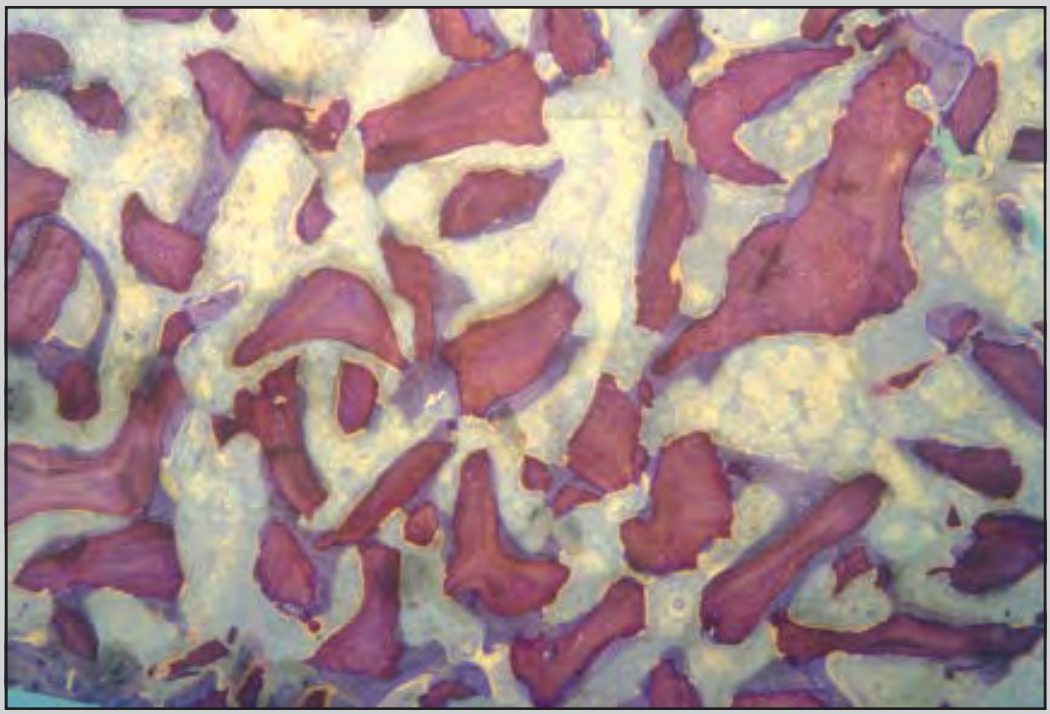
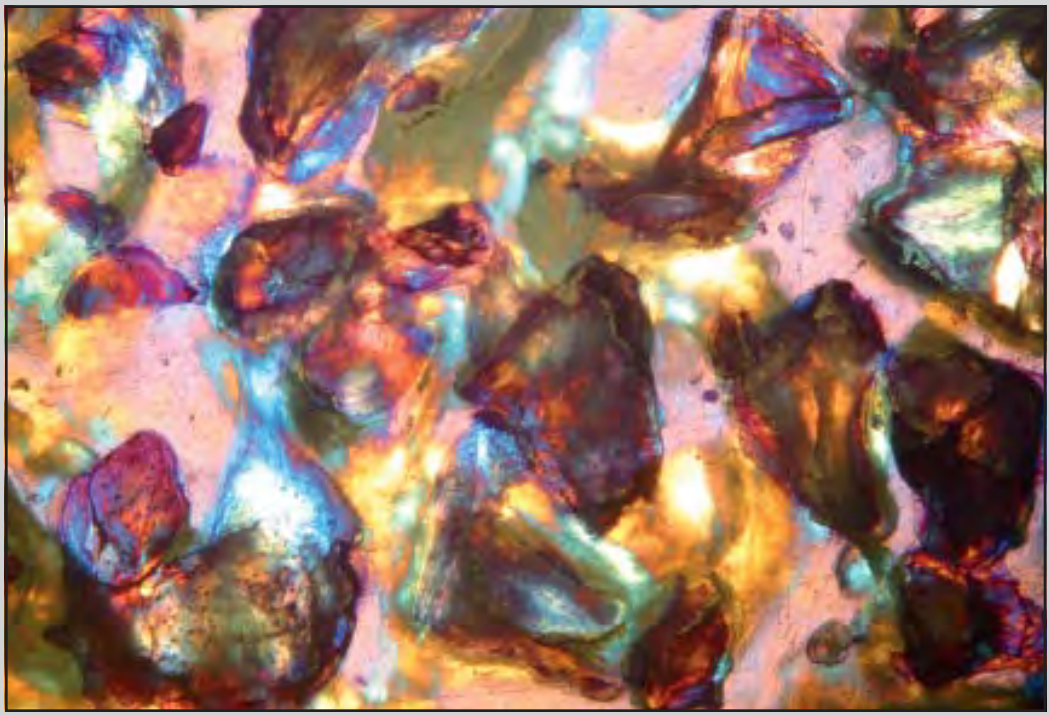
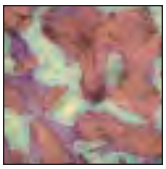




