone is stimulated and induced in host tissue to form bone through osteogenesis, the process of formation and development of bone, and osteoconduction is the process in which a matrix is provided to serve as a scaffold on which new bone can be formed[12]. In addition, the ideal bone graft should exhibit several characteristics of which are non-antigenic, non-carcinogenic, non-toxic, resilient, strong, easily fabricated, resistant to infection, inexpensive and readily available[14].

Several studies have investigated the various types of bone graft materials used in sinus augmentation procedures. Tong *et al.* [15] evaluated the survival of implants 6-60

months after placement in patients having undergone sinus lift procedures using various graft materials. Some materials that have been studied include autogenous bone grafts [2,7,16], xenografts such as the anorganic deproteinized bovine-derived product Bio-Oss® (Osteohealth)[17], synthetic bone grafts including hydroxyapatite derivatives[18], B-tricalcium phosphate[19] and bioactive glass[20], allografts such as demineralized freeze-dried bone (DFDBA)[21, 22] and a combination of these to form composite grafts[23, 24, 25,26,27]. Several growth factors including bone morphogenetic proteins (BMPs) have also been used in many sinus augmentation procedures in order to enhance regeneration such as transforming growth factor-beta (TGF-B1) and bone morphogenetic proteins including BMP-2, BMP-4 and BMP-7. These growth factors have the capacity to promote healing in soft tissues as well as in bone. As native BMPs, they are responsible for cell migration, organization and bone formation. In the adult, BMPs control the process of new bone regeneration associated with osteoclastic resorption and therefore are responsible for the maintenance of bone mass and bone remodeling[28].

Autogenous bone was at one point considered to be the ideal material of choice for sinus grafting based on a consensus conference on sinus grafts held in 1996 where participants believed that autografts were most efficacious despite little evidence-based data[29]. However, it is known that autogenous bone is limited in its use by donor-site morbidity, sparse availability, and uncontrolled resorption[30,31,32]. Deproteinized bovine bone such as Bio-Oss has been successfully used as a grafting material in the maxillary sinus[33,34]. Bio-Oss appears to undergo slow or even no resorption for up to 6 years, as confirmed by clinical biopsies of many authors [35,36,37]. It has also been shown that non-resorbable graft materials do not remodel and functionally adapt to surrounding bone[38].

The ideal bone graft criteria are best analyzed histologically and a small number of randomized controlled clinical trials have been conducted to compare various grafting materials using histology[39]. Clinical and radiographic outcomes of grafts have been evaluated and studied for extended periods of time between three to five years[40]. While Raghoebar *et al.* and Hatano *et al.*[41,42] reported similar studies extending from one to ten years, it has been shown that long-term stability of sinus-graft height is an important factor for implant success.

Based on the Cawood and Howell[43] classification of bone loss, the residual alveolus may be classified in gradations of I (dentate) to VI (paper-thin). In classes IV to VI, vertical bone volume is the primary factor limiting implant placement[44]. In addition, bone density directly influences the amount of contact between the implant and bone surface which transmits load to bone. Thus for successful implant placement, a particular interest would be to analyze height, volume and density of graft materials that are used in the sinus augmentation procedures. These factors are analyzed and compared in two bone graft materials, Accell Connexus and Bio-Oss, in the present study.

Accell Connexus

Accell Connexus® (Keystone Dental, Boston, MA) is a demineralized human bone allograft mixed with a poloxamer reverse phase medium (RPM). It is formulated into a putty form and provided in a sterile, single use package. All tissue used in Accell Connexus is recovered by tissue banks in the United States in accordance with standards established by the American Association of Tissue Banks (AATB). The poloxamer RPM thickens at body temperature and resists irrigation allowing for better graft containment.

In addition, it is inert, biocompatible and safe. The material is moldable and easy to pack into any size or shape defect and has validated osteoinductive potential. The products of the Accell Connexus demineralized bone matrix (DBM) family are comprised of the same DBM and RPM components as found in DynaGraft II Gel, Food and Drug Administration (FDA) cleared under 510(k) number K040419 and Connexus cleared under 510(k)'s K050690 and K052098. In addition, the Accell Connexus DBM family of products may contain up to a maximum of 70% of RPM carrier. This is the concentration of RPM already cleared in DynaGraft II gel. Demineralized bone matrix preparations are particularly attractive as potential carriers for growth factors because they are osteoconductive and may have some osteoinductive potential as well. The carrier/delivery system must be able to deliver the growth factor at the appropriate time and in the proper dose, enhance cell recruitment and potentiate chemotaxis, and contain void spaces that can allow for cell migration and promotion of angiogenesis Finally, the carrier must be able to biodegrade without generating an immune or inflammatory response and without producing toxic waste products that would inhibit the repair process[45,46].

Demineralized Bone Matrix

Demineralized bone matrix consists of the organic portion of bone, including osteoinductive factors such as BMPs. The removal of the mineral portion of bone exposes the BMP signal to the surrounding tissue, allowing the induction of bone formation. In the Accell Connexus processing method, the materials are sterilized as the last step in the manufacturing process. The sterilization procedure involves the use of a low-dose electron beam (e-beam) irradiation that is performed after final product processing and

packaging. It destroys any microorganisms without negatively affecting the bioactivity of the DBM products[47]. This process preserves the osteoinductive power of BMPs. The materials provided strictly adhere to tissue banking standards as provided by the FDA, the AATB, the Clinical Laboratory Improvement Amendments (CLIA) and are currently being used in many orthopedic procedures including bone augmentation procedures.

Growth Factors

Growth factors are proteins that serve as signaling agents for cells. They function as part of a vast cellular communication network influencing cell division, matrix synthesis and tissue differentiation. The results of experimental studies have shown that these growth factors play an important role in bone and cartilage formation, fracture healing and repair of musculoskeletal tissues. Some of these growth factors include Transforming growth factor beta (TGF-B), platelet-derived growth factor (PDGF), Insulin-like growth factor (IGF), vascular endothelial growth factor (VEG-F) and fibroblast growth factor (FGF)[46].

Transforming growth factor beta (TGF-B) is a protein found in many tissues but particularly in bone, platelets and cartilage. It is presumed to be released by platelets after a clot is formed at the time of fracture[48] and its release is associated with proliferation of periosteal tissue[49]. There have been several experimental studies to show that TGF-B affects the bone-healing process at all stages[50,51]. Platelet-derived growth factor (PDGF) has been found to play an important role in mitogenesis, angiogenesis, macrophage activity and upregulation of production of other growth factors. They are secreted by platelets during the early phases of healing and when topically applied, have been found to speed up tissue healing in experimental wound models[52]. Insulin-like growth factor

(IGF) also plays a critical role in skeletal development and is involved largely in bone remodeling. The expression pattern of vascular endothelial growth factors (VEGFs) and their receptors suggest that VEGF plays an important role in the regulation of bone remodeling by attracting endothelial cells and osteoclasts and by stimulating osteoblast differentiation[53]. Fibroblast growth factors (FGFs) are most abundant in normal adult tissue promoting growth and differentiation of a variety of cells, including epithelial cells, myocytes, osteoblasts and chondrocytes. These factors are associated with angiogenesis and chrondrocyte and osteoblast activation and have the potential to enhance bone-repair processes[54]. Clearly, all these growth factors play a vital role in regeneration, repair and various cell processes that enhance bone formation.

Bone Morphogenetic Proteins

Bone morphogenetic proteins are multifunctional cytokines which are members of the TGF-B superfamily[55]. They stimulate bone growth naturally in the human body and are the only signaling molecules which can induce *de novo* bone formation. Discovery of BMP growth proteins is credited to Marshall Urist, an orthopedic surgeon who was working the orthopedic clinic in Los Angeles. Since this discovery of BMPs in the 1960s, about twenty BMP family members have been identified and characterized. BMPs exert diverse biological processes ranging from early embryonic tissue patterning to postnatal tissue homeostasis.

BMPs have been implicated in a variety of functions and have been found to induce not only the formations of cartilage and bone, but also in various non-osteogenic developmental processes. Several studies have shown that BMPs are important factors in regulating chondrogenesis and skeletogenesis during embryonic development[56]. The

BMPs with the greatest osteogenic capacity are BMP 2, 4, 5, 6, 7, and 9. More specifically, BMP 2 and BMP 7 play a large role in osteoblast differentiation while BMP4 is highly expressed in perichondrium and found to highly regulate the formation of bone[57].

There are several different BMPs naturally found in the body but research has focused on BMP-2 and BMP-7. Interestingly enough, BMP-2 is the most thoroughly evaluated BMP showing success in stimulating spinal fusion equal to or better than the patient's own bone. BMPs have been used in medicine for some time with two primary goals in spinal fusion, the first being the ability to create spinal fusion as well as or better than using the patient's own bone and to eliminate the need for harvesting the patient's bone from his or her hip to avoid potential side effects and complications in the bone harvesting process. This is one of the primary reasons as to why these BMPs are being evaluated in dentistry. Several bone grafts have been used in the sinus augmentation procedure to generate more bone for placement of implants with adequate length, however the use of BMPs is thought to stimulate better quality bone in greater amounts within a short period of time.

Bio-Oss

Bio-Oss® (Osteohealth, Shirley, NY) is a natural bone mineral that is bovine derived and is classified as prion-free tissue. The raw material is obtained from officially controlled environments and the animals are judged healthy by veterinarians. Bio-Oss undergoes treatment at high temperatures for more than fifteen hours followed by several hours of cleaning with strong alkaline solutions. The result is a highly purified anorganic natural bone mineral. Bio-Oss satisfies the strict safety requirements for medical devices

in all respects and is subject to a quality-assurance system in accordance with international norms (ISO 9001:2000/ISO 13485: 2000). This is regularly checked by recognized testing institutes and international regulatory authorities. Bio-Oss is cleared for marketing by the FDA as a medical device and is currently used at Tufts University School of Dental Medicine (TUSDM) for various bone regenerative procedures including sinus augmentation surgeries.

