Deproteinized Bovine Bone Versus β-Tricalcium Phosphate in Sinus Augmentation Surgery: A Comparative Histologic and Histomorphometric Study

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Purpose: *To compare the efficacy of 2 common materials in sinus augmentation surgery and to assess their contribution when enriched with autogenous bone.* ***Materials and Methods:*** *The prospective human study was performed in 48 sinus grafting operations using β-tricalcium phosphate or deproteinized bovine bone (pure or mixed with 10% to 20% autogenous bone) or autogenous bone. Biopsy specimens were taken after 9 months. Statistical evaluation was done with a 2-sample t test (P < .05).* ***Results:*** *When autogenous bone was used, 49.2% ± 3.1% of new bone was found, which is significantly higher than in all the other groups. A higher proportion (34.2% ± 13.1%) of the new vital bone was found in the deproteinized bovine bone group, in comparison with the β-tricalcium phosphate group (21.4% ± 8.1%) and the β-tricalcium phosphate composite graft group (24.0% ± 6.6%; P < .05). No significant differences between single-component grafts and corresponding composite grafts were established.* ***Conclusions:*** *Sinus augmentation with the aforementioned augmentation materials is a well-accepted procedure. However, autogenous bone alone was the best material. More new bone was found using deproteinized bovine bone than β-tricalcium phosphate. The addition of 10% to 20% autogenous bone to the bone substitute did not significantly influence the new bone formation.* Int J Oral Maxillofac Implants 2008;23:935–942

Key words: *autogenous bone graft, β-tricalcium phosphate, composite graft, deproteinized bovine bone, histomorphometry, sinus augmentation*

Reconstruction of the atrophic posterior maxilla using dental implants is often an onerous task due to anatomic limitations. The alveolar bone is largely cancellous, and its height is usually limited by the extended maxillary sinus. Compensation can be provided for the lack of supporting bone by a sinus augmentation procedure. The technique is based on elevation of the schneiderian membrane from the maxillary sinus floor and the introduction of a bone graft or a bone substitute into the created space.[1] If the residual bone height is adequate for attaining primary stability, the implant is inserted along with augmentation (1-step procedure). If the bone height is not adequate, the implantation is done after partial consolidation of the augmentation material (2-step procedure).[1]

The choice of augmentation material is a crucial factor in sinus augmentation surgery. Autogenous bone is considered the gold standard, as it maintains a high degree of biologic viability.[2–6] Other advantages of autogenous bone are that it is not immunogenic, it is both osteoinductive and osteoconductive, and it is a source of osteoprogenitor cells and growth factors.[7,8] Autogenous bone promotes angiogenic ingrowth from the surrounding host bone.[9] Autogenous bone chips revascularize in an average time of 3 to 4 months.[10] The disadvantage of autogenous

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bone is the need for a second surgical site with increased morbidity and surgical time.[8,11] In addition, a hospital stay may be required, which adds to the overall cost and inconvenience to the patient.[8] Furthermore, the volume of the area augmented by autogenous bone can be significantly decreased over time.[9] The relatively high morbidity associated with the sinus augmentation procedure could be reduced by replacement of the autogenous bone graft by bone substitute.

Currently, there is a growing trend of using alternative graft materials, such as alloplasts (hydroxyapatite, β-tricalcium phosphate, bioactive glass), xenografts (bovine or coralline hydroxyapatite), or allografts (freeze-dried demineralized bone).[12] These biomaterials are nonviable bone substitutes that act as a scaffold for further bone formation.[13] Appositional bone growth can be considered a host response.[13] However, the process of rebuilding of the bone is slower compared to autogenous bone grafts.[1]

Bone substitutes are occasionally mixed with autogenous bone; such grafts are called composite grafts.[14–20] It was anticipated that autogenous bone could add the osteogenic and osteoinductive components that are necessary to achieve complete bone formation.[21] In larger defects, bone substitute may benefit from mixture with autogenous bone to maintain the healing time within acceptable limits.[22] The optimal proportion of autogenous material required for this benefit is still in question. The portion of autogenous bone is usually 25% to 50% of the mixture.[1,23–26] The effect of adding a smaller share of autogenous material remains unexplored. Recently, the addition of autogenous bone in composite graft has been substituted by an admixture of platelet-rich plasma or growth factors. [1,27,28]

