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COMPARISON OF TWO DIFFERENT XENOGRAFTS IN BILATERAL SINUS AUGMENTATION: RADIOGRAPHIC AND HISTOLOGIC FINDINGS

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II. Table of Contents

III. ABREVIATIONS AND SYMBOLS

ABG	Autogenous bone graft
ANS	Anterior nasal spina
AR	Alveolar ridge
BCP	Biphasic calcium phosphate
BDX	Bovine derived xenograft
BG	Bioactive glass
BIC	Bone to implant contact
CBCT	Cone Beam Computerized Tomography
CM	Collagen Membrane
CT	Computerized Tomography
DFDBA	Demineralized freeze-dried bone allograft
e-PTFE	Expanded polytetrafluoroethylene
FDBA	Freeze-dried bone allograft
GM	Graft material
HA	Hydroxyapatite
HE	Haematoxylin-eosin
IA	Infraorbital artery
MA	Maxillary artery
MSFA	Maxillary sinus floor augmentation
NB	New bone
OPT	Ortopantomograph
PI	Plaque Index
PSSA	Posterior superior alveolar artery
RFA	Resonance frequency analysis
®	Trade Mark
ß-TCP	β-Tricalcium phosphate

SUMMARY

Comparison of Two Different Xenografts in Bilateral Sinus Augmentation: Radiographic and Histologic Findings

The aim of this study was to evaluate the radiographic and histomorphometric results of two different bovine derived xenografts (BDX) in bilateral sinus augmentation in patients with posterior maxillary atrophy.

Eight patients (4 female, 4 male) with a mean age of 51.5±10.5 and less than 5 mm residual alveolar bone height were included in this study. Following lateral wall osteotomy, one side was augmented with BDX materials (Bio-Oss®) and the other side with Cerabone®. A collagen membrane (CM) was used to cover the lateral bony windows on both sides. Cone Beam Computerized Tomography (CBCT) analyses were performed before and after augmentation, and before the implant placement, in order to evaluate residual alveolar bone height, the graft height and the resorption rate of the grafts, respectively. During implant placement bone biopsies were obtained from the augmented sites and histological analysis was performed.

No post-operative complications were observed in all cases. CBCT analysis revealed a mean residual alveolar bone height of 4.32± 1.58 mm and 4.01±1.86 mm in the Bio-Oss® and Cerabone® groups, respectively. The graft heights measured on CBCT after sinus augmentation and before implantation were 16.06±1.50 mm and 14.79±2.02 mm; 16.02±1.05 mm and 14.23±2.12 mm, in the Bio-Oss® and Cerabone® groups, respectively. No statistically significant difference was found between the groups based on post-augmentation and pre-implantation graft heights ($p>0.05$). Histologic examinations revealed new bone formation in all specimens. Histomorphometric evaluation demonstrated newly formed bone 24.63% and 29.13% in the Bio-Oss® and Cerabone® groups, respectively. Residual graft particles were 14.77% and 13.01% in the Bio-Oss® and Cerabone® groups, accordingly. Intergroup differences were not significant for the mean percentage of new bone formation ($p>0.05$).

Within the limits of this study, it can be concluded that, both xenograft materials resulted in a satisfactory bone height and trabecular new bone formation and could be used for the rehabilitation of atrophic maxilla.

1. INTRODUCTION AND PURPOSE

Placement of oral implants in the posterior maxillary edentulous region presents many unique and challenging conditions compared with other regions of the jaws. The presence of the maxillary sinus as the basis of the maxillary alveolar process can be an obstacle to the placement of an implant. Also, sinus pneumatization, described as an enlargement of the maxillary sinus due to the aging process and as a result of the loss of the maxillary teeth tends to reduce the amount of bone available over time leading to difficulties in the rehabilitation of the posterior maxilla (1). As a consequence, there is usually a need to increase the bone volume in the posterior maxilla prior to implant placement. The goal of a sinus elevation procedure is to surgically increase the alveolar bone height by grafting the floor of the maxillary sinus (2).

Numerous different grafting materials have been used in maxillary sinus floor augmentation (MSFA) with varying success rate (3, 4, 5, 6, 7), above all autogenous bone is considered to be the "gold standard" for bone augmentation procedures (8, 9) since they have osteogenic, osteoinductive, and osteoconductive properties (8, 10). It can be resorbed over time and replaced with newly formed bone. However, utilization of autogenous bone graft requires a second surgical site (intraoral) or possible hospitalization (extraoral), thereby increasing the length of time of the surgical intervention, postsurgical morbidity, increased cost and an inadequate volume of graft material (11). Allografts, xenografts and alloplastic materials have been used as an alternative to autogenous bone in sinus augmentation procedures. Successful results have been reported with the use these bone substitutes (12, 13, 14, 15, 16, 17**).**

Bovine derived xenografts (BDX) consists of 100% anorganic bovine bone and has been shown to be a safe and biocompatible material with osteoconductive properties (18, 19) and is considered the most frequently used and best documented biomaterial in dentristry (15, 20, 21). Since BDX is a natural biomaterial, it is possible that the material maintains its original surface characteristics, ie, it mimics human bone, thus representing an attractive recipient surface for bone-building cells (22, 23, 24, 25, 26).

Bio-Oss® is a kind of xenograft consisting of deproteinized, sterilized bovine bone with 75-80% porosity and a crystal size of approximately 10 μ in the form of cortical granules. Bio-Oss® has a natural, nonantigenic porous matrix and is chemically and physically identical to the mineral phase of human bone (27). Several short term and long term studies have been shown that Bio-Oss® can be used in sinus augmentation with predictable and successful results (27, 28, 29). Bio-Oss®,when used alone, is better than autograft or allograft at maintaining bone volume, safety, and lack of complications (20).

The list of bone replacement grafts utilized to augment or replace autogenous bone as sinus grafting material is continuously expanding. Recently introduced xenograft Cerabone®, is a bovine derived bone mineral which shows osteoconductive properties, hard tissue regeneration and osseous organization **(**30, 31**)**. This material, due to containing the sintered inorganic part of bone (hydroxyapatite), has the interconnection porous stucture of the original bone (32, 33, 34, 35, 36). Some studies evaluated the efficacy of Cerabone® in socket preservation (37) and nasal floor augmentation (38) and reported successful results. Only one study evaluated the resoption rate of the graft in sinus augmentation procedure (39).

Although there are well established studies evaluating the clinical, radiographical and histological efficacy of Bio-Oss® in sinus augmentation, there is no study evaluating the histological outcomes of Cerabone® usage and comparative histologic evaluation of these two xenografts. Since histologic analysis of regenerated tissues in sinus elevation will provide useful information regarding the nature and amount of the newly formed bone leading to successful implant placement, the purpose of this study was to evaluate the comparative analysis of radiographic and histologic outcomes after sinus augmentation with two different xenografts.

2. GENERAL INFORMATION

2.1 Maxiller Sinus Anatomy

The maxillary sinus is an air-filled space located in the body of the maxilla. It has a quadrangular pyramidal shape with various walls: a medial wall facing the nasal cavity, a posterior wall facing the maxillary tuberosity, a mesio-vestibular wall which is the orbit floor, and finally, a lower wall that is next to the alveolar process and which is the bottom of the maxillary sinus itself (40).

The maxillary sinus communicates with the nasal fossa by means of a natural ostium located antero-superiorly on the medial surface, which drains into the middle meatus (41) and all paranasal sinuses communicate with the nasal fossae. The average size of the maxillary sinus in an adult is 12 to 15 cm^3(with large variations, from 3.5 to 35.2 cm^3) height is 36 to 45 mm; and length is 38 to 45mm (42, 43).

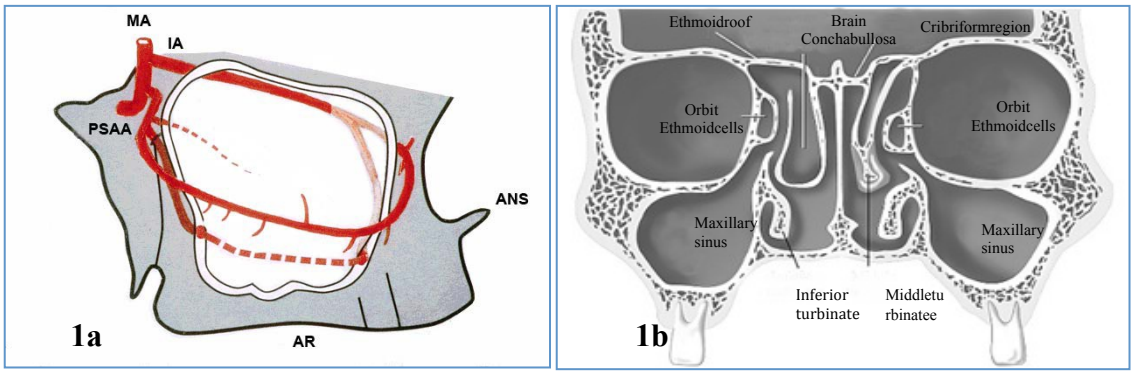
It is innervated by branches of maxillary nerve and supplied by branches of the internal maxillary artery (MA): the infraorbital artery (IA), the posterior lateral artery, and the posterior superior alveolar artery (PSAA) that have inconsistent branches running along the lateral wall of the sinus (44). The lateral maxilla is supplied by branches of the PSAA and the IA that forms anastomosis in the bony lateral wall, which also supplies the Schneiderian membrane. The presence of these branches needs to be evaluated prior to surgery to prevent preoperative hemorrhage if a lateral window approach is selected. The anterior superior alveolar branch, which branches from the infrorbital nerve at the infraorbital foramen, reaches the anterior sinus wall and the superior dental plexus, running below the inner walls of the sinus called Schneiderian membrane, which is covered by pseudo-stratified columnar ciliated epithelium formed by basal and columnar cells (45).

Sinus septa also called “Underwood septa” can be found more often at the first molar or the premolar areas. It represents a challenge during sinus elevations because the presence of maxillary sinus septa may complicate sinus elevation procedures, especially

when they are not diagnosed prior to surgery. Pommer and coworkers (46) found in a systematic review and meta-analysis that septa were present in 28.4% of 8923 sinuses investigated. Prevalence was significantly higher in atrophic sinuses compared with dentate maxilla. Septa were located in premolar, molar and retromolar regions in 24.4%, 54.6% and 21.0%, respectively.

The panoramic radiograph can lead to false-positive and false-negative findings in the visualization of septa. Septa diagnosis using panoramic radiographs yielded incorrect results in 29% of cases. While sinus septum strengthen the bony structure they may cause perforation of the sinus membrane during a sinus elevation surgery (43, 47, 48). Therefore, whenever a maxillary sinus lift is planned, a thorough study of the affected sinus using Cone Beam Computed Tomography (CBCT) could be recommended (46, 49, 50).

Figure 1a. PSAA, IA, MA, Alveolar ridge (AR), anterior nasal spina (ANS).
Figure 1b.Frontal view of maxillary sinus in relation to other structures.



2.2 Sinus Augmentation Techniques

The reduced vertical bone height in the posterior maxillary region is often a major obstacle to placement of dental implants. Augmentation of the maxillary sinus floor is an option to solve this problem. Various surgical techniques have been presented to access the sinus cavity and elevate the sinus membrane. The two main techniques to perform sinus floor elevation for dental implant placement are: a) a two stage technique with a lateral window approach, followed by implant placement after a healing period, and b) one-stage technique using either a lateral or crestal approach.
(Transalveolar approach)

A. **The lateral window approach**: Boyne and James (51) were the first authors to publish a study on elevation of the maxillary sinus floor in patients with large, pneumatized sinus cavities. They described a two stage procedure, where the maxillary sinus was grafted using autogenous particulate iliac bone at the first stage of surgery. After approximately 3 months, a second stage surgery was performed in which blade implants were placed and later used to support the prosthetic constructions. Since then, numerous articles have been published regarding different grafting materials and modifications of this technique (3, 4, 5, 6, 7, 52). This technique gives access through the lateral wall of the sinus and a window is made in the bony wall using rotary instrument. The membrane is carefully elevated, and the bone is placed in the space located below the Schneiderian membrane and above the sinus floor (52, 53).