The aim of this study was to compare and analyze two different bone graft materials that are widely used in the sinus augmentation procedures. The same sinus augmentation procedure was applied for both materials and was analyzed radiographically and morphometrically in the same patient. The study compared the bone graft product, Accell Connexus®, from Keystone Dental (Burlington, MA) to that of Bio-Oss® product from Osteohealth, (Shirley, NY). This study evaluated these bone derivatives in the augmented sinus both qualitatively and quantitatively.

The two materials described above, demineralized freeze-dried allograft (DFDBA) and deproteinized bovine bone mineral (DBBM), are currently being used in the clinic with evidence based clinical data for sinus augmentation procedures. Both materials are acceptable and stable for the long-term care of the patient and there is limited knowledge to suggest one material over the other. However, current investigation postulates that there would be a difference in terms of height loss of the materials after healing and the amount of bone maturation during the course of regeneration in volume, density and degree of mineralization.

Hypothesis

The hypothesis for this study is that both Accell Connexus and Bio-Oss are equally successful for their purpose in bone grafting the maxillary sinus clinically, however, the radiographic results of the bone regenerated with the material may show differences in height, volume, density and mineralization.

Materials and Methods

A. Research Design

The study was designed to be a randomized controlled split mouth design of bilateral sinus lifts, using one side with Bio-Oss and the other side with Accell Connexus within the same patient. A total of ten patients (two female and eight male) with an age range of 37 to 63 years old (mean 51 y/o) presented to the Periodontal Postgraduate Clinic of TUSDM with pneumatized bilateral sinuses. The study was submitted and approved by the Institutional Review Board (IRB) of Tufts University. (IRB #9374).

The inclusion and exclusion criteria are listed below. The parameters studied were gain in augmentation height using pre and post operative CT and/or panoramic radiographs for quantitative evaluation, and histomorphometric analysis for qualitative evaluation using bone core biopsy. The study compared the bone graft product, Accell Connexus®, from Keystone Dental (Burlington, MA) to that of Bio-Oss® product from Osteohealth, (Shirley, NY).

Patient Selection Criteria:

- Age range: 18 years and older
- Gender: both males and females
- Race: no criteria in this category
- Disease: disease-free (periodontally and endodontically)
- Stage of treatment (patients requiring procedure for future implant placement and treatment planned)

Inclusion Criteria:

- Healthy medical history (no significant uncontrolled medical conditions including diabetes, cardiovascular disease, stroke, asthma, cancer, drug allergies)
- Non-smokers
- Subjects treatment planned for future implants in areas of the posterior maxilla with the presence of a pre-operative CT scan
- Pre-operative assessment by CT scan to reveal severe alveolar bone atrophy with less than 5mm of alveolar bone height present between the alveolar crest and the maxillary sinus floor bilaterally.

Exclusion Criteria:

- History of disease that affects bone metabolism including osteoporosis, osteomalacia, osteopenia, hyperthyroidism, hyperparathyroidism, renal osteodystrophy and Paget's disease.
- Presence of blood diseases such as hemophilia, severe anemia, thrombocytopenia and platelet disorders.
- Pregnant patients
- Children
- HIV or hepatitis patients
- Malignancy in the maxillary region
- Chemotherapy within the last 5 years
- History of radiation therapy to the maxillary region
- Acute or chronic sinus disease (no history of infection within the last 5 yrs)

- Excessive alcohol (greater than 20 drinks per week) or drug abuse
- Severe psychological disorders
- Heavy parafunctional habits
- Bisphosphonate users

Withdrawal and Termination Criteria:

- If subject starts smoking
- If subject becomes pregnant
- If subject fails to follow post-operative instructions and is non-compliant

Surgical Procedure

The sinus augmentation procedures are standard procedures that are performed in a single visit. The standard surgical procedure involves opening a lateral bony window in the area of the pneumatized sinus in the posterior maxilla and elevating the sinus membrane (Schneiderian membrane) with instruments and the piezoelectric system (Piezotome, Acteon, Paris, France). After anesthesia was achieved with 2% lidocaine 1:100k epinephrine and 0.5% marcaine 1:200k epinephrine, midcrestal incisions were made with vertical releasing incisions one tooth mesial to the site that needed to be elevated. Once the flaps were elevated full thickness bilaterally, a bony window was created in adequate height and width to lift the sinus membrane using the piezoelectric system (Piezotome, Acteon, Paris, France). Piezoelectric tips are soft tissue friendly, designed to only cut hard tissue and are widely used for delicate procedures thereby deemed appropriate and necessary for this study.

Bone was then placed into the space between the crestal native bone and the lifted sinus membrane, one side with Accell Connexus bone graft and the other side with Bio-Oss (Figure 1 and Figure 2). The decision as to which side received the different bone grafts was determined by coin toss. Dynamatrix membrane (Keystone Dental, Burlington, MA, USA) was then placed over the window and bone graft prior to closing the flap. The areas were sutured with 5-0 Vicryl sutures and primary closure was achieved in all cases. After the surgical procedure, five followup appointments were required at one week, two weeks, one month, three months and six months. CT (iCAT software) scans and/or panoramic radiographs were taken immediately after the sinus augmentation to determine baseline graft material in each patient using the same surgical guide to ensure accurate location of the grafting, measurements and implant site preparation (Figure 3). Subjects were prescribed Medrol dose pack and Augmentin 500mg tid for 7 days and were started one day prior to the sinus lift procedure. Postoperative medications included pain medication Ibuprofen 800mg one tablet tid for 5 days and Vicodin 5/500mg, one tablet q4-6h prn pain. Subjects were asked to start an antimicrobial rinse (Peridex 0.12%, 475ml) twice a day for 30 seconds starting the day after the procedure.

Six months after the sinus augmentation procedures, the implant surgery was performed. At this visit, the surgical guide was utilized for the initial location of the implant placement. After adequate anesthesia was given with 2% lidocaine 1:100k epinephrine and 0.5% marcaine 1:200k epinephrine, the same flap design was used to open the sites bilaterally. Midcrestal incisions were made with vertical releasing incisions one tooth mesial to the site. Full thickness flap elevation was attained. Once the proper

desired implant location was determined, a bone core sample was carefully removed from the area with a trephine bur (Figure 4). The trephine bur has length and inside diameter dimensions no larger than the planned implant size (easyretrieve trephine system, ACE surgical) so as not to compromise final implant installation.

These bone cores were then placed in biopsy bottles (10% neutral buffered formalin, Path-Tec, Columbus, Georgia, USA), labeled and indexed to keep subject information confidential (Figure 5 and Figure 6). Genesis® implant system (Keystone Dental, Burlington, MA, USA) was used to place the implants in the grafted sites, achieving primary stability. The flaps were closed with 5-0 Vicryl interrupted sutures and primary closure was achieved. Postoperative medications included Amoxicillin 500mg, Ibuprofen 800mg, Vicodin 5/500mg and Peridex rinse. Biopsy bottles with the specimen were then sent to a micro-CT lab to be analyzed for the various described parameters (King Saud University, Riyadh, Saudi Arabia).

B. Study Visits

A flow chart of patient visits is outlined below.

Procedure Sequence:

Pre-treatment:

Visit one:

1) Signed written consent obtained.
2) Eligibility determined using inclusion/exclusion criteria.
3) Clinical / Radiographic analysis using surgical stent with radio-opaque marker confirmed

Visit two:

1) Try-in of radiographic stent
2) Prescription of CT scan and/or Panoramic radiograph with stent

Visit three:

1) Schedule patient for surgery
2) Prescription of medications

Bilateral sinus augmentation:

Visit one:

1) Bilateral sinus augmentation procedure performed using the two different materials (Allograft, Xenograft). One material was used on either side and determined in a randomized split-mouth fashion with the decision determined by the flip of a coin. Heads = Accell Connexus, Tails = Bio-Oss. Radiographs were analyzed for the height evaluation with the surgical stent as a marker and reference guide.

Visit two through six:

One week, two weeks, one month, three months, and six months after surgery:

1) Patient examined
2) Photographs taken

Implant installation surgery:

Bone core biopsies were taken from the osteotomy sites for dental implant installation and utilized for evaluation. Surgical procedures for the implant placements were followed as described below:

Visit one: (six months after the sinus augmentation surgery):

1) Osteotomy sites for dental implants were prepared by trephine bur for bone core biopsies with 4mm x 10 mm drill.
2) The guide was used for marking the initial location followed by sequential osteotomy burs to enlarge the site to the final desired implant height and width.

Visit two through six:

One week, two weeks, one month, three months, and six months after surgery:

1) Patient examined
2) Photographs taken

Bone height evaluation:

Bone height was analyzed radiographically using radiographic guide markers to determine the original bone height (OBH), post grafted bone height (PBH), and new bone height (NBH) after six months of healing. Radiographs taken during the course of conventional therapy were used for the evaluation. OBH was subtracted from PBH to obtain NBH.

Micro-computed tomographic analysis:

The specimen were scanned with a high-resolution 11 megapixel micro-computed tomography system (micro-CT) in the multi-slice mode (SkyScan 1172). After scanning, the three dimensional data set was segmented by using different thresholds for bone to separate the different materials. Micro-computed tomography (micro-CT) analysis measurements were related to the mineralized tissue, non-mineralized tissue and high dense bone.

Using n-Query advisor 7.0 and with alpha = 0.05, sample size calculation was performed and an N of 23 subjects would be needed to attain a power of 80%. Due to the strict inclusion/exclusion criteria, limited patient pool and time constraints, achieving N = 23 was difficult. Therefore a sample size of ten was not enough to reach adequate power but results could still be considered clinically meaningful.