Effect of Xenograft (ABBM) Particle Size on Vital Bone Formation Following Maxillary Sinus Augmentation: A Multicenter, Randomized, Controlled, Clinical Histomorphometric Trial



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The purpose of this study was a histomorphometric comparison of vital bone formation following maxillary sinus augmentation with two different particle sizes of anorganic bovine bone matrix (ABBM). Bilateral sinus floor augmentations were performed in 13 patients. Trephine bone cores were taken from the lateral window areas of 11 patients 6 to 8 months after augmentation for histologic and histomorphometric analysis. Bone samples from both the large and small particle size groups showed evidence of vital bone formation similar to that seen in previous studies, confirming the osteoconductivity of ABBM. Significant bone bridging was seen creating new trabeculae composed of the newly formed bone and residual ABBM particles. Histologic evaluation revealed the newly formed bone to be mostly woven bone with some remodeling to lamellar bone. Osteocytes were seen within the newly formed bone as well as osteoblast seams with recently formed osteoid. Isolated osteoclasts were observed on the ABBM surfaces. Vital bone formation (primary outcome measure) was more extensive in the large particle grafts compared with the small particle grafts (26.77% ± 9.63% vs 18.77% ± 4.74%, respectively). The histologic results reaffirm the osteoconductive ability of ABBM when used as the sole grafting material in maxillary sinus augmentation. The histomorphometric results at 6 to 8 months revealed a statistically significant increase (P = .02) in vital bone formation when the larger particle size was used. Additional studies should be performed to confirm these results. (Int J Periodontics Restorative Dent 2013;33:467–475. doi: 10.11607/prd.1423)

Lack of sufficient residual alveolar bone height is a common deterrent to the placement of dental implants in the posterior maxilla. This can be a consequence of alveolar bone resorption following tooth loss, bone loss due to periodontal disease, pneumatization of the maxillary sinus, or a combination of the above etiologies. Maxillary sinus augmentation surgery has proven to be a predictable way to correct this deficiency and allow for implant placement with high predictability.[1–10]

Autogenous bone has long been considered the gold standard augmentation material for maxillary sinus grafting. There are, however, numerous negative factors to consider when using an autogenous bone graft. These include the possibility of hospitalization for donor harvest, the need for a second

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surgical site, increased morbidity, an increased complication rate, and the propensity of wholly autogenous grafts to shrink during graft maturation.[11]

Numerous bone replacement grafts have been used over the past 20 years to overcome the shortcomings of the use of autogenous bone, such as the need for a secondary bone harvest and the potential for resorption and loss of volume. Of all the major bone replacement grafts used today (allografts, xenografts, alloplasts), the group with the most clinical research to date are the xenografts.

All of the aforementioned evidence-based reviews that have evaluated graft material options for maxillary sinus augmentation have come to the conclusion that, when using the outcome measure of implant survival, the results using xenografts are equal to or superior to those achieved with autogenous bone.[1–10]

Xenografts (anorganic bovine bone matrix [ABBM]) have been used alone or as a composite with autogenous bone[12,13] or other bone replacement grafts, such as allografts,[14] for over 20 years with superior clinical, histologic, and histomorphometric results. Testing procedures guarantee product safety, and clinical practice has attested to this claim with no evidence of disease transmission.[15,16]

Clinicians have available two particle sizes when using the majority of xenografts: a large particle size of 1.0 to 2.0 mm and a small particle size of 0.25 to 1.0 mm. The material can be either cortical or cancellous bovine bone. While both particle sizes have been used with histologic and clinical success, there has been only one study to date that directly compares these two particle sizes in the human sinus model.[35]

Bio-Oss (Geistlich Pharmaceutics) is one such ABBM. It is a bone substitute manufactured from bovine bone mineral obtained from extremity bones of New Zealand-sourced cattle that have been processed and sterilized by heat and strong alkaline solutions. Each batch is tested for protein residues and satisfies safety requirements in Europe as well as those of the United States Food and Drug Administration.

The present prospective, randomized, controlled clinical trial directly compares histologic and histomorphometric vital bone formation and residual graft volume in 11 human bilateral sinus augmentations performed with either large or small particle size Bio-Oss cancellous ABBM.

Method and materials

Patient selection

This study was approved by the Research Board of the University of Milan. The surgeries were performed by three experienced surgeons at three centers (University of Milan and two private offices) that provided four, five, and four bilateral cases, respectively. Thirteen subjects (five men, eight women) who were candidates for bilateral maxillary sinus augmentation and chose this treatment option were selected from the private practices of clinicians participating in this study. There were no limitations to enrollment due to sex, race, or ethnicity. Inclusion criteria required that less than 5 mm of residual crestal bone be present, as determined by a computed tomographic scan, and that each patient required bilateral maxillary sinus elevation for the placement of dental implants. Exclusion criteria included the inability to undergo standard oral surgical procedures for any reason, patients who smoked more than 10 cigarettes a day, and women who were pregnant, considering pregnancy during the duration of the study, or were currently nursing. Each patient was informed of the requirements for the study and signed an appropriate consent form.

