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Comparison of two different xenografts in bilateral sinus augmentation: Radiographic and histologic findings

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Objective: The aim of this study was to evaluate the radiographic and histomorphometric results of two different xenografts in bilateral sinus augmentation in patients with posterior maxillary atrophy. **Method and Materials:** Eight patients with less than 5 mm residual alveolar bone height were included in this study. One side was augmented with bovine bone graft-1 and the other side with bovine bone graft-2. Radiographic analyses were performed before and after augmentation, and before the implant placement. After 8 months of healing period, bone biopsies were obtained during implant placement. **Results:** No statistically significant difference was

found between the groups, based on post-augmentation and pre-implantation graft heights ($P > .05$). Histomorphometric evaluation demonstrated 24.63% and 29.13% newly formed bone in the graft-1 and graft-2 groups, respectively. Intergroup differences were not significant for the mean percentage of new bone formation ($P > .05$). **Conclusion:** Within the limitations of this study, it can be concluded that xenograft materials resulted in satisfactory bone height and trabecular new bone formation, and they could be used for the rehabilitation of atrophic maxillae. (doi: 10.3290/j.qi.a33686)

Key words: clinical study, deproteinized bovine bone, histology, sinus floor augmentation

Placement of oral implants in the posterior maxillary edentulous region presents many unique and challenging conditions compared with the other regions of the jaw. The presence of the maxillary sinus as the basis of the maxillary alveolar process can be an obstacle to the

placement of an implant.¹ 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 leading to difficulties in the rehabilitation of the posterior maxilla over time.² As a consequence, there is usually a need to increase the bone volume in the posterior maxilla prior to implant placement.³

Numerous different grafting materials have been used in maxillary sinus floor augmentation (MSFA) with varying success rates.⁴⁻⁶ Above all, autogenous bone is considered to be the “gold standard”^{7,8} since it has osteogenic, osteoinductive, and osteoconductive properties.^{7,9} It can be resorbed over time and replaced with the newly formed bone. However, utilization of autogenous bone graft requires a second surgical site (intra-

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oral) or possible hospitalization (extraoral), thereby increasing the length of time of the surgical intervention, postsurgical morbidity, cost, and possibly resulting in an inadequate volume of graft material.¹⁰ 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 of these bone substitutes.^{4-6,11-14}

Deproteinized bovine bone (DBB) consists of 100% anorganic bovine bone, has been shown to be a safe and biocompatible material with osteoconductive properties,^{15,16} and is considered the most widely used and best documented biomaterial in dentistry.^{4,13,14,17-19} Since DBB 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.¹⁸⁻²⁰ DBB-1 is a kind of xenograft consisting of deproteinized, sterilized bovine bone with 75% to 80% porosity and a crystal size of approximately 10 μm in the form of cortical granules. DBB-1 has a natural, nonantigenic porous matrix and is chemically and physically identical to the mineral phase of human bone.²¹ Several short-term and long-term studies have shown that DBB-1 can be used in sinus augmentation with predictable and successful results.^{13,14,16,20-24} DBB-1, when used alone, is better than autograft or allograft in terms of 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 DBB-2 has osteoconductive properties, with hard tissue regeneration and osseous organization.^{25,26} This material, due to containing the sintered inorganic part of bone (hydroxyapatite), has the interconnected porous structure of the original bone.²⁷⁻³⁰ DBB-2 can be used in particulate form (0.5 to 1 mm or 1 to 2 mm) or in highly porous block form.²⁷ Studies have evaluated the efficacy of DBB-2 in orthopedic surgery,²⁶ socket preservation,³¹ and nasal floor augmentation,³² and successful results were reported. The resorption rate of the graft in sinus augmentation procedures was evaluated in only one study.³³

Although there are well-established studies evaluating the clinical, radiographic, and histologic efficacy of DBB-1 in sinus augmentation, there is no study evaluating the histologic outcomes of DBB-2 and comparative histologic evaluation of these two xenografts. Since histologic analysis of regenerated tissues in sinus elevation would 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 histomorphometric outcomes of two different xenografts after sinus augmentation.