B. **The crestal approach**: A less invasive transalveolar technique for sinus floor elevation with immediate implant placement was first suggested by Tatum (53) and later developed as an osteotome technique by Summers (54) in 1994. In this technique**,** after flap elevation, bone is removed until the cortical bone of the sinus floor is exposed and greenstick fracture of the cortical bone was prepared with osteotomes and burs. After the elevation of the Schneiderian membrane, bone grafts and implant placement can be carried out (55).

Multiple studies have proved that the lateral approach is a predictable technique and allows implants survival rates of >95% over the long-term analysis (56, 57, 58). The decision to use one or two-stage techniques in lateral approach is based on the amount of residual bone available and the possibility of achieving primary stability for the inserted implants. Misch (59) suggested that in the cases with residual alveolar crest height less than 5 mm, primary stabilization could not be achieved, so using two-stage method in these cases would increase the success rate. It was suggested that new bone formation should be waited for implantation as primary stabilization cannot be achieved with the patients who have deficient residual alveolar crest height (less than 5mm) and the aim of this waiting period was to increase the bone formation and osseointegration in implant operations (60). In the cases with residual alveolar crest height less than 5mm it is suggested to wait for 6 months to 18 months according to the features of the graft material before the implantation (61, 62, 63, 64). During the sinus conference in 1996, it was reported that two-stage implantation after the waiting period in the cases with crest height less than 5mm increased the success rate up to 90 %(10). However, various authors reported that an alveolar ridge height of less than 3 mm, will also be considered for a one-stage protocol (65, 66). They reported that in some cases with good bone quality (type 2 bone), implants can be inserted simultaneously, even if there is only 1 to 3 mm of residual crestal bone (66, 67).

Systematic reviews showed that there are no statistically significant differences in implant survival rates when a lateral approach is used as opposed to a crestal approach (21,68). A recent meta-analysis reporting on 12.020 implants placed in sinus elevated sites with a lateral approach indicated an implant survival rate at 3 years of 90.1%(69) whereas the survival rate over the same period of time was 92.8% when a crestal approach was used (70). The choice of the technique should be determined by the quantity of residual alveolar bone available; if there is not sufficient bone volume to achieve primary stability two-stage approach can be the choice until the graft material has matured is necessity (71).

2.3 Healing Potential of Sinus Without Using Graft Materials

There are differences in opinion on the necessity of grafting material when elevating the maxillary sinus floor. A new viewpoint in the sinus floor is graft-free sinus technique in which the gap occurring as a result of elevation of membrane is not filled with any material. Successful results and various ratios of bone formation have been reported by the use of this technique in implant applications (72, 73, 74).

Lundgren et al. (74) applied 19 implants in 10 patients with 4-10 mm (average 7 mm) residual alveolar bone height. One stage sinus floor augmentation was performed without using any graft material. The window was re-placed on the lateral wall to allow accumulation of blood clot after elevation of membrane and application of implants. Resonance frequency analysis (RFA) was performed on each implant at the time of initial placement, at abutment surgery, and after 12 months of functional loading. It was reported that comparisons of pre- and post-operative computerized tomography (CT) analysis demonstrated new bone formation within the compartment created by the sinus membrane elevation procedure. RFA measurements showed mean implant stability quotient values of 65, 66, and 64 at placement, at abutment connection, and after 12 months of loading, respectively. Authors concluded that sinus membrane elevation without the use of additional graft material was found to be a predictable technique for MSFA.

Winter et al. (65) performed one stage sinus lifting and implantation without using any graft material in patients with crest height less than 4 mm and reported 91.4% success at 22 months follow –up.

Chen et al. (75) applied 47 implants in 33 patients with one stage lateral wall technique without using bone graft. They reported a 100% implant success rate at the end of 2-year follow-up period and no complications were observed in the cases. They suggested

that the implants placed synchronously with a good surgical application were clinically successful in posterior maxilla without graft application.

Thorwarth et al. (76) applied the implants simultaneously by elevating the sinus floor with window technique in 27 patients with crest height of average 4.5 to 5 mm. They reported 97.7% success rate for the implants that were followed up to 27 months. It was reported that there were challenges in providing primary stabilization during placement of the implants. They expressed that implants placed without graft application were osseointegrated and bone formation occurred. The authors mentioned that the technique could be an alternative for morbidity problem caused by autogenous bone graft (ABG) use.

Nedir et al. (77) evaluated the long-term stability of peri-implant bone formation following implant placement without grafting resorbed posterior maxilla. Seventeen patients posterior maxilla were rehabilitated by means of a none stage MSFA procedure without grafting. Mean residual bone height was 5.4±2.3 mm. Bone levels around implants were evaluated at 1, 3 and 5 years using periapical radiographs. All implants fulfilled survival criteria and gained peri-implant bone (mean increase 3.2±1.3 mm) after 1 year and mean crestal bone loss amounting to 0.8±0.8 mm over the 5-year observation interval. Author concluded that bone grafting material is not needed to gain at least 3mm of bone in the atrophic maxilla. The procedure appears predictable with favourable long-term results.

Cricchio et al. (78) investigated the one stage technique where 13 mm implants were inserted in 7 mm residual crest without adding any graft material. An average of 5.3±2.1 mm of intra-sinus bone formation was obtained after 6 months of healing. Morever, high implant survival rate (98.7%) was observed during a follow-up period up to 6 years.

The exact mechanisms behind the bone formation observed in the maxillary sinus are presently not well understood (73). Lundgren at al. (74) stated that the lifting of the periosteum may have initiated a resorption process, exposure of the bone marrow, and

access of stem cells to the sinus cavity, which have been observed in experimental studies (79**,** 80). It is reported that blood clot and angiogenesis in MSFA play important roles in bone formation. Melcher and Dreyer suggested that blood clot contained many growth factors such as endogenous growth factors, platelet-derived growth factor, fibroblast growth factor, insulin-like growth factor and that they observed bone regeneration only with clot without using bone grafts (81).

The accumulation of blood clot in to the space created after the elevation of sinus membrane, provides scaffold to form new bone (74). However, blood clot which has osteoinductive properties, will not sufficent to maintain the created gap, it affected by fibrinolysis which occur within the first few weeks in sinus and (82, 83) it has been reported that it is unable to prevent pneumatization composed of air pressure (83). For this purpose, bone graft materials which will provide less exposure to pneumatization and protect the crated space in the elevated position were recommended in sinus augmentation (84, 85).

2.4. Bone Grafting Materials Used in Sinus Augmentation

The ideal graft material would be osteoinductive, absorbable, easy to handle, and available in large quantities (86). The most necessary characteristic of ideal graft material to be used in MSFA is to increase the bone amount in grafted area, to increase the primary stability and replace the natural bone by resorbing by time (10, 87).

Graft materials used today aim to have one or more of osteogenesis, osteoconductive or osteoinductive properties. Osteogenesis refers to the formation or development of new bone by cells contained in the graft. Osteogenic graft material, which is derived from or composed of tissue involved in the natural growth and repair of bone, can encourage bone formation in soft tissues and can stimulate faster bone growth in bone implant sites (88). Osteoinduction is a chemical process by which molecules contained in the graft (e.g., bone morphogenetic protein) convert the neighboring cells into osteoblasts, which in turn form bone (89, 90). Osteoconduction is a physical effect by which the

matrix of the graft forms a scaffold that favors outside cells to penetrate the graft and form new bone (88).

Autogenous bone grafts are the most advantageous graft materials in the MSFA because of their characteristics such as presence of autogenous cells, endurance, high primary stabilization, vascularization ability and not causing immunological reaction. Although significant advances in the field of bone graft substitutes have been performed over the years, the use of autogenous bone still regarded as 'gold standard' because of its osteoinductive capacity (91). The oral donor areas, which are often used as ABG source, are maxilla, tuberosity area, ramus mandibular, and submaxilla symphysis areas. Intraoral donor sites offer advantages like avoidance of general anesthesia and second surgical side however the amount of bone obtained from these areas possibly is limited (91). To harvest larger amount of bone most common extraoral site for ABG is the ilium but calvarium, tibia and rib can also used (82). It is reported that cortical and cancellous types of ABG, which can be obtained from different areas, have different levels of osteogenic, osteoconductive and osteoinductive characteristics (92). Cancellous/cortical and corticocancellous form of ABG's may show varied bone healing potential (93).

It is suggested that necessary graft amount is an important factor in graft material choice in maxillary sinus to provide the desirable bone height at the end regarding recovery process and loss of bone afterwards (82). With respect to graft structure, it must be taken into consideration that cortical bone grafts have greater structural strength, greater osteoconductive capacity and undergo lower resorption. However, they are poor in osteogenic cells. Cancellous bone grafts, on the other hand, are rich in osteogenic cells and revascularization is faster. But this material has the disadvantage of a lack of rigidity and lower resistance to resorption (94).

Survival rates of implants, the new bone formation quantity and new bone formation time can be different related to the block or particulate forms of ABG used in MSFA (68, 93). The block grafts used because of their cortical components will be successful in sinus lift augmentation and especially in cases which have low residual alveolar crest height because of their rigid forms and due to their endurance providing abilities (95).

However some studies reported that in the results of histomorphometric examination new bone formation was much higher in the group, which used particulate graft (96). Lee et al. reported that block graft in sinus floor augmentation concluded in fast resorption, but grafts in cortical structure provided mechanic endurance successfully despite their failure in replacement (97).

In the study of Dasmah et al. (17) 11 patients was treated with iliac bone graft both as block and particulate. One side of the sinuses was augmented with particulate ABG and the other side with block ABG, respectively. CBCT analysis has been used at 1, 6 months and 2 years examinations. They concluded that there was no significant difference in the amount of volumetric reduction between particulate bone and block bone grafts.

Wannfors et al. (98) reported a difference between implant survival rates in block grafts and in particulate autogenous grafts were 78.8% and 89.2 % respectively at 1 years (98). In one review, 20 sinus augmentation with at least 1 year follow-up in 43 study were evaluated Implant survival rates in block autogenous grafts were 83.3% and in particulate autogenous grafts were 92.3 % respectively (21). Another meta analysis with same included criteria implant survival rates 82.9% for block autogenous grafts, 84.9% for block and particulate autogenous grafts and 92.5% for particulate graft materials were reported (68)**.** The authors concluded that the usage of particulate grafts alone or combined with block autogenous bone will increase the survival rate of the implants.

Hoexter et al. (95) concluded in a review that ABG seemed to be more effective than bone grafts during the early phase of healing, but after 9 months, no statistically significant differences were detected between the autogenous bone and grafting material. In another meta analysis Handschel et al. (99) concluded that implants placed in augmented maxillary sinuses, found similar survival rates whether autografts, allografts or alloplastic grafting material were used. Esposito et al. (100) explained in a review article that some bone substitutes appear to be as effective as autogenous bone grafts for augmenting atrophic maxillary sinuses, therefore they could be used as a replacement for ABG.

Despite certain advantages of using ABG, this bone grafts have certain disadvantages such as going under resorption process, not obtaining desirable amount, causing morbidity in donor field, causing necessity of the second operation and its price, besides, there are some risks of the second operation such as bleeding, infection, hematoma, pain, lose of sense and wound recovery (8, 11, 101). Because of the disadvantages of ABG, various bone-grafting materials have been used as alternatives or supplements to autogenous bone (19,102, 103, 104 105,106, 107). These graft materials can constitute of bone from a human donor (allogenic) or an animal donor (heterologous) or of biocompatible synthetic material (alloplastic). Most of these materials have morpho-structural connectivity properties similar to those of the bone matrix. They can be used alone or in combination with autogenous bone, in various proportions, to obtain the necessary graft volume.

Bone allograft is a bone collected from a human cadaver that is commercially available from tissue banks. They are obtained from cortical or cancellous bone within 12 hours of the death of the donor. The material may then proceed to the next steps (Mineralized Freeze-Dried Bone Allograft (MFDBA) and Demineralized Freeze-Dried Bone allograft (DFDBA) (108). Bone allografts overcome many of the shortfalls of autogenous grafts but are considered primarily osteoconductive and to some degree osteoinductive (DFDBA) in nature. The literature suggests that, DFDBA may have greater osteoinductive potential because of the availability of morphogenic proteins. (15).

Advantages of allografts include ready availability, minimalization of the amount of autogenous bone harvested from patient, reduced surgical time, decreased blood loss and fewer complications (109).