The two bone graft materials were compared via paired t-tests. The primary outcomes were to compare the height, bone density, volume and mineralization between the two groups. Means and standard deviations were reported and p-values less than 0.05 were considered statistically significant. All analyses were performed using SPSS statistical software, Version 19 (Chicago, Ill).

Height changes were evaluated radiographically by CT scan and panoramic radiographs (Table 2). Four out of the ten patients opted for panoramic radiographs. These patients (patients 4, 7, 9 and 10) were evaluated at six months with panoramic radiographs to keep the comparison consistent. The remaining patients had preliminary CT scans to be compared with post-six month CT scans.

Results

The study sample demographics and tables with the original recorded values for each outcome variable were generated. The mean age of patients was 51 years old with a standard deviation of seven. There was a majority of males in this study population

(80%) with 90% being predominantly Caucasian. Table 1 lists the demographics of this study population.

One patient had complications due to bleeding (patient 3) but was not eliminated from the study or from data analysis. One of the two samples for patient 10 was destroyed during shipping or processing and was therefore unreadable. This patient sample was eliminated from micro-CT analysis but was included in radiographic analysis.

Table 2 shows the analysis of the intra- and inter-material height changes of the two bone graft materials. The mean height at baseline for Accell Connexus was 10.63mm with standard deviation (SD) of 2.61mm and the mean height at six months was 7.94mm with SD of 2.24mm. The mean Accell Connexus height change was 2.69mm (25.3%) The mean height for Bio-Oss at baseline was 9.73mm with SD of 1.86mm and the mean height at six months was 8.38mm with SD of 1.46mm. The mean Bio-Oss height change was 1.35mm (13.9%). This shows that Accell Connexus material had almost twice as much resorption in height than the Bio-Oss material. These results were highly significant for intra-material comparison of Accell Connexus and Bio-Oss with p values of 0.001 and < 0.001 respectively. All results were conducted via t test with a 95% confidence interval. Inter-material comparison also showed a p value of < 0.001 indicating statistical significance of height changes between the two materials, with the Accell Connexus having more resorption in height than the Bio-Oss.

Table 3 shows the analysis of bone formation parameters after sinus augmentation of the two materials. These parameters include density and volume of the two materials from the core samples and extent of mineralization, percentage of mineralization and

percentage of non-mineralization. Extent of mineralization is defined as the extension of mineralized tissue occupied by three-dimensional volumetric pixels in the cross sections. Percentages of mineralized and non-mineralized tissues are defined as the percentage of the area occupied by these tissues over the total area of the cross section. From the results, it can be determined that there is no statistical significance between the two different materials used in terms of density, volume and mineralization and thus no correlation was found in these parameters. All results were conducted with a 95% confidence interval, t test was performed and the p value was > 0.05 for all pairs indicating that these results are not statistically significant.

Figures 7 and 8 show a typical example of the micro-CT image illustrating the density of Accell Connexus and Bio-Oss respectively from patient 2. Figure 9 shows an example of the analysis of the micro-CT cross section. Figure 10 shows a schematic diagram of how the cross sections were obtained during micro-CT scanning. The scan was taken in 360 degrees with a cone beam x-ray tomographic system and reconstruction. Up to five hundred cross sections were taken for each sample, however of these cross sections, ten were selected to ensure equal comparison between the samples due to varying lengths of the core samples. Region of interest (ROI) was selected and three different tissues were analyzed: native bone, bone graft and bone marrow spaces. The parameters that were analyzed were mineralized tissue, non-mineralized tissue and high dense bone. The micro-CT for the core sample from patient 2 shows these parameters; figure 7 is the sample containing Accell Connexus material and shows the non-mineralized tissue was 5.57% in this area indicating connective tissue matrix and soft tissue encapsulation. The mineralized tissue was 8.84% which indicates the regenerating

bone graft. The high dense bone area was 3.58mm^3 indicating residual bone graft material. Figure 8 contains the Bio-Oss sample showing non-mineralized tissue was 5.02%, mineralized tissue was 2.91% and high dense bone was 2.78mm^3. The high dense bone in this sample shows that the Bio-Oss material was not integrated with surrounding newly regenerated bone as compared to Accell Connexus.

Discussion

In this study, a randomized controlled clinical trial, ten patients who presented to the TUSDM clinic underwent bilateral sinus augmentation procedures with bone graft analyses of two different materials. These bone graft materials were evaluated for height changes, density, degree of mineralization and volume.

The clinical and radiographic study shows that there is resorption in height in both materials after six months of healing with resorption shown to be almost twice higher in the Accell Connexus material. There is an increased amount of growth factors in the Accell Connexus bone graft material that may suggest it to be more active in bone cell turnover which could lead to faster resorption. Further studies, however, are needed to confirm this observation. The greater resorption observed in the Accell Connexus material may also be due to the fact that this is a demineralized bone material which generally has less structural integrity to hold over a period of months as compared to a xenograft material.

In terms of density, Bio-Oss was shown to have greater density than the Accell Connexus material. This supports previous studies[58] where Bio-Oss was shown to have increased bone mineral density in grafted sites lending to its quality to function similarly to type 2 bone. In addition, it has been shown that the long-term presence of Bio-Oss particles stabilize the graft leading to retention of its architectural form as well as increased bone mineral density[58].

There is a varying pattern in the mineralization results with some specimen showing higher mineralization with the Accell Connexus product while other specimen showing higher mineralization in the Bio-Oss material. The overall mean mineralization values showed that Bio-Oss had a higher percentage of mineralized and non-mineralized tissue as compared to Accell Connexus material. However, a statistically non-significant correlation between the two different materials used was found. This is most likely due to the sample size of the study. Although there is no statistical difference between the two materials, close observation analysis of the micro-CT images of each sample showed that a distinct pattern in regeneration can be detected. The Accell Connexus samples showed the high dense (residual bone graft material) was completely surrounded by regenerated or regenerating bone. In the Bio-Oss samples, the high dense residual bone graft material was completely isolated and not surrounded by regenerated or regenerating bone. These findings confirm previous studies showing the osteoinductivity of allograft materials[59,60] while other studies have shown the osteoconductivity of xenograft materials such as Bio-Oss[61,62, 63,64]. To further the study to the next step is to evaluate the samples histologically and to determine the amount of vital cells in both materials used and the maturation over the six month period. The results would give a clearer understanding of

the correlation between the two materials with more descriptive histological analyses. It may also allow for a better understanding and extrapolation on how to compare the two different materials in their integration with implants in the sinus environment.

This study showed a trend of more bone volume amongst the sites treated with Accell Connexus bone graft material than with sites treated with Bio-Oss bone graft material, although not statistically significant. This supports the findings of Groenveld *et al* (1999) which showed that implantation of demineralized bone particles substantially increased the volume of mineralized tissue[65]. In their study, the grafted DBM in the maxillary sinus forms new bone by three different patterns. The first pattern showed new bone formed between grafted DBM that is adjacent to host bone and host bone inside the sinus. The second pattern was done by DBM's remineralization inside the center of DBM particles far from the host bone. The third pattern was seen between the grafted DBM particles and newly deposited bone tissue. These mineralization patterns increased bone volume in the maxillary sinus. Furthermore, Groenveld *et al.*[65] concluded that remineralization was an important condition for clearance of the demineralized bone matrix graft. Kim *et al.* (2009) investigated the efficacy of demineralized bone matrix and cancellous chips used in the maxillary sinus augmentation procedure[66]. They used the bone graft material DynaBlast, which is a precursor material of Accell Connexus only without the added growth factors and bone morphogenetic proteins and concluded that DynaBlast produced sufficient volume of new bone when placed in the maxillary sinus with 6 to 7 months being sufficient time for maturation of newly formed bone tissue and vascularization. This is in agreement with the present study finding. On the other hand, they found that more time may allow for a higher percentage of new bone formation in

the maxillary sinus. However, the present study showed that within the Accell Connexus material, more elapsed time may produce more activity in the bone graft, more bone turnover and greater resorption in height due to the increased amounts of growth factors and BMPs.

The micro-CT results in this study indicated that there was evidence of newly formed bone surrounding the high dense bone graft particles in the demineralized bone matrix samples. This proves that there is more osteoinductive activity as compared to the xenograft samples, which were found to be completely isolated and not surrounded by regenerating bone. Previous studies by Schizas *et al.* (2008) have confirmed that Accell Connexus bone graft material acts similarly to autologous bone in that it has a high concentration of BMPs and growth factors with a high resorption rate[67]. Although the demineralization process is known to have some effect on the osteoinductive potential of bone[68], Boyan *et al.*[69] found that the use of growth factors can modify the osteoinductivity of demineralized bone allografts. Demineralized bone graft matrix combined with other biomaterials usually reduces the amount of demineralized bone matrix present per volume which may have negative effects on the amount of BMPs and growth factors available for osteoinductivity[59]. In the present study, fast resorption rate of the Accell Connexus bone graft alone may indicate that another biomaterial may be needed to combine both qualities of growth factors and bone graft stability and structure. A material such as a xenograft or a freeze dried bone allograft may help prevent the fast resorption. It may also be suggested that due to the amount of BMPs and growth factors available in Accell Connexus, combining this material with a denser biomaterial may provide more stability of the bone graft. Hatano *et al.* [70] evaluated a 2:1

autogenous:xenograft mixture and concluded that good long-term results can be achieved with this bone graft material combination. In addition, Yildirim *et al.* [71] showed that the combination of autogenous bone to Bio-Oss material produced a high-quality implant site with osteoconductive Bio-Oss and osteoinductive autogenous bone properties.