METHOD AND MATERIALS

Eight patients with severe atrophy of the maxillary alveolar process diagnosed by preoperative panoramic radiographs and by cone beam computerized tomography (CBCT) were included in the study. Two patients out of eight were totally edentulous, and the remaining six were partially edentulous. Sixteen maxillary sinuses, which had < 5 mm subantral alveolar bone in vertical direction were treated with a maxillary sinus floor augmentation procedure and delayed implant placement. Patients were excluded if they presented systemic diseases that could interfere with the surgical procedure, ongoing pathology of the maxillary sinus, and/or a previous history of chronic sinusitis and smoking more than 10 cigarettes per day.

All surgeries were performed by the same experienced periodontist (SY) between February 2011 and May 2012. After an explanation of all aspects of the study as well as the alternative treatment regimens, written informed consent was obtained from all patients. The study was performed in accordance with the Helsinki declaration of 1975, as revised in 2000. The study design and consent forms were reviewed and approved by the University Institutional Review Board and the Ethical Committee.

Study design and randomization

This study was designed as split mouth. In this design, each of the two treatments were randomly assigned to either the right or left halves of the dentition. Right or



left sides were randomly assigned by a toss of coin to one of the two treatment groups. A coin was flipped on two different occasions. The first coin flip was performed to determine the treatment side (heads, right; tails, left) and the other for the treatment option (heads, DBB-2 + Collagen membrane [CM]; tails, DBB-1 + CM). In this way, if one side was treated with DBB-2 + CM, the other side was treated with DBB-1 + CM or vice versa.

Blinding

The surgeon was not blinded to the materials applied to the sides. However, the researchers who performed the radiographic and histomorphometric assessments (DP and VO) were both blinded to treatments.

Intra-examiner reproducibility

The examiner performed measurements on the CBCTs of five patients. The examiner evaluated the CBCTs on two separate occasions 48 hours apart.²⁴ Calibration was accepted if measurements at baseline and 48 hours were similar to the mm > 90% level.

Radiographic measurements

CBCT was used to evaluate the sinus health, morphology, and residual alveolar bone height. For all patients, radiographic assessments were recorded preoperatively, immediately after operation, and at 8 months after MSFA by the same calibrated examiner (DP). The CBCT analysis was performed using a software program (NewTom, NNT). The following method was applied for defining residual alveolar bone height:^{24,34} Two lines were selected that reflected the mesial (M) and distal (D) limits of the proposed sinus augmentation, and a center point was defined between these two lines (Fig 1). Alveolar height was measured at these three points and the arithmetic mean of these measurements was defined as average alveolar bone height.^{24,34}

Histomorphometric and radiographic measurements are given as means ± standard deviations (SD).

Surgical procedure

A two-stage procedure was performed following the method described by Boyne and James³ and Tatum.³⁵



Fig 1 Radiographic measurements.

The lateral bony wall of the maxilla was exposed via crestal incision under local anesthesia (Ultracain D-S forte, Aventis Pharma), and a mucoperiosteal flap was reflected. A buccal window was made in the lateral sinus wall using low-speed handpiece under saline irrigation. The sinus membrane was gently lifted with a blunt instrument in mesial, distal, and apical directions. Then, the DBB-2 (Cerabone®, particle size 1 to 2 mm, Botiss Dental)/CM (Coll-Protect®, Botiss Dental) or DBB-1 (Bio-Oss®, particle size 1 to 2 mm, Geistlich Pharma)/CM (Bio-Gide®, Geistlich Pharma) was applied into the created space according to the randomization. In cases of perforation of the sinus 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 (Dogsan AS) material to obtain complete coverage of the augmented area. The patients were prescribed systemic antibiotics for 1 week (amoxicillin/clavulanic acid, 1,000 mg, 2 × 1, Augmentin BID, Fako İlaçları), and anti-inflammatory and analgesics for 3 days (naproxen sodium, 550 mg, 2 × 1, Apranax Forte, Abdi Ibrahim). In addition, all patients were instructed to rinse twice daily with a 0.2% solution of chlorhexidine gluconate (Klorhex 0.2%, DrogSan) for 2 weeks. Recall appointments were scheduled in every 2 weeks during the first 2 months following the surgical procedure and once a month for the remaining observation period.