The decision about which form of allograft to use should be based on the clinical condition of the site to be grafted. Because it is still mineralized, FDBA may have better physical characterisics. However, FDBA, is not osteoinductive. Although no significant differences have been found clinically between FDBA and DFDBA in primarily

intraosseous defects (110), in sites where regeneration may be more problematic, DFDBA may be a more appropriate choice because of some degree of its osteoinductivity.

There is paucity of information comparing FDBA and DFDBA in ridge and sinus augmentations in humans. The choice of DFDBA is usually based on medical safety. The demineralization process reportedly adds an extra margin of safety that prevents viral pathogens from being transmitted to the patient (10, 111). Although FDBA has a higher mineralized content, this benefit is probably not clinically significant after 9 months of healing between FDBA and DFDBA (15).

In a retrospective study, Valentini et al. (112) evaluated the survival rate of 187 titanium plasma spray-coated cylindrical and machine screw-type implants placed in sinuses grafted with a mixture of 1:1 of Bio-Oss® and DFDBA or Bio-Oss® alone. The 58 patients included in this study were divided into four different groups and treated with either one-or two-stage technique, according to the volume of residual bone. The overall implant survival rate was 94.5% after a mean functioning period of 6.5 years. The implant survival rate was better in sinuses grafted with Bio-Oss® than with a mixture of Bio-Oss® and DFDBA (96.8% vs. 90%). Titanium plasma spray-coated cylindrical implants had a better survival rate than machine screw-type implants in sinuses grafted with a mixture of Bio-Oss® and DFDBA, but 1/3 were affected by peri-implantitis. Machine screw-type implants showed a similar survival rate compared with titanium plasma spray-coated cylinders in sinuses grafted with Bio-Oss® alone, without being affected by peri-implantitis. Bovine derived xenograft used alone appears to be a suitable material for MSFA.

In a randomized clinical trial, vital bone formation was evaluated histomorphometrically following bilateral grafting with two different materials- a mineralized cancellous bone allograft, and Bio-Oss®, at 26 to 32 weeks following graft placement in 13 bilateral cases (113). Histologically, both allograft and Bio-Oss® particles were surrounded by new bone, osteoid, and osteoblasts but in histomorphometric analysis of 10 allograft and

9 Bio-Oss® cores revealed average vital bone content of 28.25% and 12.44%, respectively. A higher average percentage of new vital bone was seen around the allograft particles than around the Bio-Oss® particles.

In another study sinus bone graft resorption and marginal bone loss around the implants were evaluated in use of either Bio-Oss® alone or combined with a demineralized allograft. The average height of the remaining alveolar bone before the surgery, immediately after the surgery, and 1 year after the surgery was 4.9 mm, 19.0 mm, and 17.2 mm, respectively, in Bio-Oss® group and 4.0 mm, 19.2 mm, and 17.8 in combined group, respectively. Implant success rates were 93.9% for Bio-Oss® group and 83.3% for Bio-Oss® combined with allograft group at the end of an average 20 months follow-up. Authors concluded that combined usage of Bio-Oss® and demineralized bone matrix for maxillary sinus bone grafting has no significant short-term merit regarding bone healing and stability of implants compared with Bio-Oss® alone (114).

The disadvantages of bone allografts are primarily associated with the antigenity of tissues harvested from another individual; transplanted bone may induce a host immune response (109). On the other hand transfer of disease from bone allograft is of particular concern. Most of the banks adhere to the guidelines of the American Association of Tissue Banks with respect to procurement, processing and sterilization of bone grafts which leads to secure usage of the materials today (115).

Alloplastic materials are synthetic, inorganic, biocompatible, and/or bioactive bone graft substitutes that are claimed to promote bone healing through osteoconduction (116). The most commonly used alloplasts are bioactive ceramics such as synthetic calcium phosphate materials. Hydroxyapatite (HA) is safe and well tolerated, but have little ability to encourage new attachments (117). Calcium phosphate ceramics act primarily as filler materials, with new bone formation taking place along their surface. The objective in using them is to help provide a scaffold for enhanced bone tissue repair and growth. HA, β-tricalcium phosphate (ß-TCP), bioactive glass (BG) have demonstrated almost equal efficacy both clinically and scientifically for use in sinus

augmentation procedures (118, 119). Resorbable and nonresorbable alloplasts are more or less indistinguishable in terms of their capacity for space maintenance, osteoconduction, and facilitation of bone migration from the sinus floor. HA has three forms available for dental use. These include a solid particulate non resorbable form, a porous non resorbable form derived from the exoskeleton of coral, and a resorbable nonceramic HA.β-Tricalcim phosphate is a porous form of calcium phosphate.

Bioactive glasses composed of SiO_2, NaO_2,P_2O_5 and is resorbable or non resorbable depending on the relative proportion of these components. When Bioglass exposed to tissue fluids, a double layer of silica gel and calcium phosphate is formed on the surface. The material promotes absorption and concentration of proteins through this layer allowing the osteoblasts to form extracellular bone matrix that theoretically may promote bone formation (120).

Alloplastic materials can be used successfully for ridge augmentation or MSFA. Histologic samples of bone grafting with different alloplastic materials show varying amounts of bone regeneration (121).

In human studies, HA, β-tricalcim phosphate and BG were proven to be biocompatible materials when used in sinus augmentation procedures (3, 122, 123). Tadjoedin et al. (124) performed sinus floor using a split mouth design. At test site 80-100% BG with 0-20% ABG was utilized and the control site ABG was used. Bone density in the test site was 27%, 36% and 39% at 4, 6 and 15 months, respectively. At the control site: this value was 39%, 41% and 42% at 4, 6 and 15 months, respectively. These results suggest that 6 months is enough for implant placement when mixtures of mainly (80-90%) BG particles and some (10-20%) ABG is used. However, when only 100% BG particles were used about 12 months healing time is needed for implantation.

The studies of Tadjoedin et al. (124) and Turunen et al., (121) suggest that BG can be used in a mixture with autogenous bone at the floor of the maxillary sinus, thus decreasing the amount of autogenous bone required.

Zerbo et al. (125) compared the new bone formation ability of β-tricalcim phosphate and ABG, in MSFA. Six bilateral, 4 unilateral sinus augmentations were performed in 10 patients. After a healing period of 6 months, implants were placed. At the time of implant surgery, biopsy samples were removed with trephine bur. Histomorphometric evaluation exhibited that the average bone volume formed in the augmented sinus at the ABG and β-tricalcim phosphateses was 41% (32-56%) and 17% (9-27%), respectively. When all nine patients were included statistically significant difference was observed (P=0.04). When only the five bilateral patients were included, mean bone volume of the β-tricalcim phosphate side was 19% (13-27%), which was also significantly different from the control side (P=0.009). Histologic samples revealed that the amount of lamellar bone at the β-tricalcium phosphate side was less than half the amount in the ABG side, indicating that remodelling had only recently started in the β-tricalcium phosphate-augmented side. These histological results indicate that β-tricalcium phosphates an acceptable bone substitute material for MSFA. Due to the osteoconductive, but not osteoinductive properties of this material, the rate of bone formation is somewhat delayed in comparison to ABG.

Cordaro et al. (126) compared the new bone formation with Bio-Oss® and Ceramic biphasic calcium phosphate (BCP) in48 maxillary sinuses in 37 patients. Residual bone width was ≥6 mm and height was ≥3 mm and < 8mm. After 180-240 days of healing, implant sites were created and biopsies taken for histological and histomorphometrical analysis. Histologic results exhibited close contact between new bone and graft particles for both groups, but no significant differences was observed in the amount of mineralized bone (21.6% for BCP vs 19.8% for Bio-Oss®) in the biopsy analysis of test and control site. Significantly less remaining percentage of graft substitute material was found in the BCP group (26.6% vs. 37.78.5% for Bio-Oss®). Authors concluded that both Bio-Oss® and BCP produced similar amounts of newly formed bone, with similar histologic appearance, indicating that both materials are suitable for sinus augmentation for the placement of dental implants.

Calcium phosphates, BG and HA have now been used successfully for sinus augmentations in the vast of situations, either alone or as an expander. Further research is still needed concerning human clinical application, in the form of randomized controlled clinical studies, long-term clinical studies and histologic data (127).

Bio-Oss®, one type of xenograft, has been shown to be a safe and biocompatible graft material, seems to be the most appropriate bone substitutes for sinus augmentation procedures (24, 128)**.** Bio-Oss® undergoes a low heat (300 °C) chemical extraction process that extracts the organic components, leaving the architecture of bone intact (129). The surface area, porosity, crystallite size, and calcium-to-phospohorous ratio resemble human cancelous bone (93). The pore system of Bio-Oss® facilitates angiogenesis and migration of osteoblasts (93) which is architecturally structured to allow vascularization of new bone (130, 131). It has been demonstrated that Bio-Oss® has a high biocompatibility and osteoconductivity when used in the sinus augmentation procedure (132, 133, 134). The efficacy of Bio-Oss® has been observed in various types of osseous regenerative procedures (135, 136), such as fresh extraction sites (137), localized anatomic alveolar ridge deficiencies (138) and sinus augmentation (114, 139, 140, 113, 25).

Animal-based experimental studies have repeatedly classified Bio-Oss® as a suitable bone substitute material (141, 142). Bio-Oss® is very slowly resorbed and seems to behave as a semipermanent grafting material (130).

An investigation into human response, Piattelli et al. (143) evaluated the long term histologic analysis of the bone response and resorption rate of Bio-Oss® when used in MSFA. Specimens were retrieved from 20 patients after varying periods from 6 months to 4 years. After the evaluation of histological specimen, most part of the Bio-Oss® particles were surrounded by mature, compact bone. In some Haversian canals it was possible to observe small capillaries, mesenchymal cells, and osteoblasts in conjunction with new bone and no gaps were present at the interface between the Bio-Oss® particles and newly formed bone. In specimens retrieved after 18 months and 4 years, it was also possible to observe the presence of osteoclasts in the process of resorbing the Bio-Oss®

particles and neighboring newly formed bone. They suggested that Bio-Oss® appears to be highly biocompatible and osteoconductive, and can be used with success as a bone substitute in MSFA.

Yildirim et al. (133) evaluated the bone formation following maxillary sinus augmentation using Bio-Oss® in combination with venous blood by means of histologic examination of human biopsies. 15 sinus cavities augmented on 11 patients. After an average healing period of 6.8 months, 22 biopsies were taken from the augmented sinus region and 38 implants were inserted. After 4- 9.5 months of healing, biopsies revealed that newly-developed bone became evident, partly invaginating the particles of apatite and forming bridges in the form of trabeculae between the individual Bio-Oss® particles. Histomorphometric results showed 14.7% new bone, 55.6% soft tissue, and 29.7% residual Bio-Oss® particles. 29% of the Bio-Oss® particles were in contact with newly formed bone. They concluded that both the histologically observed osseous integration of Bio-Oss® particles with newly formed bone and the good clinical results in the form of relatively high success rates up to the time of implant opening indicated that Bio-Oss® is a useful bone substitute material in MSFA.

In a study by Valentini et al. (144) the efficacy of Bio-Oss® as a graft material for sinus augmentation was studied in 15 patients. A total of 20 sinus augmentation procedures were performed, and 6 months later 57 implants were placed into the augmented sinuses. New bone formation was confirmed in biopsies of 3 patients. Histologic results showed that Bio-Oss® particles interconnected by bony bridges of woven bone. At 12 months, biopsy revealed intense remodeling with regenerated bone maturing from woven bone to lamellar bone. After a mean loading period of 4.0 ± 0.5 years (range 3.2 to 4.8), 56 implants remained in place. The implant survival rate was 98.1%. The authors concluded that Bio-Oss® has good osteoconductive properties which undergoes remodeling and allows successful implant placement after 6 months of healing.

Hallmann et al. (84) compared the use of particulated ABG alone with Bio-Oss® vs a mixture of 80% Bio-Oss® and 20% ABG in 21 patients in a two-stage procedure.

Several (6 to 9) months after grafting, experimental micro-implants for histological evaluation were taken and dental implants for prosthetic treatment were inserted. Six months later the micro-implants were explanted and histological and histomorphometrical evaluation was performed. There were no statistically significant differences between the bone graft groups regarding bone to implant contact (BIC) and bone area. Evaluation of implant survival after 1 year of loading showed no difference between the groups. It was concluded that ABG, Bio-Oss® alone, as well as a mixture of both, are suitable grafting materials for sinus floor augmentation.