Surgical procedures

Subjects were premedicated with amoxicillin (875 mg) and clavulanic acid (125 mg) twice daily (Augmentin, Roche) beginning the night before surgery and continuing for 10 days. If the patient was allergic to penicillin, azithromycin (500 mg, Zitromax, Pfizer Italia) was substituted. Local anesthesia was administered with 4% articaine chlorhydrate and adrenaline (1:100,000, Alfacaina N, Weimer Pharma). A full-thickness flap was reflected exposing the lateral wall, and a complete osteotomy was performed using Piezosurgery (Mectron, Carasco). If the window was removed, it was not added

to the graft material. The sinus membrane was elevated using a combination of Piezosurgery and hand elevators. Any perforations were covered with bioabsorbable collagen barrier membranes (Bio-Gide, Geistlich Pharmaceuticals). Randomly, one subantral compartment was grafted with 100% large particle Bio-Oss (1.0 to 2.0 mm) and the contralateral subantral compartment was grafted with small particle Bio-Oss (0.25 to 1 mm). A bioabsorbable collagen barrier membrane (Bio-Gide) was placed over the window and 3 mm of surrounding bone. Primary closure was achieved with a combination of Gore-Tex suture (WL Gore and Associates) and chromic gut (Covidien) sutures. There were no simultaneous ridge augmentation procedures performed in any patient. Provisional fixed or removable appliances were relieved over the surgical sites prior to insertion. Subjects continued the antibiotic protocol for 10 days, were prescribed appropriate pain medications (nimesulide, Aulin, Roche), and placed on 0.12% chlorhexidine digluconate rinses (Curasept, Curaden Healthcare, Saronno) for 2 weeks.

At stage-one implant placement surgery (24 to 32 weeks), a trephine core sample was taken (10 × 3 mm) from the superior-distal area of the former lateral window site as identified by measurements taken at the time of sinus elevation. The 10-mm-long core extends to the middle of the sinus representing the least mature part of the graft. If the grafts were not performed simultaneously, core harvests were timed to equalize the maturation times. Appropriate antibiotics and analgesics were prescribed. Suture removal was performed after 7 to 10 days.

Blinded histomorphometric analysis was subsequently performed by a single experienced examiner (PT) to determine the percent of the various tissues in the biopsied samples.

Histology and histomorphometry

The evaluated specimens were infiltrated with Remacryl resin from a starting solution of 50% ethanol and resin and subsequently 100% resin with each step lasting 24 hours. Photopolymerization was obtained using a 48-hour exposure to blue light. After polymerization, the blocks were ground to remove the excess of resin and were then glued on plastic slides using a methacrylate-based glue.

A Micromet high-speed rotating blade microtome (Remet) was used to obtain 250-μm sections. The sections were then ground to 40 μm using an LS-2 grinding machine (Remet) equipped with water-proof lining paper. Each section was then polished with polishing paper and a 3-μm grinding cream.

Toluidine-blue staining was used for histologic evaluation. Histomorphometric analysis was performed by digitizing the microscopic images via a JVC TK-C1380 color video camera (JVC) and a frame grabber. The digital images were analyzed using IAS 2000 (Delta Sistemi) image analysis software. The parameters calculated were percent total bone (TB), percent residual xenograft material (XG), and percent vital bone (VB). The percent of connective tissue/bone marrow (CT/BM) was calculated by subtraction (100 – TB%).

Statistical analysis

The results of the histomorphometric evaluation were calculated as the mean ± standard deviation (SD) and ranges (95% confidence intervals [CIs]) for each variable. The Student paired *t* test was used to assess the statistical significance of the difference between data from the small and large particle groups. A *P* value of .05 was considered as the significance threshold.

Results

Of the 26 biopsies performed, two specimens (from different patients) had to be discarded due to problems in sample processing, and 24 samples were available for histologic/histomorphometric evaluation. The paired analysis, however, could only be performed on 11 bilateral cases. Three membrane perforations occurred in the 26 sinus surgeries performed.

Histomorphometric analysis

Tables 1 and 2 report the results of the histomorphometric evaluation.

Table 1 Histomorphometric analysis of large particle grafts

Patient	XG (%)	VB (%)	CT/BM (%)
1	1.7	23.6	74.7
2	10.6	38.6	50.8
3	20.2	11.5	68.3
4	15.6	40.9	43.5
5	35.4	28.0	36.6
6	25.5	24.2	50.3
7	22.9	34.4	42.7
8	15.4	34.9	49.6
9	23.3	14.5	62.1
10	26.6	24.6	48.8
11	22.9	19.1	57.9
Mean ± SD	20.0 ± 9.0	26.8 ± 9.6	53.2 ± 11.5
95% CI	14.7–25.3	21.1–32.5	46.4–60.0

XG = residual xenograft; VB = vital bone; CT/BM = connective tissue/bone marrow; SD = standard deviation; CI = confidence interval.