It would be desirable if biomaterials could provide stability until bone formation has been largely completed and thereafter become gradually replaced by vital bone during bone remodeling.[13] Finally, the bone substitute ought to be entirely resorbed.[29] Qualities of the single bone substitutes are documented in detail. It has not yet been determined which of these materials is the most appropriate.[30]

The objective of this human study was to judge the effectiveness of the bone substitutes compared to autogenous bone grafts in the sinus augmentation procedure. The goal was to compare the efficacy of 2 commonly used but fundamentally different materials in the sinus augmentation surgery, β-tricalcium phosphate and deproteinized bovine bone. Another goal of the study was to assess contribution of these materials when enriched with a small volume (10% to 20%) of autogenous bone taken from the same surgical wound from the maxillary tuberosity.

MATERIALS AND METHODS

Patient Selection

This prospective, cross-sectional, case control study was conducted with a population of 48 patients (26 men and 22 women; mean age, 52.4 years; range, 34 to 65 years) who had defects of dentition in the posterior maxilla. The main criteria for inclusion in the study group was a residual alveolar ridge height of < 3 mm and width of ≥ 5 mm. Following a detailed clinical, radiographic, and study cast analysis, the decision to rehabilitate the missing teeth with an implant-supported prosthesis was made. The surgical phase of rehabilitation of teeth was planned with sinus augmentation surgery followed by placement of dental implants. To avoid bias, patients with unsatisfactory oral hygiene, uncontrolled diabetes mellitus or other serious systemic diseases, osteoporosis, coagulopathy, acute maxillary sinusitis, and heavy smokers (> 15 cigarettes/d) were excluded from the study population. Other smokers were educated about the ill effects of smoking and were advised to refrain from smoking for 15 days prior to surgery and 6 weeks after surgery. The study protocols and surgical technique were explained to the patients, and written informed consents were collected before the onset of the study. The ethical review committee at Charles University, which works in accordance with Helsinki declaration, approved the present study design.

Surgical Procedure

A total of 48 two-step sinus grafting procedures using a window technique were performed from January 2003 to May 2005. An average of 3 cm^3 of augmentation material was used for individual surgical procedures. All the patients were subjected to prophylactic antibiotic coverage of a combination of amoxicillin and clavulanate (625 mg orally 3 times per day) starting 2 hours before the surgical procedure, which continued for 6 days postsurgically. The postoperative care consisted of 0.2% chlorhexidine oral rinsing twice daily for 12 days. An analgesic drug, 300 mg tiaprofen acid 3 times a day, was prescribed. The dental implants were inserted in stage 2 surgery after 9 months of postgraft healing. All the surgical procedures were performed at the University Hospital (Hradec Kralove, Czech Republic) under local anesthesia (4% articaine with epinephrine 1/100,000) in a sterile hospital setting.

The study population was divided into 5 groups according to the augmentation material used for sinus augmentation (ie, 4 experimental groups and 1 control group; Tables 1 and 2). The experimental groups consisted of 10 patients each, and the control group included 8 patients. For the 10 patients in

Table 1 Distribution of Study Population

Group	No. of patients	Graft
T	10	β-tricalcium phosphate
TB	10	β-tricalcium phosphate + 10% to 20% autogenous bone
D	10	Deproteinized bovine bone
DB	10	Deproteinized bovine bone + 10% to 20% autogenous bone
B	8	Autogenous bone