The present work has some limitations common to many clinical studies. The IRB process and the inclusion and exclusion criteria made the selection of patients difficult, especially in a patient pool where the prevalence of bilateral sinus cases is few. It could be open to a multi-center type study including other institutions to increase sample size. The core retrieval was taken in the sites where bone grafting was performed and some native bone was found and included in this core sample. This is per following IRB approved protocol so as not to impair the success and ability to place implants in these regions. If the core biopsy was attained from a lateral window approach, less native bone would be included in the samples. This study was in compliance with IRB approval #9374 and it was not allowed to retrieve core biopsies laterally. The standard protocol for placing implants was followed in that an osteotomy was created at the crest and not retrieved in any other location so as not to compromise the primary stability of the implant.

Conclusion

In summary, this study shows that Accell Connexus, a DFDBA bone graft material infused with BMPs and growth factors, may act to increase bone volume and osteoinductivity of new bone in the maxillary sinus. The present study suggests that more osteoinductivity is seen with the Accell Connexus material as compared to Bio-Oss but more density is seen with Bio-Oss as compared to Accell Connexus. It also confirms that there is resorption seen with both bone graft materials with more resorption noted with Accell Connexus bone graft than with Bio-Oss bone graft. Histological study will be needed to support these findings on a microscopic level to evaluate cell activity.

References

[1] McGowan D et al. **The Maxillary Sinus and its Dental Implications.** 1993

[2] Rosen, M.D. & Sarnat, B.G. **Change of volume of the maxillary sinus of the dog after extraction of adjacent teeth.** *Oral Surgery Oral Medicine Oral Pathology 1955; 8: 420–429.*

[3] Tatum H Jr: **Maxillary and sinus implant reconstructions.** *Dental Clinics of North America 1986; 30:207-229.*

[4] Chanavaz, M. **Maxillary sinus: anatomy, physiology, surgery, and bone grafting related to implantology – eleven years of surgical experience (1979–1990).** *Journal of Oral Implantology 1990; 16: 199–209.*

[4] Smiler DG, Johnson PW, Lozada JL, et al. **Sinus lift grafts and endosseous implants. Treatment of the atrophic posterior maxilla.** *Dental Clinics of North America 1992; 36:151-186.*

[6] Truhlar RS, Ornstein IH, Morris HF, Ochi S. **Distribution of bone quality in patients receiving endosseous dental implants.** *International Journal of Oral and Maxillofacial Surgery 1997; 55:38-45.*

[7] Misch CE. **Maxillary sinus augmentation for endosteal implants: organized alternative treatment plans**. *Journal of Oral Implantology 1987; 449-58.*

[8] Kaufman, E. **Maxillary sinus elevation surgery: An overview** *Journal of Esthetic and Restorative Dentistry 2003; 15:272-283.*

[9] Boyne PJ, James RA: **Grafting of the maxillary sinus floor with autogenous marrow and bone.** *Journal of Oral Surgery 1980; 38(8):613-616.*

[10] Khoury F. **Augmentation of the sinus floor with mandibular bone block and simultaneous implantation: a 6-year clinical investigation.** *International Journal of Oral and Maxillofacial Implants 1999;14:557-64.*

[11] Wallace SS, Froum SJ. **Effect of maxillary sinus augmentation on the survival of endosseous dental implants. A systematic review**. *Annals of Periodontology 2003; 8: 328-343.*

[12] Garg AK. **Augmentation grafting of the maxillary sinus for placement of dental implants: anatomy, physiology, and procedure.** *Implant Dentistry 1999; 8:36-46.*

[13] Block MS, Kent JN: **Sinus augmentation for dental implants: the use of autogenous bone.** *Journal of Oral and Maxillofacial Surgery 1997; 55(11):1281-1286.*

[14] Wagner J. **A Clincial and histological case study using resorbable hydroxylapatite for the repair of osseous implants.** *J Oral Implantol. 1989; 15: 485-509.*

[15] Tong, D.C., Rioux, K., Drangsholt, M. & Beirne, O.R. **A review of survival rates for implants placed in grafted maxillary sinuses using meta-analysis.** *International Journal of Maxillofacial Implants 1998; 13: 175–182.*

[16] Block MS, Kent JN: **Sinus augmentation for dental implants: the use of autogenous bone.** *Journal of Oral and Maxillofacial Surgery 1997; 55(11):1281-1286*

[17] Imbronito AV, Scarano A, Orsini G, Piattelli A, Arana-Chavez VE: **Ultrastructure of bone healing in defects grafted with a copolymer of polylactic/polyglycolic acids.** *Journal of Biomedical Material Research Part A 2005; 74:215-221.*

[18] Wheeler SL, Holmes RE, Calhoun CJ: **Six-year clinical and histologic study of sinus lift grafts.** *International Journal of Oral and Maxillofacial Implants 1996; 11(1):26-34.*

[19] Szabo G, Huys L, Coulthard P, Maiorana C, Garagiola U, Barabas J, Nemeth Z, Hrabak K, Suba Z: **A prospective multicenter randomized clinical trial of autogenous bone versus beta-tricalcium phosphate graft alone for bilateral sinus elevation: histologic and histomorphometric evaluation.** *International Journal of Oral and Maxillofacial Implants 2005; 20(3):371-381.*

[20] Tadjoedin E, de Lange G, Layruu Luit Kuiper D, Burger E. **High concentrations of bioactive glass material (BioGran®) vs. autogenous bone for sinus floor elevation.** *Clinical Oral Implants Research 2002; 13: 428-436*

[21] Nishibori M, Betts NJ, Salama H, Listgarten MA: **Short-term healing of autogenous and allogeneic bone grafts after sinus augmentation: a report of two cases.** *Journal of Periodontology 1994; 65:958-966.*

[22] Wetzel AC, Stich H, Caffesse RG: **Bone apposition onto oral implants in the sinus area filled with different grafting materials. A histological study in beagle dogs.** *Clinical Oral Implants Research 1995; 6:155-163.*

[23] Kent, J.N. & Block, M.S. **Simultaneous maxillary sinus floor bone grafting and placement of hydroxylapatite-coated implants.** *Journal of Oral and Maxillofacial Surgery 1989; 47: 238–242.*

[24] Smiler, D.G., Johnson, P.W., Lozada, J.L., Misch, C., Rosenlicht, J.L., Tatum, O.H. Jr & Wagner, J.R. **Sinus lift grafts and endosseous implants.** *Dental Clinics of North America 1992; 36:151–188.*

[25] Moy, P.K., Lundgren, S. & Holmes, R.E. **Maxillary sinus augmentation: histomorphometric analysis of graft materials for maxillary sinus floor augmentation.** *Journal of Oral and Maxillofacial Surgery 1993; 51: 857–862.*

[26] Cordioli G, Mazzocco C, Schepers E, Brugnolo E, Majzoub Z. **Maxillary sinus floor augmentation using bioactive glass granules and autogenous bone with simultaneous implant placement.** *Clinical Oral Implants Research 2002;12:270-278.*

[27] Velich N, Nemeth Z, Toth C, Szabo G: **Long-term results with different bone substitutes used for sinus floor elevation.** *Journal of Craniofacial Surgery 2004; 15(1):38-41.*

[28] Ole Jensen, "The Sinus Bone Graft" 2nd edition, Quintessence Publishing

[29] Jensen OT, Shulman LB, Block MS, Iacono VJ: **Report of the sinus consensus conference of 1996.** *Journal of Oral and Maxillofacial Implants 1998; 13 Suppl:11-45.*

[30] Aaboe, M., Pinholt, E.M. & Hjorting-Hansen, E. **Healing of experimentally created defects: a review.** *British Journal of Maxillofacial Surgery 1995; 33: 312–318.*

[31] Haas, R., Donath, K., Fodinger, M. & Watzek, G. **Bovine hydroxyapatite for maxillary sinus grafting: comparative histomorphometric findings in sheep.** *Clinical Oral Implants Research 1998; 9: 107–116.*

[32] Kaptein ML, Hoogstraten J, de Putter C, de Lange GL, Blijdorp PA: **Dental implants in the atrophic maxilla: measurements of patients' satisfaction and treatment experience.** *Clinical Oral Implants Research 1998; 9:321-326.*

[33] Yildirim, M., Spiekermann, H., Biesterfeld, S. & Edelhoff, D. **Maxillary sinus augmentation using xenogenic bone substitute material Bio-Osss in combination with venous blood. A histologic and histomorphometric study in humans.** *Clinical Oral Implants Research 2000; 11: 217–229.*

[34] Mayfield, L.J.A., Skoglund, A., Hising, P., Lang, N.P. & Attstrom, R. **Evaluation following functional loading of titanium fixtures placed in ridges augmented by deproteinized bone mineral. A human case study.** *Clinical Oral Implants Research 2001; 12: 508–514.*

[35] Schlegel, A.K. & Donath, K. **BIO-OSS – a resorbable bone substitute?** *Journal of Long-Term Effects of Medical Implants 1998; 8: 201–209.*

[36] Piattelli, M., Favero, G.A., Scarano, A., Orsini,G.& Piattelli, A. **Bone reactions to anorganic bovine bone (Bio-Oss) used in sinus augmentation procedures: a histologic long-term report of 20 cases in humans.** *International Journal of Oral and Maxillofacial Implants 1999; 14: 835–840.*

[37] Hallman, M., Hedin, M., Sennerby, L. & Lundgren, S. **A prospective 1-year clinical and radiographic study of implants placed after maxillary sinus floor augmentation with bovine hydroxyapatite and autogenous bone.** *Journal of Oral and Maxillofacial Surgery 2002; 60: 277–284.*

[38] Gosain, A.K. **Hydroxyapatite cement paste cranioplasty for the treatment of temporal hollowing after cranial vault remodeling in a growing child.** *Journal of Craniofacial Surgery 1997; 8: 506–511.*