Table 2 Histomorphometric analysis of small particle grafts

Patient	XG (%)	VB (%)	CT/BM (%)
1	19.6	16.4	64.0
2	12.1	16.2	71.7
3	37.8	15.2	47.0
4	9.9	19.7	70.4
5	6.9	18.5	74. 7
6	16.0	29.4	54.6
7	33.8	21.7	44.5
8	17.0	22.4	60.6
9	23.2	20.5	56.4
10	32.5	13.6	53. 9
11	29.6	13.0	57.4
Mean ± SD	21.7 ± 10.5	18.8 ± 4.7	59.6 ± 9.9
95% CI	15.5–27.8	16.0–21.6	53.8–65.4

XG = residual xenograft; VB = vital bone; CT/BM = connective tissue/bone marrow; SD = standard deviation; CI = confidence interval.

Vital bone formation (primary outcome measure) was 26.77% ± 9.63% vs 18.77% ± 4.74% for the large particle and small particle grafts, respectively. Residual xenograft was 20.01% ± 8.97% vs 21.66% ± 10.47% for the large and small particle grafts, respectively. The statistical analysis revealed that only the percent VB was significantly different between the groups (P = .02), while no significant difference was found for CT/BM percent (P = .25) and XG percent (P = . 69). The Shapiro-Wilk test was performed for assessing normality of distribution for vital bone (P = .82), xenografts (P = .64), and bone marrow (P = .64).

Histologic analysis

Histologic analysis of the regenerated tissues showed the presence of nonresorbed graft particles (Fig 1) in both the newly formed bone tissue and the newly formed connective tissue. At the 24- to 32-week time interval, the new bone appeared as woven bone with several large rounded osteocyte lacunae (Fig 2). Polarized light microscope analysis showed the presence of a woven bone structure with several marrow-vascular spaces. In some areas, bone trabeculae had a more mature aspect with primary parallel-fibered bone filling the vascular spaces on the bulk of immature woven bone. In the most central areas of these trabeculae, the woven bone core could still be observed. The direct connection between the newly formed bone and the residual graft particles form "bridges" of trabecular bone. These bridges tend to create, with the included particles, an irregular network of new trabeculae, different from the trabecular structure of the native bone since their direction and interconnection is influenced by the arrangement of the granules that determined its formation. Bone remodeling is evidenced by the presence of

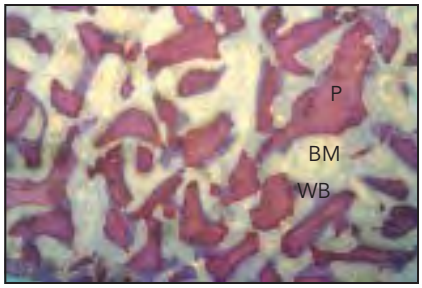

Fig 1 *Histologic analysis of regenerated tissues (WB = woven bone, BM = bone marrow) shows the presence of several nonresorbed small graft particles* (P) *(toluidine blue staining; original magnification ×25).*

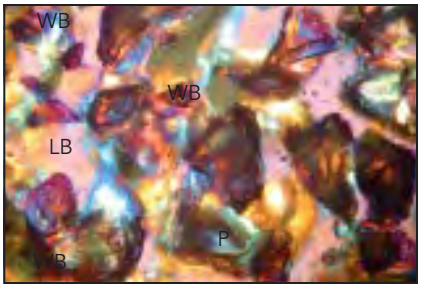

Fig 2 *New bone appears as woven bone* (WB) *and lamellar bone* (LB) *with small graft particles* (P) *(toluidine blue staining, polarized light; original magnification ×50).*

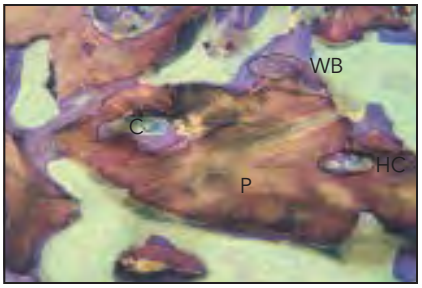

Fig 3 *Bone penetrates into large graft particle* (P) *pores in which capillaries* (C), *Haversian canals* (HC), *and woven bone* (WB) *with large rounded osteocytes can be observed (toluidine blue staining; original magnification ×100).*

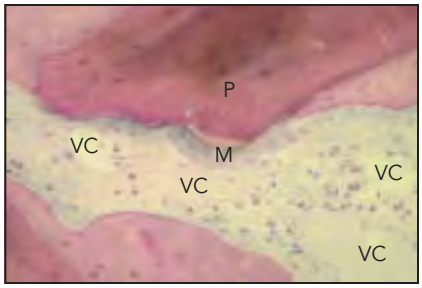

Fig 4 *Histologic analysis of large graft particle* (P). *Vascular canals* (VC) *and multinucleated macrophages* (M) *are observed in the marrow spaces of the newly formed bone (toluidine blue staining; original magnification ×200).*

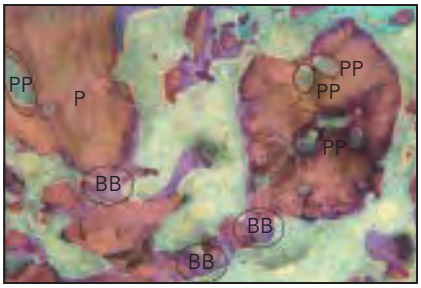

Fig 5 *View of large graft particles* (P) *shows particle pores* (PP) *colonized by marrow cells. Bone bridging* (BB) *between the particles can be observed (toluidine blue staining; original magnification ×50).*