Histologic preparation and evaluation

After 8 months of healing period, bone biopsies were obtained from pre-planned implant sides during the



implant surgery. A 2.3-mm diameter trephine bur was used to obtain bone biopsy. As soon as bone biopsies were taken, they were stained with tissue marking dye. 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 the samples were dehydrated in serial steps of alcohol (70%, 80%, 90%, 100%), embedded in paraffin wax, sectioned at 4 to 5 μm , and stained with hematoxylin-eosin (h&e).

Histomorphometric evaluation under high power magnification was performed in three different areas. All the parameters, such as new bone formation and residual graft particles, were calculated in each area, and the arithmetic means of these three areas were taken. All histomorphometric analyses were performed using an image analysis system (Olympus Analysis 5). The following morphometric measurements were performed:

1. total area (mm^2)
2. total area of new bone (mm^2 and % of 1)
3. total area of residual graft particles (mm^2 and % of 1).

Statistical analysis

A power and sample size program was used to perform power analysis. According to the results of power analysis, the sample size of six subjects was defined for 80% statistical power, β .20 and α .05 to detect, Δ 6, SD 5.5. During the assessment of the data, SPSS for Windows 15.0 program was used. Radiographic parameters (vertical bone height) were measured at baseline, and immediately and 8 months after surgery. Quantitative data was recorded as the mean value \pm SD. The conformity of the parameters to the normal distribution was assessed by the Kolmogorov–Smirnov test. Paired sample *t* test was used for the intragroup comparisons of the 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 $P < .05$.

RESULTS

Clinical results

Ten patients with total or partial maxillary edentulism were selected based on the inclusion criteria. Two patients did not want to attend the implant surgery because of their systemic health. The remaining eight patients were included in the study. During the surgery, sinus membrane perforation was observed in two of the operated 16 sinuses, and all of them were small perforations (12.5%). All perforations were in the DBB-1 + CM group and all were sealed with a CM. No patients were lost for the follow-up and all returned for implant placement. Clinical evaluation of postsurgical healing revealed a good soft tissue response to the combinations with no adverse complications. Both groups presented similar baseline characteristics in terms of alveolar bone height values. The age of eight patients (four women, four men) ranged from 42 to 62 with an average age of 51.5 ± 10.5 years.

Radiographic analysis

The radiographic findings showed that both treatment modalities resulted in bone gain at 8 months in both groups (Table 1). The increase in alveolar bone height scores was significant between pre-augmentation and 8 months after in both groups ($P < .01$) (Table 1). There was no difference between the alveolar bone height results obtained immediately and 8 months after augmentation in both groups ($P > .05$) (Table 1). Intergroup differences were found to be insignificant for all of the compared time periods ($P > .05$) (Table 2).

Histomorphometric analysis

The histologic appearance of all samples was 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 osteocytic lacunae and eosinophilic bone matrix. New bone was seen in contact with the graft materials and separated with an apposition line. No evidence of inflammatory cell infiltration was present in the samples. Mild osteoclastic activity was also seen in all the sam-



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

	DBB-1 + CM	DBB-2 + CM	P*
Pre-augmentation (mean ± SD, mm)	4.32 ± 1.58	4.01 ± 1.86	.747
Immediate (mean ± SD, mm)	16.16 ± 1.50	14.79 ± 2.02	.175
8 months (mean ± SD, mm)	16.02 ± 1.05	14.23 ± 2.12	.069
Pre-augmentation/immediate (P [†] , mm)	.001**	.001**	
Pre-augmentation/8 months (P [†] , mm)	.001**	.001**	
Immediate/8 months (P [†] , mm)	.708	.058	

*Student t test.
[†]Paired sample t test.
 **P < .01.
 P > .05, not significant.

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

	DBB-1 + CM, mean ± SD (median)	DBB-2 + CM, mean ± SD (median)	P*
Pre-augmentation/immediate*	11.84 ± 1.56	10.77 ± 2.06	.296
Pre-augmentation/8 months*	11.70 ± 1.52	10.22 ± 2.46	.201
Immediate/8 months [†]	0.14 ± 0.97 (0.3)	0.56 ± 0.59 (0.7)	.482

*Student t test; [†]Mann Whitney U test; P > .05 (not significant).