[39] Handschel, J., Simonowska, M., Naujoks, C., Depprich, R., Ommerborn, M., Meyer, U. & Kubler, N. **A histomorphometric meta-analysis of sinus elevation with various grafting materials.** *Head and Face Medicine 2009; 5:12*

[40] Buchmann, R., Khoury, F., Faust, C. & Lange, D.E. **Peri-implant conditions in periodontally compromised patients following maxillary sinus augmentation. A long-term post-therapy trial.** *Clinical Oral Implants Research 1999; 10: 103–110.*

[41] Hatano N, Shimizu Y, Ooya K. **A clinical long-term radiographic evaluation of graft height changes after maxillary sinus floor augmentation with a 2 : 1 autogenous bone/xenograft mixture and simultaneous placement of dental implants.** *Clinical Oral Implants Research 2004; 15: 339–345*

[42] Raghoebar, G.M., Timmenga, N.M., Reintsema, H., Stegenga, B. & Vissink, A. **Maxillary bone grafting for insertion of endosseous implants: results after 12–24 months.** *Clinical Oral Implants Research 2001; 12: 279–286.*

[43] Cawood HI, Howell RA. **A classification of the edentulous jaws.** *International Journal of Oral and Maxillofacial Surgery 1988; 17: 232-236*

[44] Cawood JI, Howell RA. **Reconstructive preprosthetic surgery. I. Anatomical considerations.** *International Journal of Oral and Maxillofacial Surgery 1991; 20: 75-82.*

[45] Lieberman JR, Daluiski A, Stevenson S, Wu L, McAllister P, Lee YP, Kabo JM, Finerman GA, Berk AJ, Witte ON. **The effect of regional gene therapy with bone morphogenetic protein-2-producing bone-marrow cells on the repair of segmental femoral defects in rats.** *J Bone Join Surg Am. 1999; 81:905-17.*

[46] Johnson EE, Urist MR, Finerman GA. **Resistant nonunions and partial or complete segmental defects of long bones. Treatment with implants of a composite of human bone morphogenetic protein (BMP) and autolyze, antigen-extracted, allogeneic (AAA) bone.** *Clin Orthop. 1992; 277:229-37*

[47] Wientroub S, Reddi AH. **Influence of irradiation on the osteoinductive potential of demineralized bone matrix.** *Calif Tissue Int 1988;42:255-60.*

[48] Joyce ME, Jingushi S, Bolander ME. **Transforming growth factor-beta in the regulation of fracture repair.** *Orthop Clin North Am. 1990; 21:199-209*

[49] Robey PG, Young MF, Flanders KC, Roche NS, Kondaiah P, Reddi AH, Termine JD, Sporn MB, Roberts AB. **Osteoblasts synthesize and respond to transforming growth factor-type beta (TGF-beta) in vitro.** *J Cell Biol. 1987; 105: 457-63*

[50] Lieberman JR, Daluiski A, Einhorn TA. **The Role of Growth Factors in the Repair of Bone: Biology and Clinical Applications.** *J Bone Joint Surg Am. 2002;84:1032-1044.*

[51] Sumner DR, Turner TM, Purchio AF, Gombotz WR, Urban RM, Galante JO. **Enhancement of bone ingrowth by transforming growth factor-beta**. *J Bone Joint Surg Am. 1995; 77:1135-47*

[52] Klinge B, Alberius P, Isaksson S, Jönsson J. **Osseous response to implanted natural bone mineral and synthetic hydoxylapaptite ceramics in the repair of experimental skull bone defects.** *J Oral Maxillofac Surg 1992; 50:241-249*

[53] Deckers MM, Karperien M, van der Bent C, Yamashita T, Papapoulos SE, Löwik CW. **Expression of Vascular Endothelial Growth Factors and their Receptors during Osteoblast Differentiation.** *Endocrinology* 2000; 141: 1667- 1674

[54] Wang JS **Basic fibroblast growth factor for stimulation of bone formation in osteoinductive or conductive implants.** *Acta Orthop Scand Suppl. 1996; 269:1-33.*

[55] Bragdon B, Moseychuk O, Saldanha S, King D, Julian J, Nohe A. **Bone morphogenetic proteins: a critical review.** *Cellular Signalling 2011; 23:4: 609-620.*

[56] Hogan BL. **Bone morphogenetic proteins: multifunctional regulators of vertebrate development.** *Genes Dev. 1996; 10: 1580-1594.*

[57] Xiao YT, Xiang LX, Shao JZ. **Bone morphogenetic protein.** *Biochemical and Biophysical Research Communications 2007 Oct 26; 362(3): 550-553.*

[58] Jensen O. **The Sinus Bone Graft** 2nd edition. Quintessence Publishing Co. Inc. 2006 (211-239).

[59] Boyan BD, Weesner TC, Lohmann CH, Andreacchio D, Carnes DL, Dean DD, Cochran DL, Schwartz Z. **Porcine Fetal Enamel Matrix Derivative Enhances Bone Formation Induced by Demineralized Freeze Dried Bone Allograft In Vivo** *J. Periodontol. 2000 Aug;71(8): 1278–86.*

[60] Boyan BD, Ranly DM, McMillan J, Sunwoo M, Roche K, Schwartz Z. **Osteoinductive ability of human allograft formulations.** *J Periodontol. 2006;77(9):1555-1563.*

[61] Fukuta K, Har-Shai Y, Collares MV, Lichten JB, Jackson IT. **Comparison of inorganic bovine bone mineral particles with porous hydroxyapatite granules and cranial bone dust in the reconstruction of full-thickness skull defect.** *J Craniofac Surg. 1992 Jul;3(1):25-9.*

[62] Berglundh T, Lindhe J. **Healing around implants in bone defects treated with Bio-Oss. An experimental study in the dog.** *Clin Oral Impl Res 1997;9:117-24.*

[63] Hammerle CH, Chiantella G, Karring T, Lang NP. **The effect of a deproteinized bovine bone mineral on bone regeneration around titanium dental implants.** *Clin Oral Impl Res 1998;9:151-62.*

[64] Hurzeler MB, Quiñones CR, Kirsch A, Gloker C, Schüpbach P, Strub JR, Caffesse RG. **Maxillary sinus augmentation using different grafting materials and dental implants in monkeys. Part I. Evaluation of anorganic bovine-derived bone matrix.** *Clin Oral Impl Res 1997;8:476-86.*

[65] Groenveld EH, van den Bergh JP, Holzmann P, ten Bruggenkate CM, Tuinzing DB, Burger EH. **Mineralization process in demineralized bone matrix grafts in human maxillary sinus floor elevations.** *J Biomed Mater Res 1999; 48(4): 393-402.*

[66] Kim DM, Nevins ML, Camelo M, Camelo JM, Schupbach P, Hanratty JJ, Uzel NG, Nevins M. **The Efficacy of Demineralized Bone Matrix and Cancellous Bone Chips for Maxillary Sinus Augmentation.** *Int J Periodontics Restorative Dent 2009;29:415-423.*

[67] Schizas C, Triantafyllopoulos D, Kosmopoulos V, Tzinieris N, Stafylas K. **Posterolateral lumbar spine fusion using a novel demineralized bone matrix: a controlled case pilot study.** *Arch Orthop Trauma Surg. 2008 Jun;128(6):621-5.*

[68] Zhang M, Powers RM Jr, Wolfinbarger L Jr. **Effect(s) of the demineralization process on the osteoinductivity of demineralized bone matrix.** *J Periodontol.1997 Nov;68(11):1085-92.*

[69] Boyan BD, Ranly DM, Schwartz Z. **Use of growth factors to modify osteoinductivity of demineralized bone allografts: lessons for tissue engineering of bone.** *Dent Clin North Am. 2006 Apr;50(2):217-28, viii.*

[70] Hatano N, Shimizu Y, Ooya K. **A clinical long-term radiographic evaluation of graft height changes after maxillary sinus floor augmentation with a 2:1 autogenous bone/xenograft mixture and simultaneous placement of dental implants.** *Clin Oral Impl Res 15;2004:339-345*

[71] Yildirim M, Spiekermann H, Handt S, Edelhoff D. **Maxillary sinus augmentation with the xenograft Bio-Oss and autogenous intraoral bone for qualitative improvement of the implant site: a histologic and histomorphometric clinical study in humans.** *Int J Oral Maxillofac Implants. 2001 Jan-Feb;16(1):23-33.*