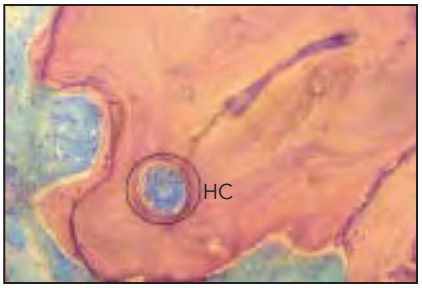

Fig 6 *View of a large graft particle. Pores exhibit the Haversian canal* (HC) *structure of bovine bone (toluidine blue staining; original magnification ×200).*

resorption lacunae and areas of new bone deposition. Thanks to the different chromatic affinity between grafted material and vital bone, it is possible to differentiate Bio-Oss from new vital bone. Close contact between graft granules embedded in the mineralized bone and bone matrix is observed. The interface between particles and bone shows irregular borders that may be due to an initial resorption process starting before bone integration.

Bone penetrates into the particle pores, in which capillaries can also be observed (Fig 3). It can be assumed that the initial healing process is mediated by a vascular invasion with subsequent bone deposition on the ceramic walls that leads to the subsequent pore obliteration. Vascular canals can be observed in the marrow spaces of the newly formed bone, and multinucleated macrophages can be seen on the graft surface (Fig 4).

Osteocytes in the newly formed bone, closely adhering to the granules surfaces, can be observed in the bonding areas between newly formed bone and the residual graft particles. The surface shows the typical cracks, presumably caused by histologic preparation.

1- to 2-mm particles

Biopsy specimens from large particle grafts show the porous structure of the grafted particles (Fig 5). Particle pores have the typical structure of the Haversian canals of the bovine bone from which the graft material is derived (Fig 6). Marrow cells and newly formed bone can be observed within these porosities. The surfaces of the graft particles are almost totally covered by newly formed bone. Bone density is considerably higher than that of the residual basal bone. From a structural point of view, the residual particles, which are completely included in newly

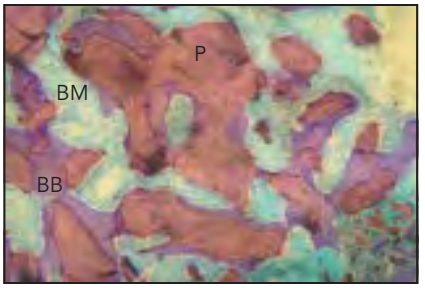

Fig 7 *Residual small graft particles are evenly dispersed and randomly interconnected by newly formed bone bridges* (BB), *creating an irregular network of new trabeculae between bone marrow* (BM) *(toluidine blue staining; original magnification ×50).*

formed bone, become part of large bone trabeculae. A rather thick cortical bone layer often tends to surround the grafted granule while bone trabeculae develop.

0.25- to 1-mm particles

Biopsy specimens retrieved from this group show the presence of small, variably shaped particles (Fig 7). The pores that are typically observed in larger particles cannot be observed in this case. Particles are evenly scattered within the biopsy sample volume and are randomly interconnected by newly formed bone bridges. These bridges tend to create, with the included particles, an irregular network of new trabeculae, different from the trabecular structure of the native bone since their direction and interconnection is influenced by the arrangement of the ABBM granules that determine its formation. Newly formed bone can be observed from the coronal to the apical portion of the specimens, showing the excellent osteoconductivity of this ABBM.

Wide marrow spaces can be seen throughout the specimen. These marrow areas contain adipose cells, vascular canals of different dimensions, capillaries, mesenchymal cells, and a few inflammatory cells. As with the large particle graft, bone density is higher than that of the residual native bone.

Discussion

Autogenous bone has long been considered the gold standard of grafting materials because of its ability to form bone though the three processes of osteogenesis, osteoinduction, and osteoconduction. While the value of autogenous bone in large out-of-the-envelope regenerative procedures has not been questioned, its use in maxillary sinus augmentation has. In fact, all evidence-based reviews that evaluate a variety of grafting material have shown that the use of osteoconductive xenografts (ABBM) results in equal or better implant survival outcomes than does the use of autogenous bone.[1–10] With this in mind, it was the purpose of this study to evaluate the possibility that ABBM particle size may have an effect on vital bone formation and ultimately a possible effect on implant survival.

A search of the literature yielded 19 articles published from 1998 to 2011[17–35] that used 100% Bio-Oss as the grafting material and reported histomorphometric data (Osteograf/N, PepGen P-15, Nu-Oss, and Endobon were excluded as the present study used Bio-Oss). The main characteristics and histomorphometric findings of these studies are summarized in Table 3. Of these studies, 14 used 100% small particles, 4 used large particles, and 2 used a 50:50 mix of large and small particles. This results in a sample size of 266 small-particle and 30 large-particle histologic samples plus 24 50:50 histologic samples. The combined data indicate a range of vital bone formation from 12.1% to 50% for small particle and 22.9% to 53% for large particle grafts. It would appear to be of little value to combine these data as the number of confounding variables (surgical protocol, time of sampling, site of core harvest, histomorphometric methodology, statistical analytic methodology) would negate any significance that could be accorded.