In another clinical study in 10 patients, Maiorana et al.(145) used a mixture of particulate cancellous bone and marrow and Bio-Oss® for sinus floor elevations. Starting from the 5th month up to 7 months later, implants were placed and histologies were analyzed. Although in the 5-month specimens, areas filled with connective fibrous tissue surrounding the bone substitute particles, in the 7-month biopsies natural bone mineral was integrated and inter-connected by newly formed bone. These results indicated that longer periods of healing more than 5 months may be favorable for better quality of the new bone formation.

A histologic case report by Scarano et al. (132) evaluated newly formed bone 4 years after sinus augmentation procedure. Histological evaluation revealed that all Bio-Oss® particles were surrounded by newly formed bone and no Bio-Oss® particles was direct contact with the implant surface. Between the implant surface and the particles there was newly formed bone. Researchers concluded that very high BIC percentage can be achieved when utilizing Bio-Oss® in sinus augmentation procedure.

A study by Wallace et al.(128) analyzed the histological and clinical outcome of Bio-Oss® in sinus augmentation procedure. Sinus augmentations were performed on 51 patients with delayed placement of implants. Histological data revealed the presence of osteoblasts directly on the surface of the Bio-Oss® particles. Authors stated that the osteoconductive properties of Bio-Oss® derive from its chemical composition as well as

its macro- and micromorphology. They concluded that Bio-Oss® perform as well as or better than 100% ABG in MSFA.

A case report by Traini et al. (139) evaluated long term histologic analysis of Bio-Oss® retrieved 9 years after a sinus augmentation procedure. After 9 years, histologic findings showed that the obtained biopsy was composed mainly of grafted particles in close relation to newly formed bone that had different levels of maturation and numerous osteocytes. The residual particles of biomaterial appeared to be surrounded and connected by bone. The mean amount of newly formed bone, the natural bone mineral remnants and the percentage of marrow spaces was 46± 4.67%, 16±5.89%, and 38±8.93%, respectively. A greater number of osteocytes were found in the bone close to Bio-Oss® particules**.** Authors stated that Bio-Oss® has high level of osteoconductivity and a biomimetic behaviour over long term usage.

Various studies have demonstrated that Bio-Oss® is slowly resorbed by osteoclast in the normal remodeling process of bone (84, 139, 143, 146, 147). Thereby it seems to serve as a long-lasting matrix for new bone and helps to maintain the graft volume (112, 139). Several long-term follow-up studies have concluded that osteoconduction proceeds for several years, but no data are available to determine whether a mixture of ABG and Bio-Oss® may shorten the healing time of the graft (84,139). Long-term maintenance of the histologic results obtained with Bio-Oss® has been shown at 9 years by Traini et al (139). However healing period of 8 months is recommended for Bio-Oss® when used as the only grafting material, compared with a healing period of 6 months for ABG (84, 145). It is also stated that Bio-Oss® appears to be graft materials of choice today because when used in MSFA, approximately 25% vital bone formation occured by volume about 6-8 months time and, since it is a slowly resorbing material, it added approximately 25%to the mineral content of the future implant receptor sites (25% new bone formation and 25% residual non vital graft material) (148).

Recently, a new graft material, Cerabone® is introduced and contains high-temperature sintered bovine bone minerals (>1200°C) (32). The manufacturing process based on

high-temperature heating, removes all organic components, proteins and eliminates potential immunological reactions. Material can be used as particulate form (0,5-1mm or 1-2 mm) or as a highly porous block form (32). The open interconnecting pore structure is identical to the biological characteristics of the bovine material and arises from the physiological structure of the human body. The surface, porosity and chemical composition of material shows resemblance to human bone (32, 33, 34). Cerabone®'s macroporous structure is ideal for its osteoconductive function and promotes the ingrowth of blood vessels and nerves. The adhesion and spread of osteoblasts over the Cerabone® surface creates an open, interconnecting pore structure, which prompts a bioactive reaction with bone tissue formation, bone tissue strengthening and bone tissue interlinking leading to the restoration of the bone and its function. Cerabone® does not contain any pharmacologically active constituents. Large patient populations have confirmed the good biocompatibility of hydroxyapatite ceramic. Not one single rejection reaction has been reported to date. The efficacy of Cerabone® have been observed in orthopedic surgery (31), fresh extraction sites (37), nasal floor elevation sites (38) and sinus augmentation (39). The Cerabone® is very hydrophilic and can be easily be mixed with the patient's blood before insertion. The Cerabone®/ blood mixture demonstrates excellent coagulation properties and can be taken off the spatula confidently and applied with pinpoint accuracy. Bone regeneration can be promoted in combination with autologous blood and bone (30).

In animal studies, Cerabone® and Bio-Oss® were evaluated in dehiscence like defects in dog models with two different membranes (35). Defects were augmented with Cerabone®/Bio-Gide®or Bio-Oss®/Remotis®. The morphologic structure of two different native collagen membranes was examined using scanning electron microscope. For biocompatibility testing membranes were incubated with SaOs-2 osteoblastlike cells. Proliferation of the cells on the membranes was evaluated at 2 hours, 3 days, and 7 days. Also histologic analysis was performed at 4,8,12 and 24 weeks. They concluded that both membranes allowed early vascularization, however considerable biodegradation was noted within 4-8 weeks with Bio-Gide® while Remotis resorbed generally within the first 8 to 12 weeks. No difference was found regarding new bone formation with respect to the different bone substitute materials. After 24 weeks defects were completely organized with newly formed bone. New bone matrix either localized on the

surface of the bone substitute particles or bridging two or more particles leading to a three dimensional mineralized network. The authors reported that both combinations are suitable therapies for dehiscence like defects.

When it comes to the human studies, Cerabone® solid form and another resorbable nanocrystalline hydroxyapatite paste were used in treatment of large tibia compression fractures in twenty-four patients (31). Titanium locking compression plate was used for bone stabilization and Cerabone® and hydroxyapatite paste were used for cavity filling. The patients were called for clinic and radiographic control in 6 weeks, 12 weeks, 12 months and the results of the examinations were assessed according to Rasmussen score for tibia and head fractures (149). No local or systemic reactions were observed to the implanted materials in any of the patients. According to Rasmussen score, good (score average 26 points) results were accomplished. At the end of the study authors concluded that hydroxyapatite paste in combination with the central hydroxyapatite ceramic core presents reliable results in the treatment of tibia fractures.

Mazor et al. studied Cerabone® particulate form in nasal floor augmentation in 32 patients (38**)**. Pre-operative available bone height, implant dimensions and survival of the implants were evaluated. After the operation via lateral approach nasal cavity filled with Cerabone® and no barrier membranes were used to seal it. The pre-operative available bone height according to CT scan was 9.1±0.9 mm and bone height increase was 3.4±0.9 mm following augmentation. After healing period a total of 100 implants were placed with a average length of 12.5±0.9 mm (range 10 to 16 mm). During 27.8±12.4 months follow-up period no implant failure was recorded. The authors concluded that nasal floor elevation might be a predictable procedure in areas with significant atrophy for implant placement.

Riachi et al.(39)evaluated radiographic bone loss after MSFA with Cerabone® or Bio-Oss® in bilateral sinuses. In addition, this study evaluated the resorption rate of those two materials 8 months after augmentation, one and 4 year after implant placement. Furthermore, particle size, rate of calcium release and the type of crystal structure of each graft were evaluated. Crystal structure and particle size of each graft material was calculated using X-ray diffraction technique. Solubility of the graft material in demineralized water was evaluated using atomic absorption spectrophotometer. The

authors stated that the greatest amount of vertical loss of graft material was observed after one year of sinus surgery in both groups. Moreover, after 4 years, panoramic radiographic analysis revealed that Bio-Oss® demonstrated significantly higher volumetric loss (%33.4) compared to Cerabone® (%23.4)($p<0.05$). In this study, Bio-Oss® particle size (1mm) was smaller than Cerabone® group (2.7 mm). Authors stated that small particle size of Bio-Oss® resulted significantly higher surface area, higher calcium release rate and smaller crystallite size compared to Cerabone® group.

The review of literature reveals very limited number of studies for the application of Cerabone® in dentistry for augmentation before implant placement. Further studies are warranted to assess the clinical, radiographical and histological benefits of the material to the clinicians.

2.5 The Use of Barrier Membrane in Sinus Augmentation

Surgical objective of using membrane in sinus augmentation, is to position an effective barrier over the lateral window in such a manner as to exclude the connective tissue from the wound. Various membranes have been used over the lateral wall sinus augmentations, including nonresorbable expanded polytetrafluoroethylene (e-PTFE) membranes (150), long- and short-term bioabsorbable cross-linked collagen membranes (150, 151, 128), titanium mesh membranes, calcium sulfate barriers, and the repositoned original lateral bony window. Studies of the effectiveness of bioabsorbable barriers have found them to be similar to e-PTFE membranes with regard to vital bone formation. An advantage of the bioabsorbable membrane is elimination of the re-entry procedure required for e–PTFE.

Membranes prevent non osteogenic connective tissue from developing in the grafted area and in the sinus, which could lead to loss of graft ossification. From a biologic point of view, the exclusion of connective tissue cells should favor the population of the sinus graft with perivascular osteoblasts emanating from the adjacent bony walls and now-exposed vascular supply (152). Histologic sections taken through the lateral window that contain the barrier membrane reveal bone formation in contact with the membrane in such manner as to restore bony wall (152, 153).

A randomized controlled trial (152) utilizing a bilateral sinus model demonstrated that vital bone formation in the membrane-covered sinus would be, on average, twice that of the non-membrane side. This study, as well as controlled trial (154, 155) show higher implant survival rate on the membrane side than on the control side. A review by Wallace (21) shows implant survival rates for sinuses grafted with particulate grafts to be higher when a barrier membrane is placed over the window (94.6% vs 88.7%). A study (128) compared vital bone formation and implant survival with 100% BDX sinus graft when using non-absorbable or bioabsorbable barrier membranes over the lateral window. Average vital bone formation without a membrane, with an absorbable membrane (BioGide®), and with an e-PTFE membrane (Gore-Tex) was 12.1%, 17.6% and 16.9%, respectively. Further, there was no significant difference in implant survival between the two membrane groups. Histologic appearance and histomorphometric data were similar for the two membrane groups. A representative specimen from the BioGide® group demonstrates direct contact between the newly formed bone and the BDX particles. The evidence-based literature review by Wallace and Froum on implant survival following sinus augmentation and histologic/histomorphometric data documents the benefits of using a membrane over the lateral window (21). Positive effects have been obtained by placing a membrane over the lateral window, because it increases vital bone formation and implant survival rate, it results in positive outcome when used for perforation repairs. Berengo et al. (156) applied 16 implants with osteotomy technique in which position of the graft, replacement of graft and integration of membrane were investigated with endoscopic analysis. It was reported that perforation that did not result in graft loss was detected in two cases. It was reported that implant success rate was 100% during the 8-month period after loading of the implants and 12 of the 16 were in contact with the membrane as a result of the resorption of graft in the apex. They reported that osteotomy technique with the use of Bio-Oss® which is an acceptable procedure and small perforations are acceptable complications within the recovery period of sinus.

The available evidence suggests that the use of a membrane over the lateral window should be considered in all sinus graft procedures in lateral approach (157).

AIM

To our knowledge, there have been no published reports on the histological differences of the 2 xenografts, Cerabone® and Bio-Oss®, in MSFA. Such a comparison would contribute to the comprehensive body of information available and will aid the clinician in formulating successful strategies for MSFA. The degree of osseous integration is determined by the biological processes at the surface of the implant and bone quality. Therefore, it is utmost important to assess the bone quality in terms of histology before implant placement.

The aim of this study is to compare histologically and radiographically the efficacy of two different xenografts, Cerabone® and Bio-Oss®, in bilateral MSFA.

The hypothesis of this study is not to find radiographical and histological differences between these two graft materials.

3. MATERIALS AND METHODS

3.1 Patient Selection

This study was carried out on the patients who applied to Yeditepe University Faculty of Dentistry Department of Periodontology with the intention of having implant supported prosthesis for the posterior maxilla area. The study population included 8 patients with bilateral atrophy with less than 5 mm residual alveolar ridge height.