List of Figures

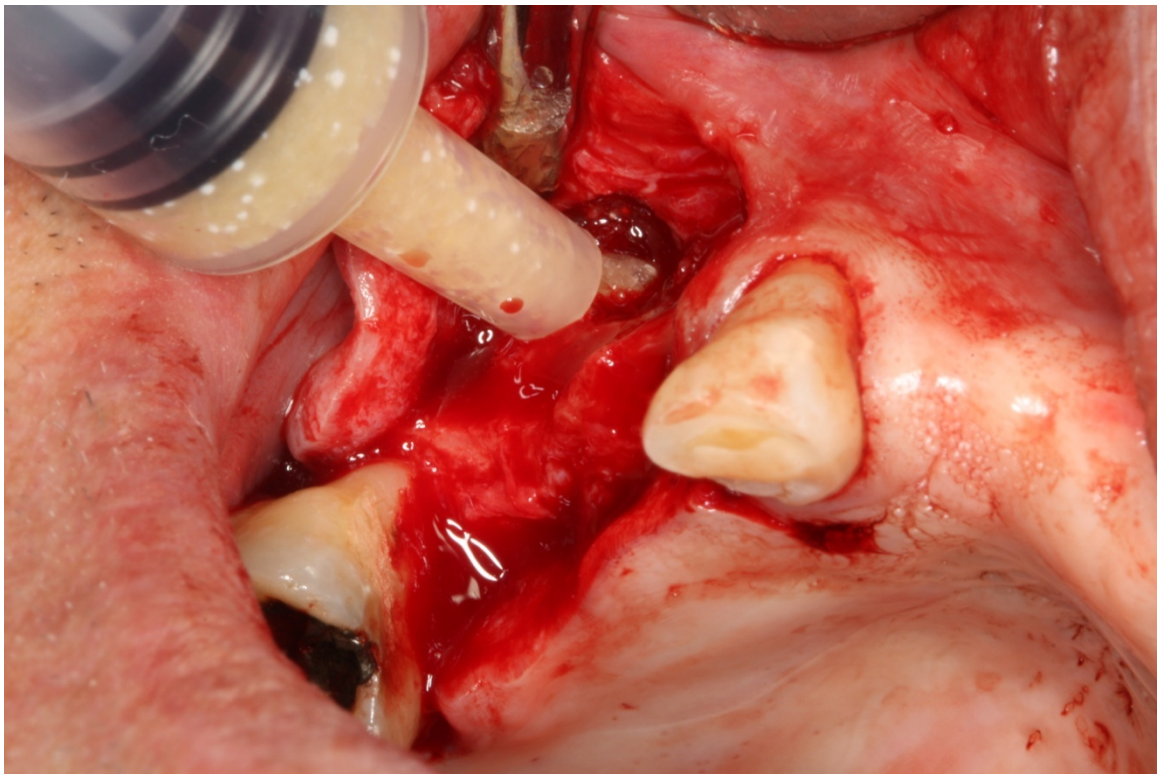


Figure 1. Accell Connexus bone graft in sinus augmentation

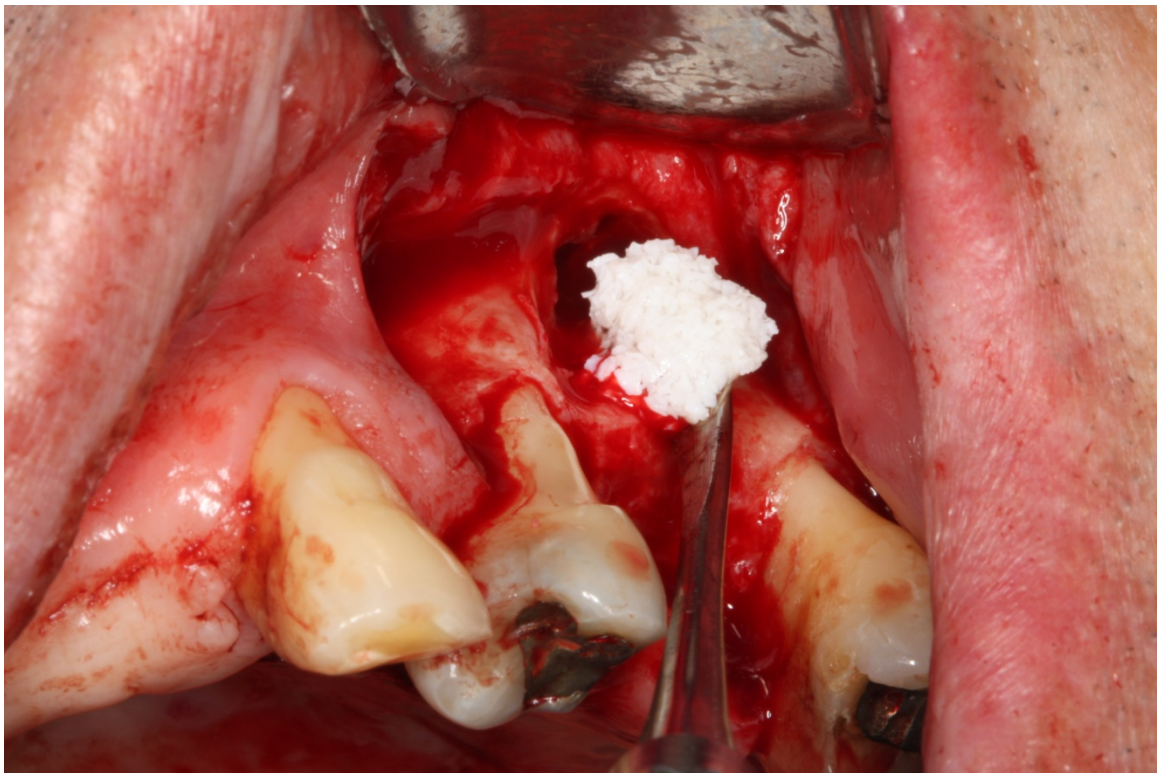
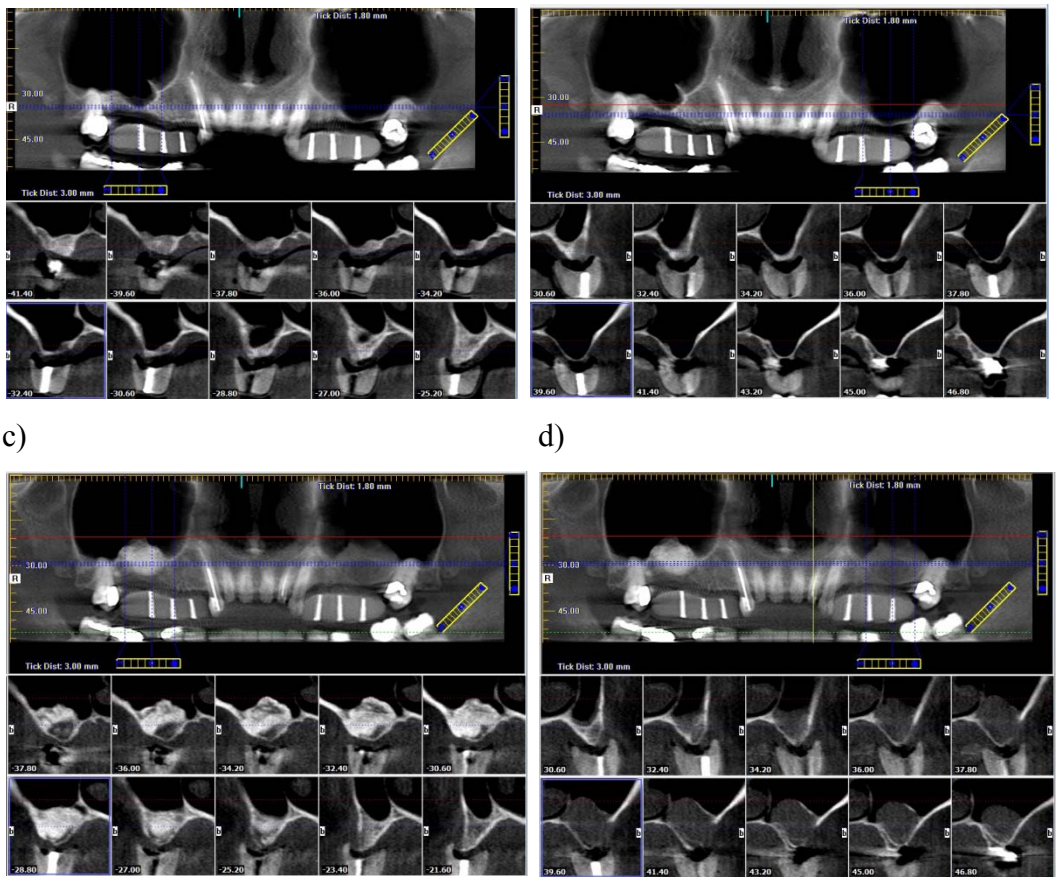


Figure 2. Bio-Oss bone graft in sinus augmentation

a) b)



c) d)

Figure 3. Pre and post sinus augmentation. a) baseline Bio-Oss, b) baseline Accell Connexus; c) six months Bio-Oss; d) six months Accell Connexus