There has been only one study that has directly compared the two particle sizes in a bilateral sinus model.[35] In this randomized controlled clinical trial of 10 bilateral cases, core samples taken from implant site preparations were evaluated at 6 to 9 months by both microcomputed tomography (CT) and histomorphometric analysis. In this study, the histomorphometric analysis was deemed the more accurate of the two as the micro-CT analysis tended to underestimate the new bone formation. The histomorphometric analysis showed no statistical difference in new bone formation, with 27.14% ± 3.89% vs 28.6% ± 6.0% for the large and small particle grafts, respectively. Similarly, there were no differences in the residual graft or connective

Table 3 **Characteristics of studies providing histomorphometric data on Bio-Oss used for maxillary sinus augmentation**

Author	Year	Healing time (mo)	No. of samples	Granule size (mm)	Cover membrane type	VB (%)	XG (%)	CT/BM (%)
Valentini et al[18]	1998	12	1	0.25–1	None	28	28	44
Valentini et al[17]	2000	6 12	3 3	0.25–1	None	21.08 27.55	39.17 27.01	39.76 45.44
Yildirim et al[19]	2000	6, 8	22	0.25–1	Collagen	14.7	29.7	55.6
Artzi et al[20]	2001	12	10	0.25–1	Collagen	42.1	24.7	33.3
Karabuda et al[21]	2001	6	3	0.25–1	None	50	20	30
Froum et al[22]	2002	7.25 11	2 1	0.25–1	Collagen e-PTFE	16 32	NR NR	NR NR
Hallman et al[23]	2002	14.75	10	0.25–1	Collagen	41.7	11.8	46.5
Tadjoedin et al[24]	2003	8	1	1–2	None	22.9	36.3	40.8
Wallace et al[25]	2005	6 to 10	46 83 6	0.25–1	e-PTFE Collagen None	16.9 17.6 12.1	51.2 56 63.6	31.9 26.4 24.3
Froum et al[26]	2006	6.6	13	50:50*	Collagen	12.44	33	54.56
Lee et al[27]	2006	6 12	14 14	0.25–1	Collagen	18.3 26.6	29.8 28.7	52 44.7
Cordaro et al[28]	2008	6.7	23	0.25–1	Collagen	19.8	37.7	40.4
Froum et al[29]	2008	7.17	11	50:50*	Collagen	22.27	26	51.73
Iezzi et al[30]	2008	60	1	0.25–1	Collagen	40	12	50
Simunek et al[31]	2008	9	10	1–2	None	34.2	30.8	35
Traini et al[32]	2008	20	10	0.25–1	None	38	29	36
Torres et al[33]	2009	6	5	0.25–1	None	21	50	29
Kim et al[34]	2009	4 6	5 4	1–2	Collagen	35.6 53	45.64 22.27	18.76 24.73
Chackartchi et al[35]	2011	6 to 9	10 10	0.25–1 1–2	Collagen	28 27.14	34.57 33.71	37.42 39.14

VB = vital bone; XG = residual xenograft; CT/BM = connective tissue/bone marrow; e-PTFE = expanded polytetrafluoroethylene; NR = not recorded.
*not included in statistical analysis.

tissue components between the two groups.

The present study showed similar results to the Chackartchi et al[35] study for the large particle graft (26.77% ± 9.63%) but had less favorable results for the small particle graft (18.77% ± 4.74%). This difference in results for only the small particle graft cannot be explained by any of the differences in study designs (6- to 8-month vs

6- to 9-month sampling time, crestal vs lateral window sample sites, differences in histologic staining and technique, or differences in statistical method) as any differences should have affected both large and small particles alike. It would seem that the likely explanation is that the difference is the result of the small sample size in each study.

The low perforation rate in this study, 3/26 or 11.5%, is slightly higher than that reported in the literature for piezoelectric sinus elevation.[37]

It is of interest to note that there is no known relationship between the percentage of new vital bone and the implant survival rate with the use of ABBM in maxillary sinus grafting. A study by Proussaefs et al[36] showed vital bone formation in bilateral sinus grafts with one side having a membrane perforation to be 33.58% on the nonperforated side and 14.17% on the perforated side. The resulting implant survival rates were 100% and 69.6%, respectively. This is likely due to other effects from the perforation than just poor bone quality. An earlier study by the present authors reported excellent bone formation following properly performed collagen barrier membrane repairs.[38] This conclusion is further evidenced by the very high implant survival rates in all the ABBM studies, regardless of the percentage of vital bone present.[12]

Further, one might look at early high failure rates of Branemark implants in poor quality bone[39] and reach a similar conclusion. This would be incorrect as the confounding variables of implant surface technology and implant macrogeometry may override poor bone quality by providing more favorable primary stability and greater implant-bone contact.[40]

There is a practical benefit to the fact that vital bone production is the same with both large and small particle ABBM grafts[35] or higher with large particle grafts as in the present study. The volume of graft material in a 2-g bottle of Bio-Oss small particle is 4.2 mL. The volume of 2 g of large particle Bio-Oss is 7.2 mL. It is therefore obvious that fewer grams of graft material will be required, and a lower cost realized, to complete a sinus augmentation surgery if large particle graft material is used.