Table 2 Distribution of Age of Study Population

	Group				
Age group	T	TB	D	DB	B
34–44	2	2	3	2	2
45–54	4	5	3	4	4
55–65	4	3	4	4	2
Total	10	10	10	10	8

group T, β-tricalcium phosphate was used in the form of Cerasorb, sized 1,000 to 2,000 μm (Curasan, Kleinostheim, Germany). For the 10 patients in group TB, β-tricalcium phosphate mixed with the autogenous bone taken from the same surgical wound from the maxillary tuberosity was used. Autogenous bone was harvested using a bone forceps, and procured bone chips were particulated to the size of 1 to 2 mm and incorporated with β-tricalcium phosphate, which made up 80% to 90% of the mixture. In the next 10 patients in group D, only deproteinized bovine bone was used, Bio-Oss spongiosa type, with a particle size of 1 to 2 mm (Geistlich, Wolhusen, Switzerland). For the 10 patients in group DB, 10% to 20% of autogenous bone was added to the deproteinized bone substitute, as in group TB. During the surgical procedure, all the experimental combinations of graft materials were mixed with coagulable venous blood taken from the same patient before surgery for easier manipulation and placement of graft materials.[32,33] For the 8 patients in control group B, only autogenous bone was used for sinus augmentation. The autogenous bone graft was harvested from the chin under local anesthesia. The donor site was prepared after a 2-cm incision was made in the mucogingival junction in the anterior mandible. Three to 5 bone cores containing external compact and cancellous bone were harvested using a surgical trephine (inner diameter of 9 mm) under coolant. These bone cores were reduced to particles (size 1 to 2 mm) using a bone mill (R. Quétin, Leimen, Germany).

Harvesting of the Specimens

After the postgrafting healing stage of 9 months, a full-thickness flap was raised at the sites where the dental implants were to be placed. Instead of predrilling, vertical biopsy specimens were taken from the future implant bed using a trephine with an internal diameter of 2.0 or 3.4 mm under copious irrigation with cool saline. The size of the trephine was selected according to the diameter of the future implant (3.7 or 5.0 mm, Impladent Bio surface, Lasak, Prague, Czech Republic). The harvested vertical bone cores were about 10 to 15 mm in length. The bone bed for the implant was prepared using a final drill, the implants were inserted, and the mucoperiosteal flap was sutured in place (Vicryl 5-0, Johnson & Johnson, Somerville, NJ). Only a single vertical biopsy specimen per patient was harvested. In situations in which more than 1 implant was to be placed, the biopsy specimen was selected from the area of lowest height of the alveolar bone before surgery.

Histomorphometry and Histology

Harvested cylindrical specimens were fixed in Burkhardt's solution at room temperature for 20 hours and dehydrated through increasing concentrations of ethanol, with 12 hours for each step. The dehydrated specimens were embedded in methylmetacrylate (MMA, Merck, Germany) at 30°C for 90 minutes. Those parts of the specimen which originated from the residual alveolar ridge were excluded from the subsequent evaluation. Five cut sections of 4-μm thickness were sectioned from each specimen parallel to the long axis of the cylindrical core using a microtome (Jung, Heidelberg, Germany). Of these 5 sections, 3 sections were stained with Giemsa stain and used for histomorphometric evaluation. The remaining 2 sections were stained with Gömöri and Ladewig stains, respectively, to qualitatively evaluate the features of the bone tissue. Morphological examination of the specimen was primarily done to evaluate area values for bone and biomaterial. Further quantitative analysis of bone and bone substitute was histomorphometrically evaluated after digitalization of the light microscopic picture using LUCIA M software, version 3.0 (Laboratory Imaging, Prague, Czech Republic). The percentage of the different components of the harvested tissue (ie, hard bone tissue, residual bone substitute, and fibrovascular tissue) were calculated and recorded. A 2-sample *t* test was employed to find any statistically significant difference between the study groups.