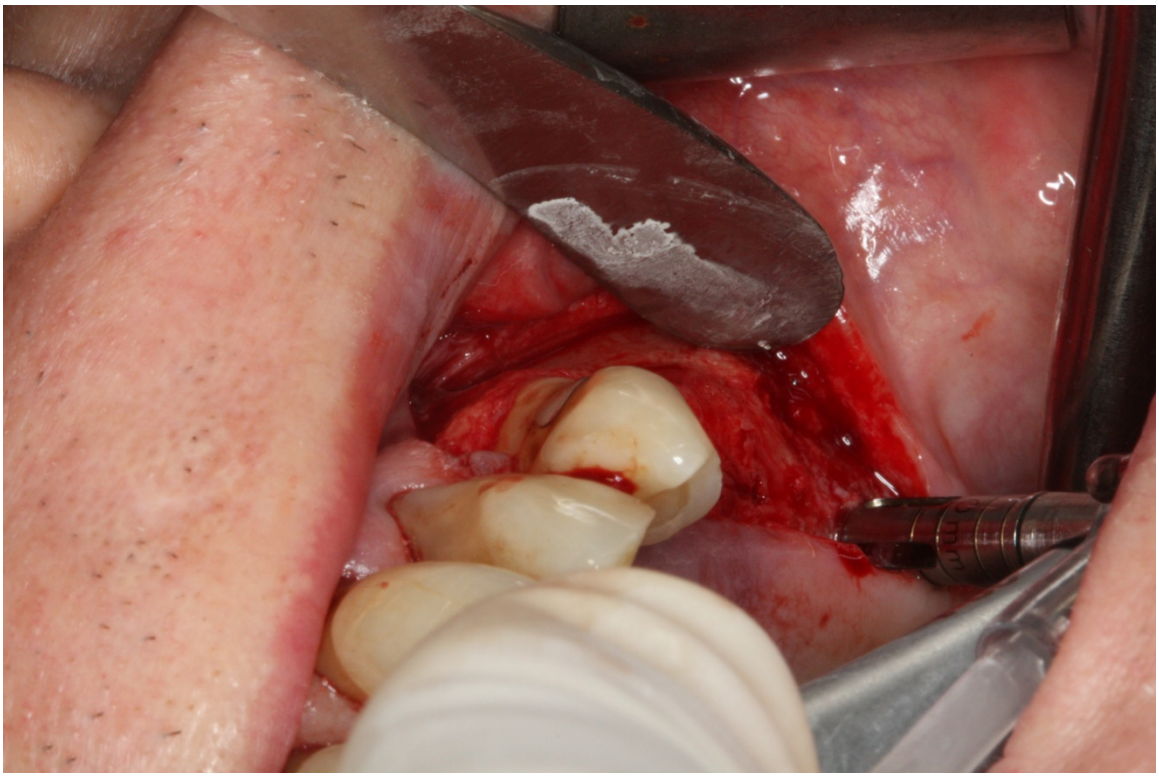


Figure 4. Bone core retrieval at time of implant surgery

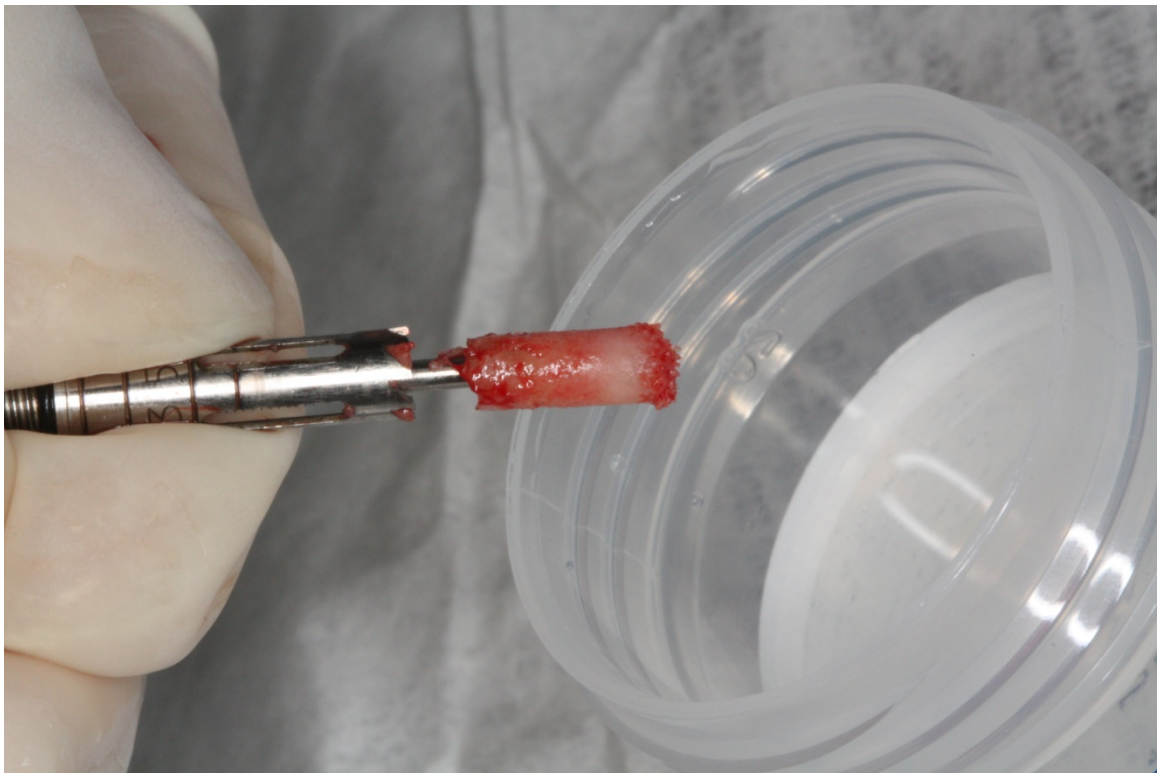


Figure 5. Accell Connexus bone graft core retrieved using trephine bur.

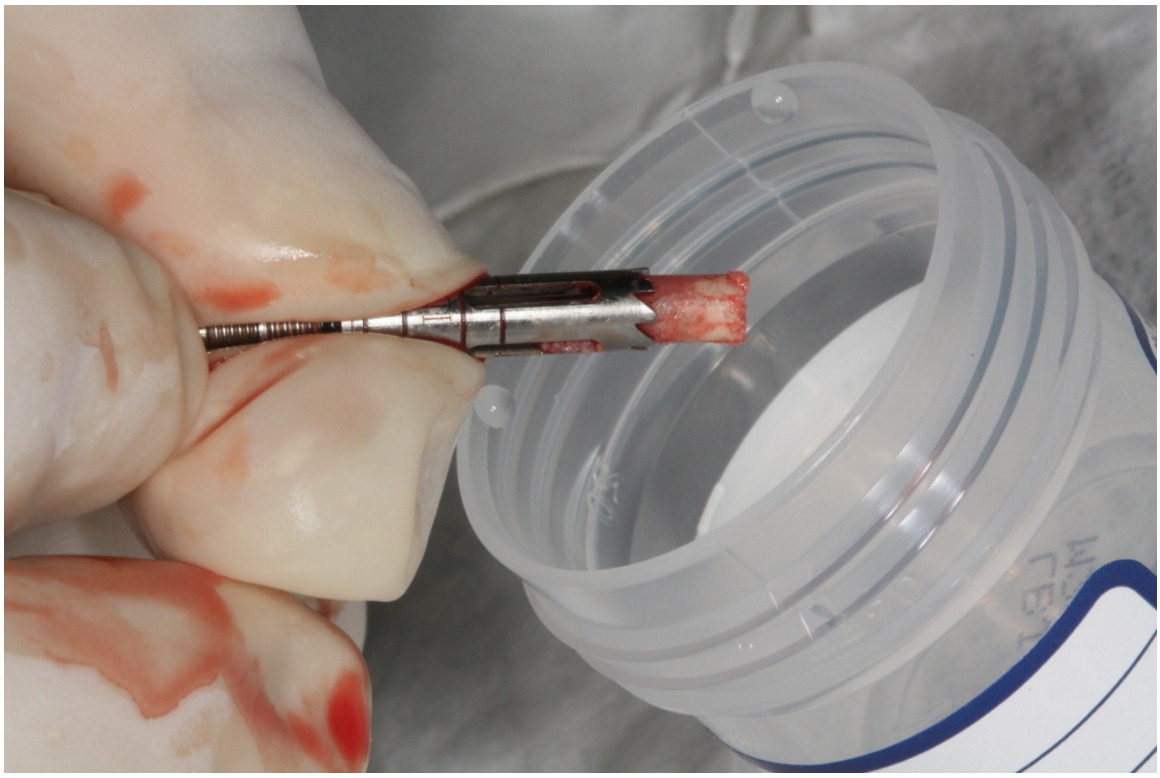


Figure 6. Bio-Oss bone graft core retrieved using trephine bur.