Conclusions

The histologic results of this study reaffirm the osteoconductive ability of the ABBM (Bio-Oss) when used as the sole grafting material in maxillary sinus augmentation. The histomorphometric results indicate a statistically significant increase in vital bone formation when the larger particle size is used. Further studies with a larger sample size should be performed to validate these results.

Acknowledgment

The authors reported no conflicts of interest related to this study.

References

1. Wallace SS, Froum SJ. Effect of maxillary sinus augmentation on the survival of endosseous dental implants. A systematic review. Ann Periodontol 2003;8:328–343.
2. Del Fabbro M, Testori T, Francetti L, Weinstein R. Systematic review of survival rates for implants placed in grafted maxillary sinus. Int J Periodontics Restorative Dent 2004;24:565–577.
3. Aghaloo T, Moy PK. Which hard tissue augmentation techniques are the most successful in furnishing bony support for implant placement? Int J Oral Maxillofac Implants 2007;22(suppl):49–70.
4. Pjetursson BE, Tan WC, Zwahlen M, Lang NP. A systematic review of the success of sinus floor elevation and survival of implants inserted in combination with sinus floor elevation. Part I: Lateral approach. J Clin Periodontol 2008;35 (suppl 8):216–224.
5. Del Fabbro M, Rosano G, Taschieri S. Implant survival rates after maxillary sinus augmentation. Eur J Oral Sci 2008; 116:497–506.
6. Nkenke E, Stelzle F. Clinical outcomes of sinus floor augmentation for implant placement using autogenous bone or bone substitutes: A systematic review. Clin Oral Implants Res 2009;20(suppl 4): 124–133.
7. Jensen SS, Terheyden H. Bone augmentation procedures in localized defects in the alveolar ridge: Clinical results with different bone grafts and bone-substitute materials. Int J Oral Maxillofac Implants 2009;24(suppl):218–238.
8. Esposito M, Grusovin MG, Rees J, et al. Interventions for replacing missing teeth: Augmentation procedures of the maxillary sinus. Cochrane Database Syst Rev 2010;(3):CD008397.
9. Del Fabbro M, Bortolin M, Taschieri S, Rosano G, Testori T. Implant survival in maxillary sinus augmentation. An updated systematic review. J Osteol Biomater 2010;1:69–79.
10. Del Fabbro M, Wallace SS, Trisi P, Capelli M, Zuffetti F, Testori T. Long-term implant survival in the grafted maxillary sinus: A systematic review. Int J Periodontics Restorative Dent (in press).
11. Mardinger O, Chaushu G, Sigalov S, Herzberg R, Shlomi B, Schwartz-Arad D. Factors affecting changes in sinus graft height between and above the placed implants. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:6–11.