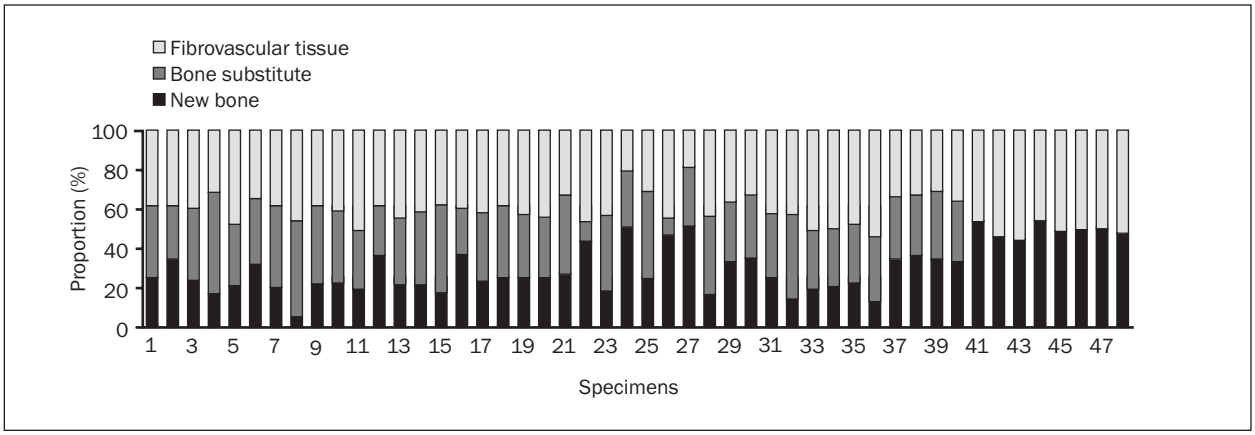

Fig 1 Histomorphometric data. Group T comprised specimens 1 to 10; group TB comprised specimens 11 to 20; group D comprised specimens 21 to 30; group DB comprised specimens 31 to 40; and control group B comprised specimens 41 to 48.

Table 3 Histomorphometric Data

	New vital bone		Bone substitute		Fibrovascular tissue	
Group	%	SD	%	SD	%	SD
T	21.4	8.1	39.0	7.2	39.6	4.8
TB	24.0	6.6	33.8	6.2	42.2	4.0
D	34.2	13.1	30.8	12.4	35.0	10.2
DB	24.4	9.1	33.3	4.1	42.3	8.3
B	49.2	3.1	0.3	0.5	50.5	3.5

Table 4 Statistically Significant Differences Found During Comparison of Augmentation Materials

Components	Compared groups	Two-sample *t* test
New vital bone	B–T	$P < .001$
	B–TB	$P < .001$
	B–D	$P < .01$
	B–DB	$P < .001$
	D–T	$P < .05$
	D–TB	$P < .05$
Bone substitute	T–B	$P < .001$
	TB–B	$P < .001$
	D–B	$P < .001$
	DB–B	$P < .001$
	T–DB	$P < .05$
Fibrovascular tissue	B–T	$P < .001$
	B–TB	$P < .001$
	B–D	$P < .001$
	B–DB	$P < .05$

RESULTS

Healing after surgeries proceeded uneventfully in all the cases. All the biopsy specimens were examined histologically and histomorphometrically. Representation of their single components is given in Fig 1 and in Table 3. Statistically significant differences between the 5 study groups are presented in Table 4.

Descriptive Histology

Histologically, round or oval areas of tiny refractive granules, which represented residual alloplastic augmentation material, were noticed at the site of augmentation with β-tricalcium phosphate (group T; Fig 2). Along with fibrotic tissue, mild chronic inflammatory infiltrates were found throughout this section. Newly formed vital bone in the form of wider trabeculae adjacent to areas of augmentation material and tiny lacelike trabeculae among individual granules of the bone substitute were noticed. Foreign body granulomatous reaction was not observed in any sample.

In group D, the remnants of deproteinized bovine bone were observed microscopically as irregular foci of fragmented refractive material. The total amount of fibrotic tissue among deproteinized bovine bone was minimal. In a few specimens, areas of mild infiltration with chronic inflammatory cells (lymphocytes, plasma cells, and histiocytes) were noticed. Trabeculae of varying widths of the newly formed bone were present on the edges of the foci of the augmentation material. However, a few foci of the xenogeneic grafts were completely surrounded by newly formed trabeculae (Fig 3). There was no evidence of granulomatous reaction.