The following patient inclusion criteria were used in the study:

1. Plaque index (PI) score<1 after initial periodontal therapy,
2. No periapical pathology of the teeth next to the planned sinus augmentation areas,
3. Partial or total edentoulism in the posterior maxilla,
4. Bilateral pneumatized maxillary sinus with less than 5 mm of residual alveolar bone height in posterior maxilla detected by CBCT or Ortopantomograph (OPT),
5. Patients without ongoing pathology of the maxillary sinus diagnosed by otolaryngologist before the operation,
6. Non smoker patients or patients smoking less than 10 cigarettes per day,
7. Patients without allergy of any medication,
8. Patients who did not have any systemic diseases.

All procedures were explained in detail to the patients. All eight patients accepted and signed a written informed consent form.

3.2 Patient Groups and Research Plan

Each patient received comprehensive periodontal examination and evaluation of oral hygiene habits. Presurgical preparation included detailed oral hygiene instructions, scaling and root planning under local anesthesia using ultrasonic devices[1] and Gracey curettes[2], and occlusal adjustment, if indicated.

Patients were re-evaluated 4 weeks after initial therapy, and afterwards surgical periodontal therapy was performed when necessary. After the healing period, eight patients with less than5 mm of residual alveolar bone height in the posterior maxilla underwent bilateral MSFA by using Bio-Oss® in one side and Cerabone® on the other. Then lateral bony windows were covered with resorbable collagen membranes (CM). Randomization was performed with coin toss method. Coin carried out random selection. Two flipping was done. First flipping was performed to determine the treatment side (head: right, tail: left) and the other for treatment option (head: Cerabone® + CM, tail: Bio-Oss® + CM). In this way, if one side was treated with Cerabone® + CM, the other side was treated with Bio-Oss® + CM or vice versa. In all patients, PI measurements were recorded before the sinus augmentation procedure.

The research plan is presented in Figure 2. The measurement of the residual alveolar crest height of the patients at the posterior maxilla was performed by means of CBCT and OPT before, immediately after and at 8 months after sinus augmentation procedures.

During 8 months healing period, patients were evaluated at 1, 3 and 6 months and professional tooth cleaning was performed in partial edentulous patients. After completion of the graft consolidation, CBCT and OPT were re-taken at 8 months after sinus augmentation.

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[1]**Piezon® OEM built-in kit,** EMS, Switzerland

[2]**Gracey, SG-**$^{3}/_{4}$ $^{5}/_{6}$ $^{7}/_{8}$, **Mini-Five** SAS $^{3}/_{4,}$Hu-Friedy, USA

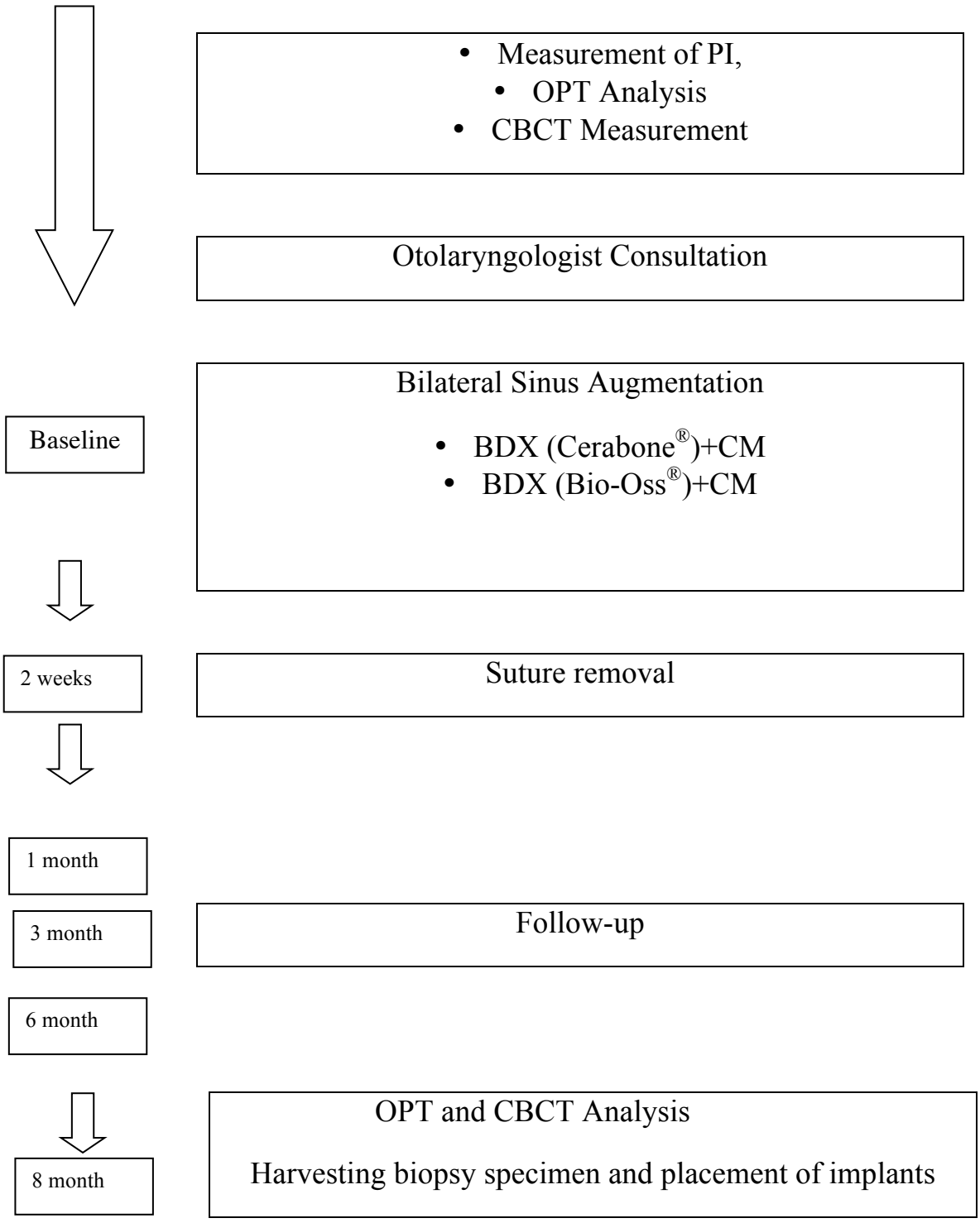

Figure 2. Research Plan

At the time of the implant surgery, biopsy samples were taken using trephine drill and implants were located. Then all patients received prosthetic rehabilitation.

3.3 Clinical& Radiographic Evaluation

3.3.1 Plaque Index(PI)

Teeth were isolated by cotton wool rolls and after drying by air syringe, the microbial dental plaque on the teeth surfaces were evaluated by the explorer in four areas of mesio-buccal, mid-buccal, disto-buccal and mid-lingual and scores between 0-3 were given for each point (158).

3.3.2 Radiographic Evaluation

CBCT was used to evaluate the sinus health, morphology and the residual alveolar bone height. For all patients, radiographic assessments were recorded preoperatively, immediately after and at 8 months after MSFA by the same calibrated examiner (D.P) using CBCT to detect the vertical bone height changes. The CBCT analysis was performed by using a software programme[3].

The following method was applied for defining residual alveolar bone height, using the CBCT (25, 159): two lines were selected that reflected the mesial (M) and distal (D) limits of the proposed sinus augmentation, then, a center point was defined between these two lines. Alveolar height was measured at these three points and arithmetic mean of these measurements was defined as average alveolar bone height (Figure 3).

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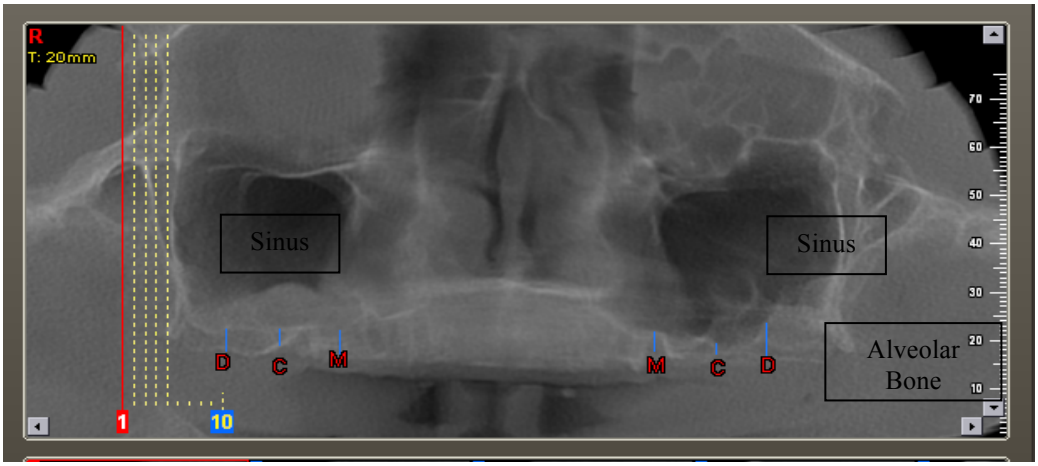
[3]**NNT Newtom Workstation 3G,**ImageWorks, Elmsford, New York, USA.



D:Distal border **M:** Mesial Border **C**: Center point

Figure 3.CBCT measurement points

3.3.3 Histologic Evaluation

Bone biopsies were obtained from the augmented sites during implant placement at 8 months after the sinus augmentation surgery, using a trephine bur of 2.3 mm diameter. Biopsy specimen was stained with tissue marking dye[4]. Biopsy samples were removed from the trephine and fixed in 10% buffered formalin and decalcified in formic acid and sodium citrate solution. After 48 hours of fixation, the samples were demineralized with a solution consisting of 50% formic acid 20% sodium citrate and rinsed in running water overnight. Then dehydrated in serial steps of alcohol (70%, 80%, 90%, 100%), embedded in paraffin wax, sectioned at 4-5µm, and stained with hematoxylin-eosin.

Histomorphometric analysis was performed using " Olympus analysis 5[5]" image analysis program. New bone formation and residual graft material were calculated as micron square in 3 different areas per each slide and mean values were obtained.

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[4]**CDI's Tissue Marking Dye** Cancer Diagnostics, INC, Durham, USA

[5]**Olympus Analysis 5,** Tokyo, Japan.

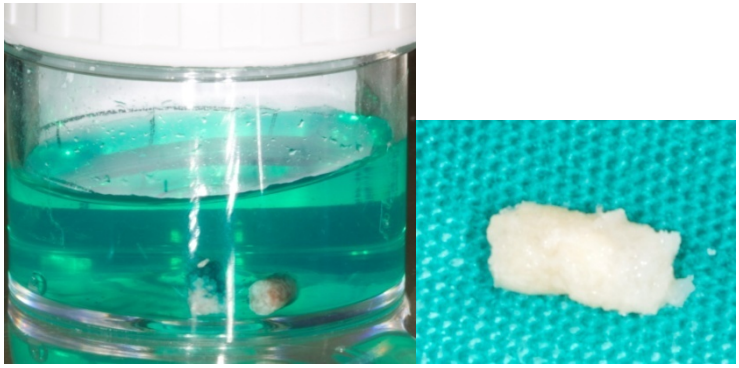

Figure 1. Bone biopsy specimen.

3.4 Biomaterials Used in MSFA

3.4.1 BDX (Bio-Oss®)

In this study, Bio-Oss®[6] granules with a particle size of 1-2 mm, were used to augment one of the sinuses (Figure 2). Bio-Oss® includes bovine deproteinized bone and has non-antigenic matrix with a porosity of 75% to 80% and cortical granule at 10μm crystal size, that shows chemical and physical similarity with human bone (27). Bio-Oss® undergoes a low heat (300 °C) chemical extraction process that extracts the organic components, leaving the architecture of bone intact (129). The pore system of Bio-Oss® facilitates angiogenesis and migration of osteoblasts (84), which is architecturally structured to allow vascularization of new bone.

3.4.2 BDX (Cerabone®)

Cerabone®[7] granules with a particle size of 1-2 mm were used in contralateral sinuses (Figure 3). Cerabone® is a high-temperature (>1200°C) sintered bovine bone mineral, containing the sintered inorganic part of bone (hydroxyapatite) (32).

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[6]**Bio-Oss®**, GeistlichPharma AG, Wolhusen, Switzerland.