12. Froum SJ, Tarnow DP, Wallace SS, Rohrer MD, Cho SC. Sinus floor elevation using anorganic bovine bone matrix (OsteoGraf/N) with and without autogenous bone: A clinical, histologic, radiographic, and histomorphometric analysis—Part 2 of an ongoing prospective study. Int J Periodontics Restorative Dent 1998;18:528–543.
13. Hallman M, Sennerby L, Lundgren S. A clinical and histologic evaluation of implant integration in the posterior maxilla after sinus floor augmentation with autogenous bone, bovine hydroxyapatite, or a 20:80 mixture. Int J Oral Maxillofac Implants 2002;17:635–643.
14. Valentini P, Abensur DJ. Maxillary sinus grafting with anorganic bovine bone: A clinical report of long-term results. Int J Oral Maxillofac Implants 2003;18:556–560.
15. Sogal A, Tofe AJ. Risk assessment of bovine spongiform encephalopathy through bone graft material derived from bovine bone used for dental applications. J Periodontol 1999;70:1053–1063.
16. Benke D, Olah A, Möhler H. Protein-chemical analysis of bovine bone substitute and evidence on its carbonate content. Biomaterials 2001;22:1001–1112.
17. Valentini P, Abensur D, Wenz B, Peetz M, Schenk R. Sinus grafting with porous bone mineral (Bio-Oss) for implant placement: A study on 15 patients. Int J Periodontics Restorative Dent 2000;20: 245–253.
18. Valentini P, Abensur D, Densari D, Graziani JN, Hammerle CHF. Histological evaluation of Bio-Oss in a 2-stage sinus floor elevation and implantation procedure. A human case report. Clin Oral Implants Res 1998;9:59–64.
19. Yildirim M, Spiekermann H, Biesterfeld S, Edelhoff D. Maxillary sinus augmentation using xenogenic bone substitute material Bio-Oss in combination with venous blood. A histologic and histomorphometric study in humans. Clin Oral Implants Res 2000;11:217–229.
20. Artzi Z, Nemcovsky CE, Tal H, Dayan D. Histopathological morphometric evaluation of 2 different hydroxyapatite-bone derivatives in sinus augmentation procedures: A comparative study in humans. J Periodontol 2001;72:911–920.
21. Karabuda C, Ozdemir O, Tosun T, Anil A, Olgaç V. Histological and clinical evaluation of 3 different grafting materials for sinus lifting procedure based on 8 cases. J Periodontol 2001;72:1436–1442.
22. Froum SJ, Wallace SS, Tarnow DP, Cho SC. Effect of platelet-rich plasma on bone growth and osseointegration in human maxillary sinus grafts: Three bilateral case reports. Int J Periodontics Restorative Dent 2002;22:45–53.
23. Hallman M, Sennerby L, Lundgren S. A clinical and histologic evaluation of implant integration in the posterior maxilla after sinus floor augmentation with autogenous bone, bovine hydroxyapatite, or a 20:80 mixture. Int J Oral Maxillofac Implants 2002;17:635–643.
24. Tadjoedin ES, de Lange GL, Bronckers AL, Lyaruu DM, Burger EH. Deproteinized cancellous bovine bone (Bio-Oss) as bone substitute for sinus floor elevation. J Clin Periodontol 2003;30:261–270.
25. Wallace SS, Froum SJ, Cho SC, et al. Sinus augmentation utilizing anorganic bovine bone (Bio-Oss) with absorbable and nonabsorbable membranes placed over the lateral window: Histomorphometric and clinical analyses. Int J Periodontics Restorative Dent 2005;25:551–559.
26. Froum SJ, Wallace SS, Elian N, Cho SC, Tarnow DP. Comparison of mineralized cancellous bone allograft (Puros) and anorganic bovine bone matrix (Bio-Oss) for sinus augmentation: Histomorphometry at 26 to 32 weeks after grafting. Int J Periodontics Restorative Dent 2006; 26:543–551.
27. Lee YM, Shin SY, Kim JY, Kye SB, Ku Y, Rhyu IC. Bone reaction to bovine hydroxyapatite for maxillary sinus floor augmentation: Histologic results in humans. Int J Periodontics Restorative Dent 2006;26:471–481.
28. Cordaro L, Bosshardt DD, Palattella P, Rao W, Serino G, Chiapasco M. Maxillary sinus grafting with Bio-Oss or Straumann bone ceramic: Histomorphometric results from a randomized controlled multicenter clinical trial. Clin Oral Implants Res 2008;19:796–803.
29. Froum SJ, Wallace SS, Cho SC, Elian N, Tarnow DP. Histomorphometric comparison of a biphasic bone ceramic to anorganic bovine bone for sinus augmentation: 6- to 8-month postsurgical assessment of vital bone formation. A pilot study. Int J Periodontics Restorative Dent 2008;28:273–281.
30. Iezzi G, Scarano A, Mangano C, Cirotti B, Piattelli A. Histologic results from a human implant retrieved due to fracture 5 years after insertion in a sinus augmented with anorganic bovine bone. J Periodontol 2008;79:192–198.
31. Simunek A, Kopecka D, Somanathan RV, Pilathadka S, Brazda T. Deproteinized bovine bone versus beta-tricalcium phosphate in sinus augmentation surgery: A comparative histologic and histomorphometric study. Int J Oral Maxillofac Implants 2008;23:935–942.
32. Traini T, Degidi M, Sammons R, Stanley P, Piattelli A. Histologic and elemental microanalytical study of anorganic bovine bone substitution following sinus floor augmentation in humans. J Periodontol 2008;79:1232–1240.
33. Torres J, Tamimi F, Martinez PP, et al. Effect of platelet-rich plasma on sinus lifting: A randomized-controlled clinical trial. J Clin Periodontol 2009;36:677–687.
34. Kim Y-K, Yun P-Y, Kim S-G, et al. Analysis of the healing process in sinus bone grafting using various grafting materials. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107:204–211.
35. Chackartchi T, Iezzi G, Goldstein M, et al. Sinus floor augmentation using large (1–2 mm) or small (0.25–1 mm) bovine bone mineral particles: A prospective, intra-individual controlled clinical, micro-computerized tomography and histomorphometric study. Clin Oral Implants Res 2011;22:473–480.
36. Proussaefs P, Lozada J, Kim J, Rohrer MD. Repair of the perforated sinus membrane with a resorbable collagen membrane: A human study. Int J Oral Maxillofac Implants 2004;19:413–420.
37. Wallace SS, Mazor Z, Froum SJ, Cho S-C, Tarnow DP. Schneiderian membrane perforation rate during sinus elevation using Piezosurgery: Clinical results of 100 consecutive cases. Int J Periodontics Restorative Dent 2007;27:413–420.
38. Testori T, Wallace SS, Del Fabbro M, et al. Repair of large sinus membrane perforations using stabilized collagen barrier membranes: Surgical techniques and histological and radiographic evidence of success. Int J Periodontics Restorative Dent 2008;28:9–17.
39. Jaffin R, Berman C. The excessive loss of Branemark fixtures in type IV bone: A 5-year analysis. J Periodontol 1991;62:2–4.
40. Trisi P, Lazzara R, Rebaudi A, Rao W, Testori T, Porter SS. Bone-implant contact on machined and dual acid-etched surfaces after 2 months of healing in the human maxilla. J Periodontol 2003;74:945–956.