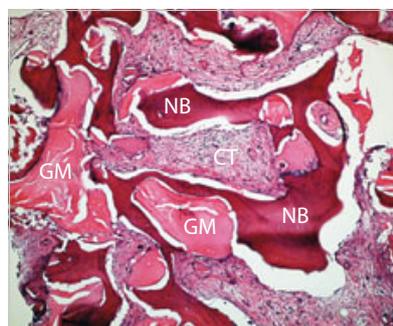
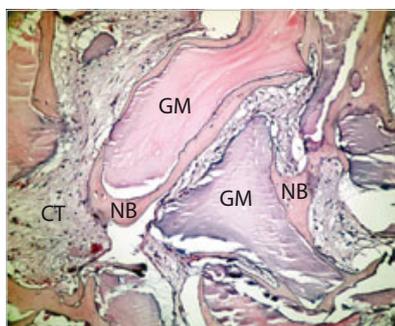


Fig 2 Histologic section from a DBB-1 + CM group. New bone formation (NB) is seen connecting with the graft materials (GM), separated by a resorption-apposition line, in the fibrous connective tissue (CT) (h&e, 200× magnification).

Fig 3 Histologic section of DBB-2 + CM group. NB formation is seen connecting with the graft materials. There is also a resorption-apposition line between the bone and graft material in the fibrous connective tissue (CT) (h&e, 200× magnification).

ples. In all specimens, newly formed trabecular bone and residual DBB particles have different staining properties that ascribe the two configurations. Remaining DBB particles were different in shape (Fig 2). In DBB-2 + CM group, remaining particles had a more rough appearance than in DBB-1 + CM group (Fig 3). Regarding the histomorphometric evaluation, new bone formation and residual graft materials were 29.13% and 24.63%, and 13.01% and 14.77%, for DBB-2 + CM and DBB-1 + CM groups, respectively (Tables 3 and 4).

DISCUSSION

This study demonstrated that sinus augmentation with both DBB-1 and DBB-2 produce an increase in the vertical bone dimension compared to baseline values, which accommodates dental implant placement. No statistically significant differences in radiographic and histomorphometric parameters were found between the graft materials, supporting that both materials can be successfully used in MSFA procedures.



Table 3 Minimum, maximum, and mean ± standard deviation (SD) 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)	0.00–0.24	0.05 ± 0.06
New bone (%)	2.63–68.42	26.88 ± 16.63
Residual graft particles (%)	0.00–63.16	13.89 ± 14.86

Table 4 Intra-group comparison of histomorphometric parameters (in each group, n = 8)

	DBB-1 + CM, mean ± SD (median)	DBB-2 + CM, mean ± SD (median)	P*
Total area (mm ²)	0.34 ± 0.10 (0.38)	0.31 ± 0.13 (0.38)	.535
New bone (mm ²)	0.09 ± 0.08 (0.07)	0.09 ± 0.06 (0.07)	.832
Residual graft particles (mm ²)	0.05 ± 0.08 (0.02)	0.04 ± 0.02 (0.04)	.526
New bone (%)	24.63 ± 19.76 (18.42)	29.13 ± 13.81 (24.73)	.289
Residual graft particles (%)	14.77 ± 21.01 (9.1)	13.01 ± 5.49 (12.76)	.316

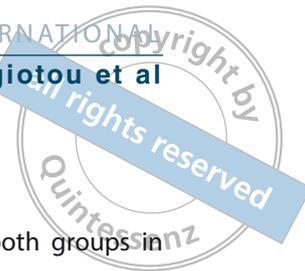
*Mann Whitney U test; P > .05 (not significant).

The most rigorously evaluated graft in the literature is xenograft. Among them, DBB-1, has been demonstrated to be a biologically inert osteoconductive material for sinus augmentation procedures.^{15,16,20,36-38} Application of this material in MSFA was reported to have equal or better results that was achieved with autogenous graft.³⁹⁻⁴¹ The aforementioned properties of the graft material lead the researchers to choose DBB-1 as the gold standard of the xenografts. On the other hand, DBB-2 is a new alternative from the same origin that warrants further investigation. Therefore, this randomized, controlled clinical study aimed to compare the percentage of new bone formation of DBB-1 and DBB-2 in bilateral sinus augmentation as an informative and practical contribution to clinicians.