[7]**Cerabone®,** Botiss Dental GmbH, Berlin, Germany

All organic components and proteins were removed by the manufacturing process based on high-temperature heating. This system reduce the risk of immunological reactions. Material can be used as particulate form (0,5-1mm or 1-2mm) or as a highly porous block form (33). The surface, porosity and chemical composition of material resemble to human bone (32, 33, 34).

3.4.3 CM

After MSFA of both sides, the lateral windows were closed by resorbable porcine derived CMs. The sinuses augmented with Bio-Oss® and Cerabone® were covered with Bio-Gide®[8]and Collprotect®[9], respectively (Figures 4,5).

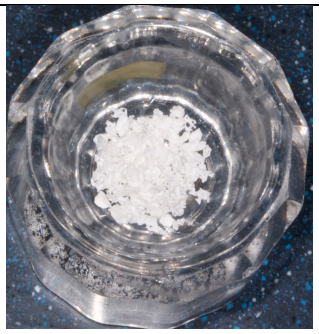

Figure 2. Bio-Oss®.

Figure 3. Cerabone.®

Figure 4. Bio-Gide®.

Figure 5. Coll-Protect®.

[8] **Bio-Gide**®GeistlichPharma AG, Wolhusen, Switzerland.
[9] **Coll-Protect®,** Botiss Dental GmbH, Berlin, Germany

3.5 Sinus Augmentation Procedure

Under local anesthesia[10], the lateral bony wall of the maxilla was exposed via crestal incision and muco-periostal flap was reflected. A buccal window was made in the lateral sinus wall by using low speed handpiece under saline irrigation. Schneiderian membrane was gently lifted with blunt instrument in mesial, distal and apical direction. Then, the Cerabone®/Coll-Protect®or Bio-Oss®/ Bio-Gide® was applied into the created space according to the randomization. In cases of perforation of Schneiderian membrane, CM was used to seal it. Finally, tension-free flap approximation was validated and the flaps were replaced and sutured with a 3-0 silk material[11] to obtain complete coverage of the augmented area. After 8 months of healing period, bone biopsies were obtained with trephine bur and implants were placed.

3.6 Post-Operative Care

3.6.1 Infection Control and Medication

Patients were given written postoperative instructions, including home care and medication usage. The patients were prescribed systemic antibiotic for a period of 1 week amoxicillin clavulanate[12]postoperatively (1000 mg, 2x1, 7 days). When sinus membrane perforation is occurred, the antibiotic is changed to levofloxacin[13] (500 mg, 1x1, 5 days).For pain medication, analgesics naproxen sodium[14](550mg, 2x1, 3 days) were prescribed. Patients were advised to avoid hard chewing in the surgical areas and to rinse twice daily with a 0.2% solution of chlorhexidine gluconate[15] for 10 days

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[10]**Ultracain D-S forte,** Aventis Pharma, Istanbul, Turkey.

[11]**3-0 A travmatic silk®,**Dogsan A.Ş. Trabzon, Turkey.

[12]**Augmentin BID 1000 mg,**Fakoİlaçları A.Ş., Istanbul, Turkey.

[13]**Tavanic film tablet,** 500 mg, AventisPasteur Aşı Tic A.Ş. Istanbul, Turkey.

[14]**Apranax Forte 550 mg,**Abdi Ibrahim A.Ş, Istanbul, Turkey.

[15]**Klorhex 0.2%,** DrogsanIlaçları San ve Tic. A.S., Ankara, Turkey.

In addition, cetirizine hydrochloride[16]antihistaminic was prescribed (10 mg, 1x1, 7 days) to treat symptoms such as allergic rhinitis, sneezing, runny nose and itching. Two weeks after sinus surgery, the sutures were removed. Regular controls of the patients were made postoperatively on 1st week, 2nd week, 1st, 3rd, 6th and 8th months. During regular controls, oral hygiene reinforcement and supragingival plaque control was performed. Two weeks after surgery temporary removable prosthesis was fabricated. If the patient has already removable prosthesis, this prosthesis was rehabilitated with resin[17] (89).

3.7 Histologic Sampling and Implant Placement

At 8 months after MSFA, biopsies were taken and implants were placed. Crestal incision was made extending from the maxillary tuberosity to the canine area. A vertical incision distal to the tuberosity was made to allow bone harvesting from this area. Mucoperiosteal flap was reflected. Then block bone samples were obtained using trephine drill with a diameter of 2.3 mm as a first drill in implant surgery and the implants[18] were placed at the related area. The block bone from the trephine drill was removed without disturbing the integrity of the tissue samples. Then the block bone was placed into 10% neutral buffered formalin solution and sent to Istanbul University Faculty of Medicine, Pathology Department for histological and histomorphometrical evaluation. Primary stability was obtained in all of the placed implants.

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[16]**Zyrtec 10 mg,**UCBPharma, Istanbul, Turkey.

[17]**Viscogel,** Dentsply, York, PA, USA.

[18]**The Astra Tech Implant System™**, Astra Tech Dental, Mölndal, Sweden.

3.8 Statistical Analysis

Power and sample size program was used to perform power analysis. To calculate the required sample size, for the percentage of newly formed bone %, using determined as Δ:6, SD:5.5, power: 0.80, β: 0.20 and α: 0.05, the n number for each group is 6. During the assessment of the data, Statistical Package for Social Sciences (SPSS)[19] for Windows 15.0 program was used. Radiographic parameters (vertical bone height) were measured at baseline, immediately and 8 months after the surgery. Data analysis was done for full mouth for PI at baseline. Quantitative data was recorded as the mean value ± standard deviation. The Kolmogorov–Smirnov test, assessed conformity of the parameters to the normal distribution. Paired Samples t test was used for the intra group comparisons of parameters with normal distribution. Student t test was used for the intergroup comparisons of parameters with normal distribution. Mann Whitney U test was used for the intergroup comparisons of parameters without normal distribution. Significance was evaluated at a level of $p<0.05$.

[19] **SPSS for Windows, version 15.0,** SPSS Inc., Chiago, IL, USA.

4. RESULTS

4.1 Demographical Results

Eight patients (4 female, 4 male) aged between 42 and 62 (mean age of 51.5±10.5) were included in the study. Bilateral MSFA procedure was performed using Bio-Oss®/CM in 8 and Cerabone®/CM in 8 sinuses. A total of 16 sinus augmentations were performed. No complications were observed in all 8 patients at postoperative healing period. Two patients out of eight were totally edentulous, and the remaining six was partially edentulous. Two patients were non-smokers, whereas 6 patients were light smokers.

4.2 Clinical Results

Before sinus augmentations, no sinus pathology was detected in any of the patients. During the surgery, sinus membrane perforation was observed in two of the operated 16 sinuses, and all of them were small perforations (≤5 mm). All perforations were in the Bio-Oss® + CM group and all were sealed with a CM (Bio-Gide®) (12,4 %).

Clinical evaluation of post-surgical healing revealed a good soft tissue response to the combinations with no adverse complications. Wound healing was uneventful on both sites. The intraoral pictures of the one representative case including both treatment approaches are documented in Pictures 8a-i with the radiographic images (Figures 9a-c).

4.3 Radiographic Results

The mean values and standard deviations of alveolar bone height scores before augmentation, immediately and 8 months after augmentation, intra- and inter-group comparisons are presented in Table 1. Baseline alveolar bone height scores were similar in both groups ($p>0.05$) (Table 1). The increase in alveolar bone height scores was significant when a comparison was performed between pre-augmentation and immediately after; in favor of the values obtained immediately after augmentation in both groups ($p<0.01$) (Table 1). The increase in alveolar bone height scores was significant when a comparison was performed between pre-augmentation and 8 months

after; in favor of the values obtained 8 months after augmentation in both groups ($p<0.01$) (Table 1). There was no difference between the alveolar bone height results obtained immediately and 8 months after augmentation in both groups ($p>0.05$) (Table 1). Comparison of differences are presented in Table 2. Intergroup differences were found to be insignificant for all of the compared time periods ($p>0.05$) (Table 2).

Table 1. The mean values and standard deviations of alveolar bone height scores at pre-augmentation, immediately and 8 months after MSFA, and intra and inter –group comparisons (In each group n=8).

	Cerabone®+ CM Mean±SD	**Bio-Oss®+ CM Mean±SD**	***+p***
Pre-augmentation (mm)	4,01±1,86	4,32±1,58	*0,747*
Immediate (mm)	14,79±2,02	16,16±1,50	*0,175*
8 months (mm)	14,23±2,12	16,02±1,05	*0,069*
Pre-augmentation/Immediate (mm) ++p	***0,001*****	***0,001*****	
Pre-augmentation/8 months (mm) ++p	***0,001*****	***0,001*****	
Immediate/8 months (mm) ++p	*0,058*	*0,708*	

+ Student t test, ++ Paired sample t test, ** p<0.01, p>0.05 (not significant).

Table 2. Comparison of differences at different time intervals (In each group n=8).

	Cerabone®+ CM Mean±SD Median	**Bio-Oss® + CM Mean±SD Median**	**+*p***
+Pre-augmentation/Immediate	10,77±2,06	11,84±1,56	*0,296*
+Pre-augmentation/8 months	10,22±2,46	11,70±1,52	*0,201*
++Immediate/8 months	0,56±0,59 (0,7)	0,14±0,97 (0,3)	*0,482*

+ Student t test,++ Mann Whitney U test, p>0.05 (not significant).

4.4 Histological Results

Microscopic Findings

Histologic appearance of all the samples were nearly similar. New bone formation and the residual graft materials were observed in a vascularization rich fibrous stroma. Graft materials were seen as trabecular bone with a cellular osteocyte lacunae and eosinophilic bone matrix. New bone was seen in contact with the graft material and separated from them with an apposition line. No evidence of inflammatory cell infiltration was present in the samples. Mild osteoclastic activity was also seen in all the samples. In all specimens, newly formed trabecular bone and residual BDX particles have different staining properties that ascribe the two configurations. Remaining BDX particles were in different shapes. In Cerabone®+ CM group, remaining particles were in a more roughly appearance than Bio-Oss®+ CM group. When it comes to the histomorphometric evaluation, new bone formation and residual graft materials were 29,13% and 24,63% ;13,01% and 14,77%, in Cerabone®+ CM and Bio-Oss®+ CM groups, respectively.

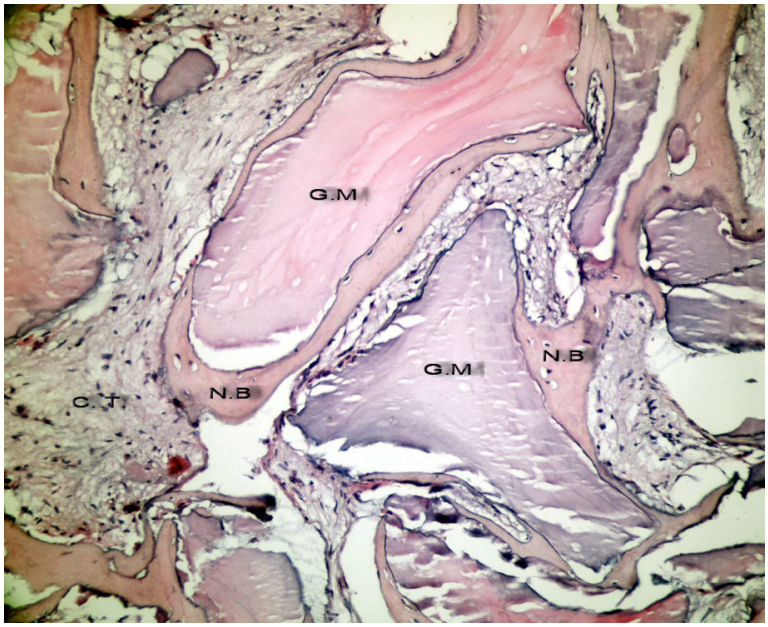

Figure 6. Histological section from a Bio-Oss®+ CM group. New bone formation (NB) is seen connecting with the graft materials (GM), separated by a resorption-apposition line, in the fibrous connective tissue (H&E X200).