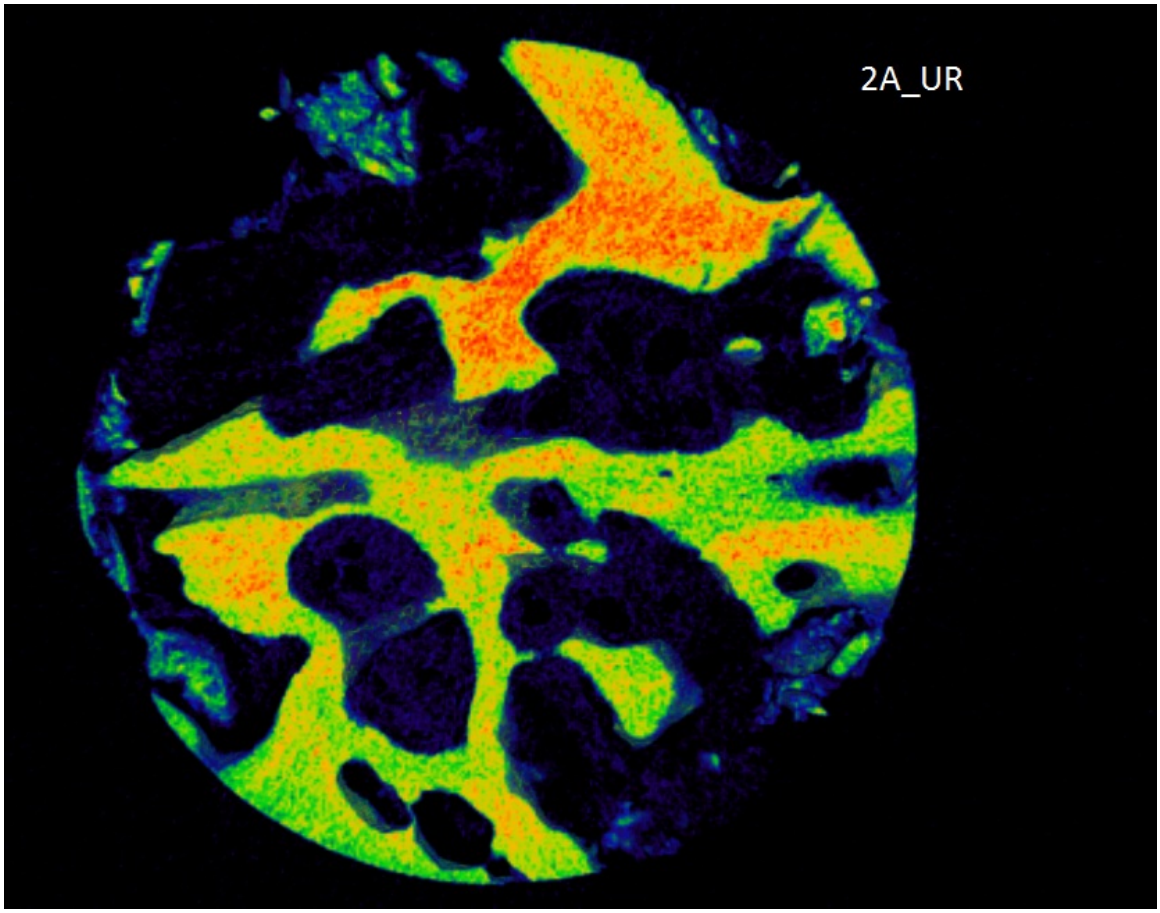


Figure 7. Micro-CT of Accell Connexus

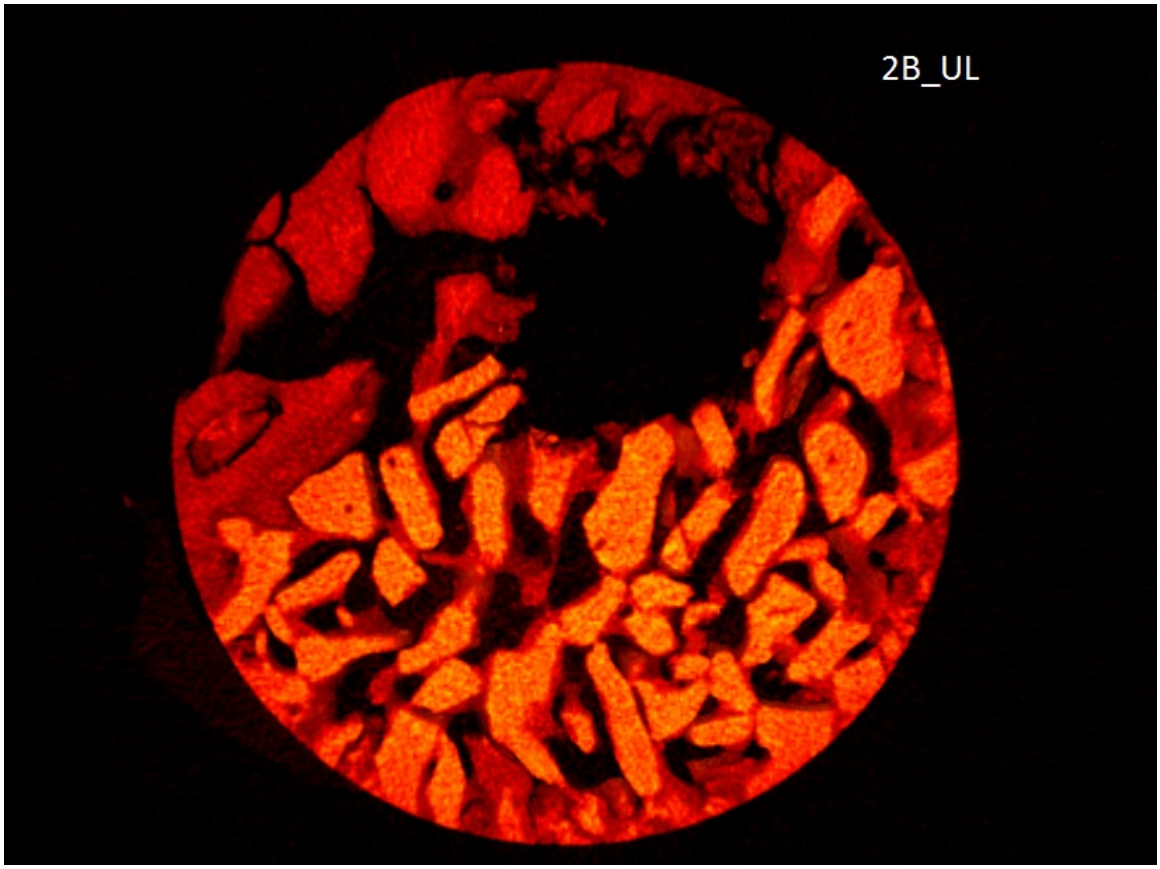


Figure 8. Micro-CT of Bio-Oss

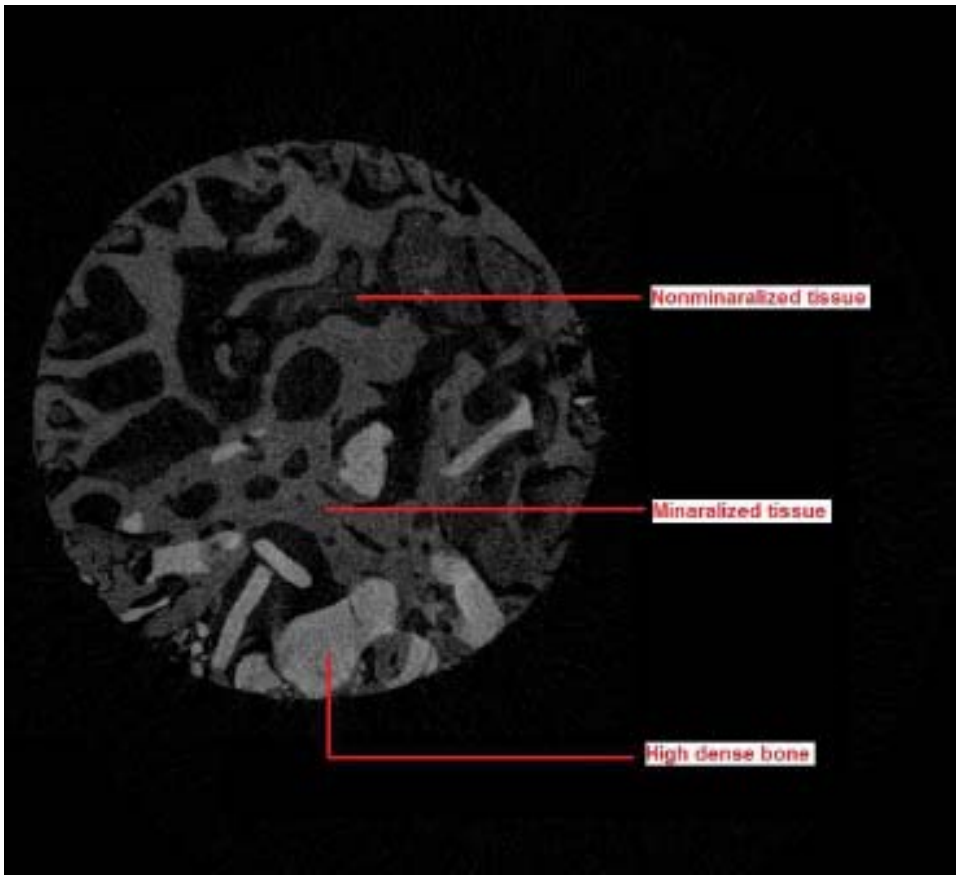


Figure 9. Analysis of micro-CT cross section indicating mineralized, non-mineralized and high dense bone areas

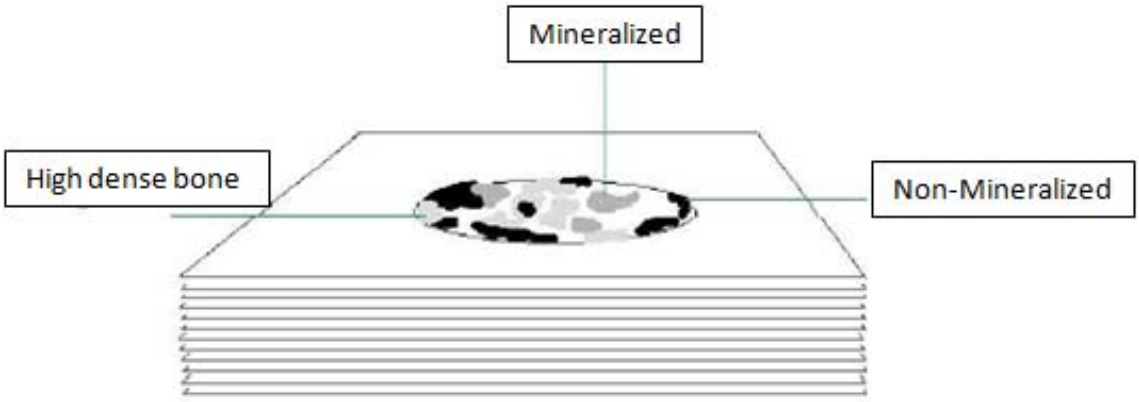


Figure 10. Schematic diagram of cross-sectional micro-CT of a core sample

List of Tables

Age	Mean 51 y/o SD $\pm$ 7
Gender	Male: 80% (8/10) Female: 20% (2/10)
Race	Caucasian 90% (9/10) Asian: 10% (1/10)

Table 1. Demographics of study population

	Accell Connexus		**Bio-Oss**		**P value (inter-material)**
Height (mm)	**Mean**	**SD**	**Mean**	**SD**	
time (t)=0	**10.63**	**2.61**	**9.73**	**1.86**	
time (t)=6	**7.94**	**2.24**	**8.38**	**1.46**	
P value (intra-material)	**0.001**		**0.000**		
Height changes (mm)	**2.69**		**1.35**		**0.000**

Table 2. Analysis of height changes (intra- and inter-material comparison)

	Accell		Bio-Oss		P value
	Mean	SD	Mean	SD	
Density (g/mm^3)	2.46	1.01	3.38	1.71	0.102
Volume (mm^3)	3.58	1.58	2.90	2.47	0.487
Extent of Mineralization (mm^2)	2.24	0.86	3.84	2.36	0.130
% Mineralization	6.20	2.84	11.29	14.86	0.336
% Non-mineralization	5.38	3.71	7.30	4.84	0.263

Table 3. Analysis of bone formation parameters after sinus augmentation (density, volume, mineralization)