DBB-2 is a newly introduced graft material and contains high-temperature sintered bovine bone minerals (> 1,200°C) with a mean pore diameter of 800 µm and a range of 100 to 1,500 µm.²⁷ The manufacturing process, based on high-temperature heating, removes all organic components and proteins, and eliminates potential immunologic reactions. Animal studies

reported new bone formation at the sides of bone defects.^{25,42,43} Only one study exists in the literature evaluating its biodegradation rate in sinus augmentation procedure.³³ This study evaluated the resorption rate of the two DBB materials at 8 months, 1 year, and 4 years after implant placement. DBB-1 demonstrated the greatest amount of vertical loss of graft material volume after 1 year of sinus surgery (55% to 65% of total bone loss). In addition, after 4 years, radiographic analysis revealed that DBB-1 still demonstrated significantly higher volumetric loss (33.4 ± 3.1%) compared to DBB-2 (23.4 ± 3.6%). In the present study, CBCT analysis at 8 months revealed a bone height increase of 10.22 ± 2.46 mm for DBB-2 and 11.70 ± 1.52 mm for DBB-1 groups, respectively. Only a small amount of bone height loss (0.56 ± 0.59 mm and 0.14 ± 0.97 mm for DBB-2 and DBB-1 groups, respectively) was observed at 8 months and there was no difference between the groups (P > .05).

In histomorphometric analysis, new bone formation and residual graft materials were 29.13% and 24.63%, and 13.01% and 14.77%, in DBB-2 + CM and DBB-1 +



CM groups, respectively. In the literature, biopsies obtained after MSFA with DBB-1 revealed new bone formation of 25% after 3 to 5 months,⁴⁴ 35% after 6 to 8 months,⁴⁵ and 34% after 9 months.⁴⁶ On the other hand, the proportion of newly formed bone varied from 12% to 69% after 3 to 12 months of observation.^{37,45,47,48} The histomorphometric results of the study for DBB-1 are in accordance with the literature. There are no data regarding the histologic and histomorphometric analysis of DBB-2. The present 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 materials were still observed in the specimens, demonstrating the slow resorption rate of the materials. Although there is no statistically significant difference between the percentages of residual graft particles, DBB-1 has a lower percentage of residual graft particles than DBB-2. DBB-1 undergoes a low heat (300°C) chemical process that extracts the organic components, while DBB-2 deproteinization occurs at a very high temperature (1,200°C) that enhances material crystallinity.^{27,49} Because DBB-1 has a less crystalline structure compared to DBB-2 and might be more prone to degradation, residual DBB-1 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 a long-unanswered question whether particle size of the graft material may affect and accelerate the bone healing since inter-particle space seems to be an important determinant for osteoconduction.^{50,51} While some researchers advise to use 1:1 mixture of small (0.25 to 1 mm) and large (1 to 2 mm) particles which may result in optimal inter-particle spacing leading to vascular ingrowth and new bone formation,⁵² Chackartchi et al⁵³ 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 al⁵⁴ 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 litera-

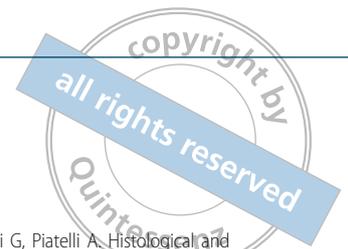
ture, large particle size was used in both groups in order to achieve best treatment results.

Although today MSFA is accepted as a predictable technique, each surgical step may give rise to complications. In the literature, the rate of sinus membrane perforation is in the range of 0% to 44%.^{41,55,56} Resorbable CM can be used to cover small- to medium-sized perforations in the sinus membrane.^{57,58} 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 the present 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.

This is the first study that has evaluated the effectiveness of DBB-2 for sinus augmentation. DBB-2 is exposed to deproteinization in higher temperatures compared to DBB-1. This increases the crystallinity of the material which results in long-term presence after sinus augmentation, which is a clinical advantage. Although DBB-1 is the gold standard, the high price of this material can be a disadvantage in a sinus augmentation procedure where excessive graft material will be used. DBB-2, with a similar clinical performance to DBB-1, can be considered as an alternative material with the aforementioned advantage.

CONCLUSION

This is the first study to compare the radiographic and histomorphometric findings of the two different DBB materials in MSFA. Within the limits of this study with a small sample size, both materials have similar radiographic and histomorphometric outcomes, which might encourage the use of the newly released material, DBB-2, as an alternative to DBB-1 in implant placement following MSFA.



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