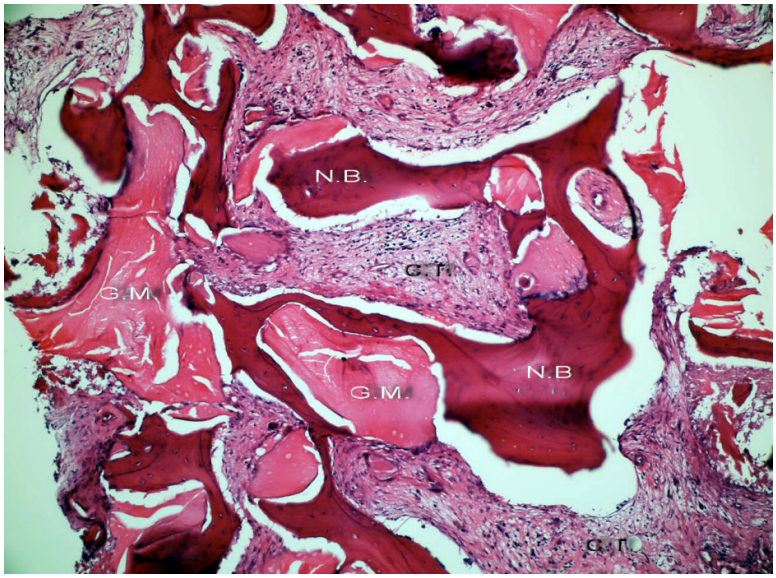

Figure 7. Histological section of Cerabone®+ CM group. NB formation is seen connecting with the graft materials. There is also a resorption- aposition line between the bone and graft material in the fibrous connective tissue (H&E X200).

Histomorphometric Findings

Histomorphometric evaluation comprised measurements of residual graft material and the newly formed bone incorporated with the graft material, reported as a % of the area of the whole section. Measurements were analyzed in a three high power field and mean of these measurements were calculated. All histomorphometric analysis was performed using a 'Olympus Analysis 5' image analysis system. The minimum, maximum, mean, median, and standard deviation of all parameters were presented in Table 4. Intra-group comparisons of histomorphometric evaluation were presented in Table 5.

Table 4. Minimum, maximum, mean&standard deviations and median values for histomorphometric parameters in all samples (n=16)

	Min-Max	**Mean±SD**
Total area (mm^2)	0,10-0,38	0,33±0,11
New bone (mm^2)	0,01-0,26	0,09±0,07
Residual graft particles (mm^2)	0-0,24	0,05±0,06
New bone (%)	2,63-68,42	26,88±16,63
Residual graft particles (%)	0-63,16	13,89±14,86

Table 5. Intra-group comparison of histomorphometric parameters (In each group n=8).

	Cerabone®+ CM (Mean±SD)(Median)	**Bio-Oss®+ CM (Mean±SD)(Median)**	**+p**
Total area (mm^2)	0,31±0,13 (0,38)	0,34±0,10 (0,38)	*0,535*
New bone (mm^2)	0,09±0,06 (0,07)	0,09±0,08 (0,07)	*0,832*
Residual graft particles (mm^2)	0,04±0,02 (0,04)	0,05±0,08 (0,02)	*0,526*
New bone (%)	29,13±13,81 (24,73)	24,63±19,76 (18,42)	*0,289*
Residual graft particles (%)	13,01±5,49 (12,76)	14,77±21,01 (9,1)	*0,316*

+Mann Whitney U test, p>0.05 (not significant).

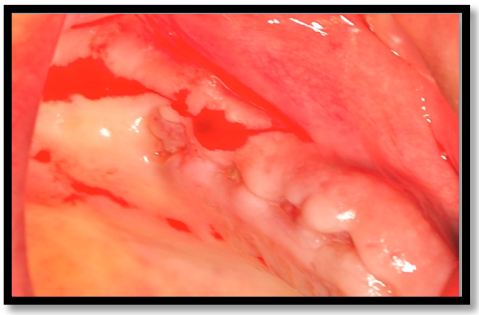

Figure 8a

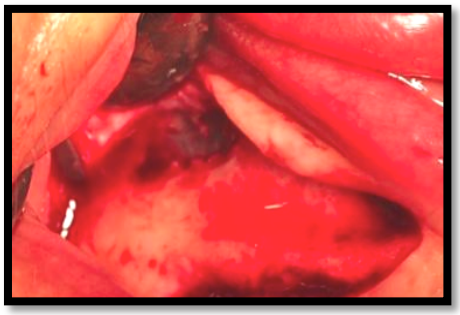

Figure 8b

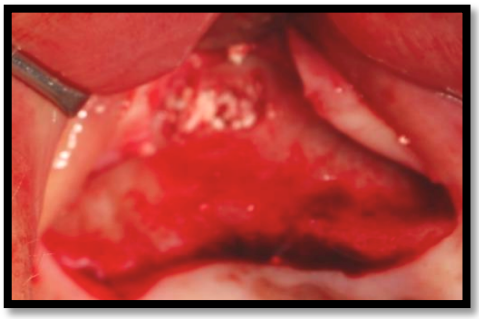

Figure 8c

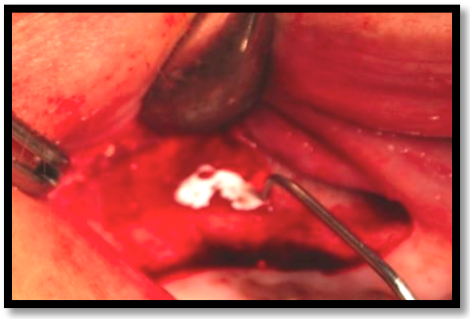

Figure 8d

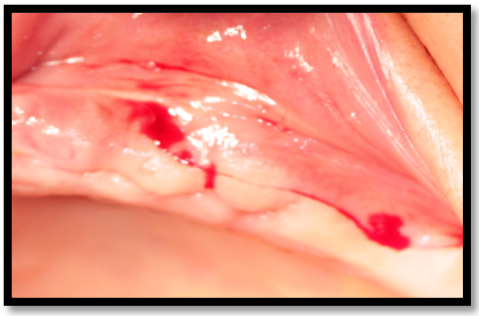

Figure 8e

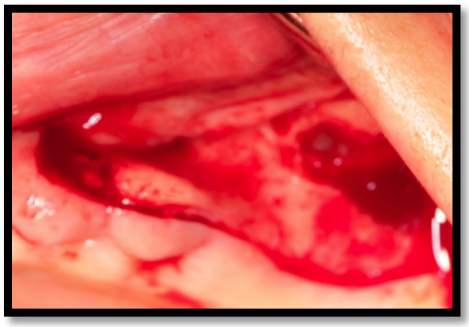

Figure 8f

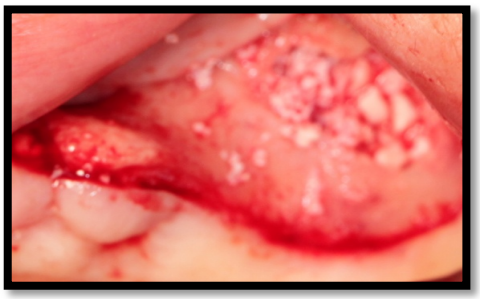

Figure 8g

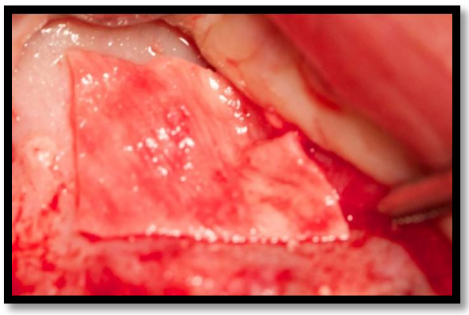

Figure 8h

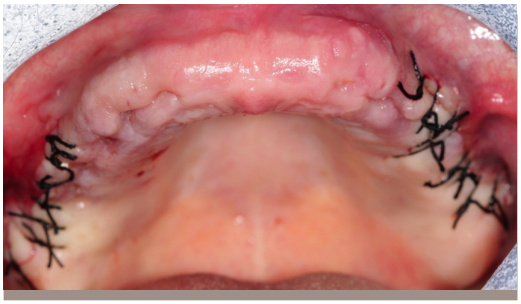

Figure 8i

Figure 8a	Crestal incision of the right side during operation.
Figure 8b	Lateral bony window of the sinus
Figure 8c	Application of BDX (Cerabone®) into sinus
Figure 8d	Application of CM upon the lateral window
Figure 8e	Crestal incision of the left side during operation
Figure 8f	Lateral bony of the sinus
Figure 8g	Application of BDX (Bio-Oss®) into sinus
Figure 8h	Application of CM upon the lateral window
Figure 8i	Primary closure of both sinuses

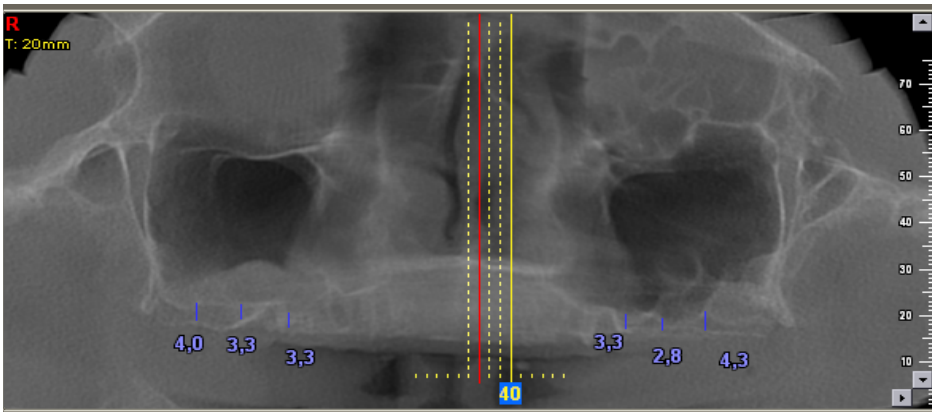

Figure 9a

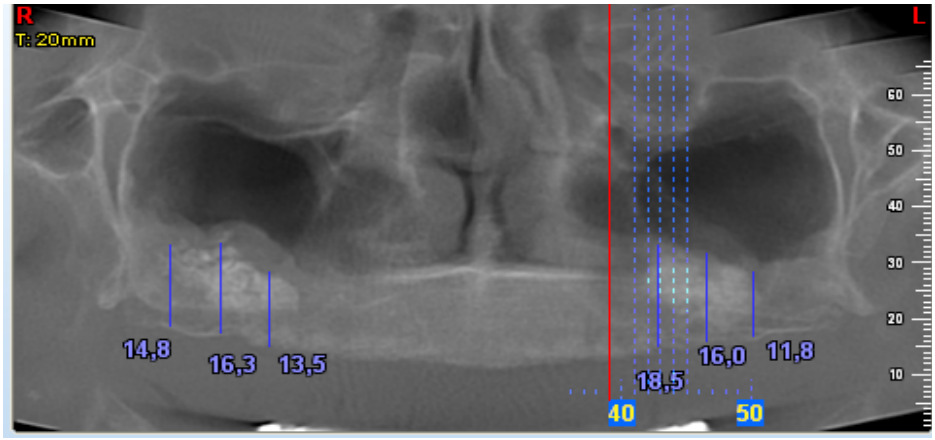

Figure 9b

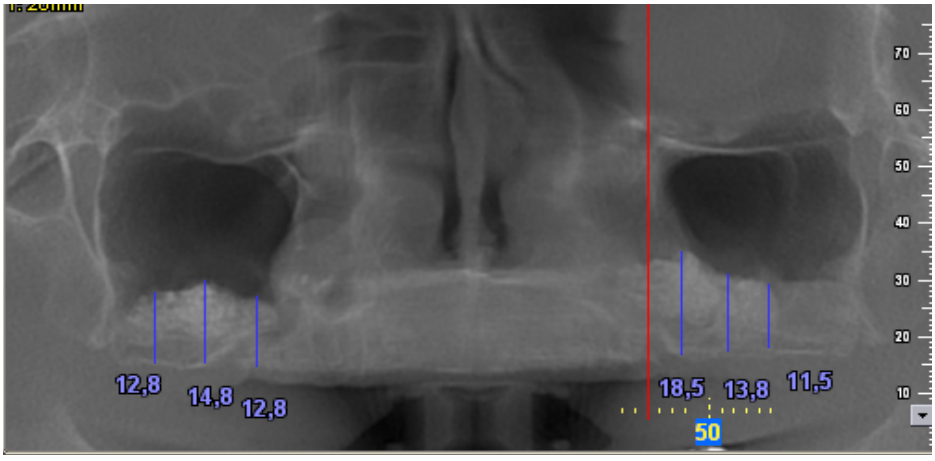

Figure 9c

Figure 9a CBCT analysis before augmentation operation.

Figure 9b CBCT analysis immediately after augmentation.

Figure 9c CBCT analysis 8 months after augmentation.

5. DISCUSSION AND CONCLUSION

The rehabilitation of the maxillary edentulous area with implant therapy is often hampered by atrophic ridges that result from bone resorption following tooth extraction or from the effects of periodontal disease (65). The dimension in height of the posterior maxilla reduces as a result of dual resorption from the crest of the ridge together with the pneumatization of the sinus, causing a lack of height for dental implants to support occlusal loads (160). It was reported that the processes of resorption and pneumatization speeded up by age and the bone loss increases depending upon the early loss of the teeth (161, 61, 162). This process compromise or prevent implant placement without an augmentation procedure (65).

Maxillary sinus floor augmentation is an internal augmentation of the maxillary sinus which was applied by Tatum (51, 53) during 1970's for the first time with ABG. This procedure has become popular and shows high success ratios of usage of alternative materials at the present time by means of the innovations made in the field of the tissue engineering (163). Today, two main techniques of MSFA for dental implant placement are in use: a two –stage technique with lateral window approach, followed by implant placement after a healing period, and a one-stage technique using either a lateral or transalveolar approach. The decision to apply the one- or two-stage techniques is based on the amount of residual bone available and the possibility of achieving primary stability for the inserted implants (69). In the cases that have 5 mm and higher crest heights, in the applications performed with sinus lift augmentations as one stage and with alternative graft materials, higher success ratios are reported (68, 69, 70). In the cases that have 3 to 5 mm and lower crest height, the success of the usage of the ABG is highlighted (10, 68). Related studies state that also successful results could be achieved with the usage of BDX alone or in combination with ABG in MSFA (84, 164, 165). In the cases, which have 1 to 3 mm crest heights, the importance of using block ABG bone grafts recommended (10, 68). Berg et al. (163) stated that the one stage implant application could be carried out only in the cases which has enough bone quality and quantity that leads to predictable primary stability. Researchers stated that when residual crest height is lower than 5 mm which is the sublimit for the residual alveolar crest

necessary for the primary stability, it is necessary to use the two stage method (163, 69). In two-staged technique, long time period helps vascularization, graft maturation and new bone formation thus the results of treatment are positively affected (166). In this study residual alveolar bone heights were 4.01±1.86mm and 4.32±1.58 mm in Cerabone®+ CM and Bio-Oss® + CM groups, respectively. Therefore, a two stage lateral approach is chosen for MSFA that is accepted as a valid and predictable approach by the researchers (69, 166, 167).

Autogenous bone graft has always been considered the "gold standard" of grafting materials because it possesses osteoconductive, osteoinductive and osteogenic properties (168). In late 1996, the majority opinion of the Academy of Osteointegration Consensus Conference was that ABG was appropriate for sinus grafting and that allografts, alloplasts, and xenografts may be effective in selected clinical situations (10). From that time to present several evidence-based reviews reported on the efficacy of all forms of graft materials (68, 69, 148, 169). The reviews are in agreement that more favorable results have been achieved with allografts, alloplasts, and xenografts rather than with ABG. The characteristics of the graft material, the stability of the clot, resorption ratios, and configuration of the maxillary sinus also effect the outcomes after MSFA (21, 68, 170, 127). The most rigorously evaluated graft in the literature is xenografts. Application of these materials in MSFA has reported to demonstrate equal or better results that achieved with ABG (148). In this study, two different xenografts were compared in MSFA. Bio-Oss® was chosen as the gold standard of the xenografts that has evidence based information in the literature and Cerabone®, is a new alternative from the same origin that warrants further investigation.

Although today MSFA is accepted as a predictable technique, each surgical step may give rise to complications. Incisions, elevation of the mucoperiosteal flap, antrostomy design, membrane elevation, placement of block or particulate grafts, and suturing may each give rise to complications if not performed correctly (61,171). After the procedure, complications can be classified as early or late post-operative complications and include incision line opening, barrier membrane exposure, and inadequate graft retention (171). Early postoperative complication occurs within the first 3 weeks after the surgery.

Delayed complications are evident after 3 weeks. Late complications may occur months or years after surgery and are due to improperly treated maxillary sinusitis. Early postoperative complications consist of wound dehiscence and oral fistula formation, acute graft infection, severe postoperative hemorrhage/hematoma, early exposure of bone graft in cases of adjunctive procedure for vertical or horizontal augmentation. Immediate intraoperative complications are membrane perforation, loss of graft material through the window, hemorrhage from vessels supplying the sinus, mechanical obstruction of the ostium, and neurological complications (171). The group of delayed postoperative complications includes chronic sinusitis with or without displacement of bone graft (172, 173). In the literature, the rate of Scneiderian membrane perforation is in a range of 0-44% (69, 114,168, 172, 174, 175). Resorbable CM can be used to cover small-to medium-sized perforations in the Schneiderian membrane (176). Hallmann et al. (84) reported on perforated Schneiderian membranes in 9 out of 30 sinus augmentation procedures. They used a resorbable membrane to cover these perforations. Collagen seems to be a suitable material because in most conditions the collagenous structure sticks to the sinus membrane and seals the tears. Thereby loss of graft particles into the sinus cavity is avoided. It can be assumed that this may also protect against postoperative infection via the respiratory tract. In this study, the only observed complication was sinus membrane perforation, seen in 12.4 % (2 of 16) of the cases. All of them were small and sealed with a CM.

Computerized tomography scans have become the widely used evaluation method by which a comprehensive implant treatment plan is determined and post-operative alveolar bone height is assessed after MSFA, before implantation. There is a debate about the radiation for the patient when obtaining a CT (177). When CT is the choice of the assessment, usually 2 CTs are obtained in MSFA, one at baseline and the other before implant placement. On the other hand, CBCT provides a lower dose and cost alternative to conventional CT. The effective dose with the CBCT technique is significantly smaller than achieved with conventional CT imaging methods and is within the range of dental imaging modalities (178, 179). In this study CBCT was used to evaluate the alveolar bone height changes. In the literature, there is only one research similar to our study, which compared Bio-Oss® versus Cerabone® by means of

panoramic X-rays in MSFA (39). This study evaluated the resorption rate of those two xenograft materials 8 months, 1 year, and 4 years after implant placement. Riachi et al. (39) stated that Bio-Oss® has demonstrated the greatest amount of vertical loss of graft material volume after one year of sinus surgery (55-65% of total bone loss). In addition, after 4 years, X-ray image analysis revealed that Bio-Oss® still demonstrated significantly higher volumetric loss (33.4±3.1%) compared to Cerabone®(23.4±3.6%). In this study, CBCT analysis at 8 months revealed a bone height increase of 10.22±2.46 mm for Cerabone® and 11.70±1.52 mm for Bio-Oss® groups, respectively. In this study, only a little amount of bone height loss (0.56±0.59 and 0.14±0.97 for Cerabone® and Bio-Oss® groups, respectively) was observed at 8 months and there was no difference between the groups ($p > 0.05$). It is impossible to compare these two studies since the evaluation time periods are different.

Smoking is an important risk factor in the success of MSFA and implant placement (66, 180, 181, 182). Toxic by products of smoking, such as nicotine, carbon monoxide and hydrogen cyanide have been implicated as risk factors for impaired healing. Nicotine, with its vasoconstriction effect, decreases the oxygen concentration in the blood vessels thereby delaying wound healing (181). Nicotine also inhibits cellular proliferation. Furthermore, smoking is known to be associated with an increased susceptibility to allergy and infection because it interferes with ciliary function and secretory immunity of the nasorespiratory tract. In the maxillary sinus, this may effect immune exclusion and suppression because both surface immunoglobulin A (sIgA) and sIgM responses are reduced, whereas IgE responses are increased (183). It has been reported that tobacco results in poor bone quality and healing capacity due to vascular and osteoblastic dysfunction (184). Patients who smoke more than 15 cigarettes per day are considered to be at risk for bone graft and implant failure in both short and long term observation (180, 184). Furthermore, if the patient is a smoker, some researchers suggest that smokers who abstain from smoking prior to surgery and 10 days afterward can avoid the complications that frequently observed in smokers after MSFA and implant placement (66). In this study, patients who smoke less than 10 cigarettes per/day were included.

Histological and histomorphological data about the comparison of Bio-Oss® and Cerabone® in MSFA is not available and is of special interest for the clinicians to define

the resorption, integration and efficacy of the used material. In this study, histologic appearance of the treatment groups revealed trabecular new bone formation with cellular osteocyte lacune in a vascular rich fibrous stroma. There was no inflammatory cell infiltration detected in any of the samples. Bio-Oss® and Cerabone® particles were still observed in the specimens, demonstrating the slow resorption rate of both materials. In histomorphometric analysis, new bone formation and residual graft materials was 29.13% and 24.63%; 13.01% and 14.77%, in Cerabone®+CM and Bio-Oss®+CM groups, respectively. In literature, biopsies obtained after MSFA with Bio-Oss® revealed new bone formation of 25% after 3-5 months (164), 35% after 6-8 months (185) and 34% after 9 months (165). On the other hand, the proportion of newly formed bone varied from 12% to 69% after 3-12 months of observation period (113, 133, 144, 164, 185). The histomorphometric results of the study for Bio-Oss® are in accordance with the literature. There is no data about the histologic and histomorphometric analysis of Cerabone®. These data suggest that the process of bone formation is in its earlier stages and needs time for maturation in both groups. The particles related to both graft material were still observed in the specimens, demonstrating the slow resorption rate of the materials. Although there is no statistically significant differences between the % residual graft particles, Bio-Oss® has a lower percentage of residual graft particles than Cerabone®. Although both materials are commercial hydroxyapatite compounds, Bio-Oss® undergoes a low heat (300 °C) chemical process that extracts the organic components, while Cerabone® deproteinization occurs at a very high temperature (1200 °C) that enhances material crystallinity (32, 186). Because Bio-Oss® has a less crystalline structure compared to Cerabone®, might be more prone to degradation, residual Bio-Oss® particles might resorb faster. However, to clarify this speculation, long term histomorphometric analysis and biochemical evaluation of the materials is needed.

Particle size of the graft material is another important issue in MSFA. It has been long unanswered question that if particle size of the graft material may affect and accelerate the bone healing since inter-particular space seems to be an important determinant for osteoconduction (187, 188). While some researchers advise to use 1:1 mixture of small (0.25–1 mm) and large (1–2 mm) particles which may result in optimal inter-particle

spacing leading to vascular ingrowth and new bone formation (189), Chackartchi et al. (190) reported a non significant difference between small and large particle grafts in terms of bone formation in MSFA. On the other hand, a recent study by Testori et al. (180) has shown a statistically significant difference with new bone formation of 28% versus 18.8 % at 6 months for large and small particle size, respectively. In accordance with the relevant literature, large particle size was used in both groups in order to achieve best treatment results.

The process of graft maturation after MSFA, which varies in duration depending on the graft material used, consists of cellular proliferation, migration, differentiation, gene expression, adhesion and apoptosis (191). When autograft is used, this phase generally lasts 4 months; for allograft and xenograft 7 to 8 months; and for alloplast 1 year or longer. The goal of this non mechanical process is to make functionally adaptable bone (191). In the literature, there is no consensus for graft maturation process even for same kind of bone substitutes (2, 25, 131, 140, 164, 192). Wallace et al. (193) reported that when Bio-Oss is the choice of the graft material in MSFA, gradual bone formation is observed and the necessary duration for the development of the newly formed bone is between 12 to 20 months. Other researchers reported a waiting period between 6 to 16 months for bone maturation before implant placement (182, 194). When Bio-Oss® is the material of the choice for MSFA, it has been stated that 6 month period is not sufficient for the maturation of newly formed bone and it is advised to wait for 8 months to obtain primary stability for the implants (84). In this study, 8 months healing period is selected in order to achieve maturation of the graft material and to obtain primary stability of the implants.

To our knowledge, there have been no published reports on the histological analysis of the 2 xenografts, Cerabone® and Bio-Oss®, in MSFA. This study is the first study comparing the clinical and histological findings of Bio-Oss® and Cerabone® in MSFA. Within the limits of this study, both materials have similar histologic appearance and new bone formation that accomodates the placement of dental implants.

6. REFERENCES

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