In the case of the autogenous bone graft group (group B), the microscopic analysis showed the presence of different-sized fragments of necrotic bone, surrounded by fibrosis showing a few foci of infiltra-

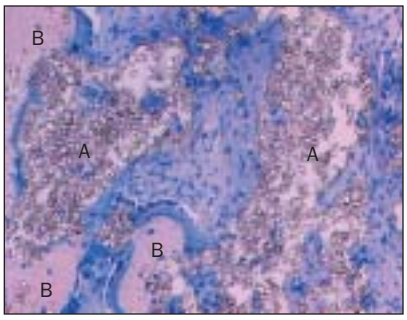

Fig 2 Areas of finely granular refractive β-tricalcium phosphate *(A)* surrounded by connective tissue and 2 trabeculae of newly formed bone *(B)* from group T (Giemsa; original magnification ×200).

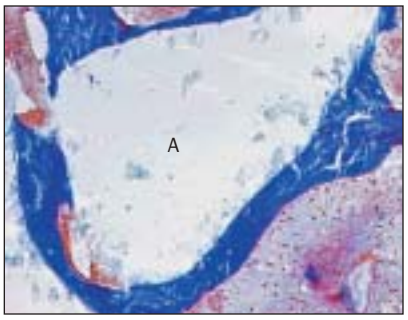

Fig 3 Foci of deproteinized bovine bone *(A)* bordered by trabeculae of the mineralized bone tissue *(blue).* Group D (Ladewig; original magnification ×200).

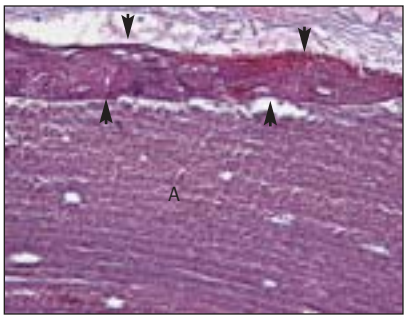

Fig 4 A part of necrotic bone fragment *(A)* with a layer of the newly formed bone on the surface *(arrows)*. Group B (Gömöri; original magnification ×400).

tion with chronic inflammatory cells. The newly formed vital bone was deposited on the surface of these necrotic bone fragments (Fig 4) and occasionally was connected with neighboring bone fragment. There was no foreign body granulomatous reaction in this group.

In the composite graft material groups (TB and DB), the histologic picture was a combination of cellular activity of the aforementioned groups.

DISCUSSION

Pure β-tricalcium phosphate Cerasorb is synthetic graft material composed of ceramic granules of 1,000 to 2,000 μm in size and having 45% to 50% porosity.[22] β-tricalcium phosphate is osteoconductive and biocompatible, but it is not an osteoinductive material. Osteoconductive properties are responsible for appositional bone growth on the surface or into pores, channels, or pipes[22,34] without evidence of toxic reaction. Since it is ceramic in nature there is no risk of transmission of certain infectious diseases, which is theoretically possible with xenograft material. This graft material is resorbable and the matured bone is organized in bone defect in a period of 24 months.[29]

Deproteinized bovine bone Bio-Oss is an inorganic bovine bone matrix of calcium-deficient carbonate apatite having a crystal size of 10 nm.[1] It is procured from calf bones and processed to remove all organic components. This results in an increase in the surface area of the granules up to 100 m^2/g.[33] Deproteinized bovine bone material is also biocompatible and osteoconductive but has no osteoinductive property.[11] The appositional bone growth from the surrounding bone forms a bone bridge between and around the granules.[25] Since the xenograft is of animal origin, safety of such material has been questioned on the grounds that some trace protein may theoretically remain after deproteinization.[30,35] Complete resorbability of this graft material is also questionable. However, Sartori et al in their 10-year study proved that resorption of the Bio-Oss is a slow but continuous process.[36] Further, they found that the resorption rate was 3.6% per year for the initial 2 years and then decreased consistently in the following 8 years, with a mean value of 0.58% per month.[36] In contrast, Schlegel et al could not find any signs of resorption of the Bio-Oss scaffold.[9] This kind of bone substitute seemed to behave like a permanent implant.[9] These results have been substantiated by other studies.[29,37] However, prevention of unwanted early resorption of graft material in sinus augmentation seems to be an added advantage with this graft material.[9,38]

In the present study, biopsy specimens were harvested after a 9-month healing period, because by that time cellular level differentiation of augmentation materials is sufficiently evident.[16] Histologic findings of the biopsy specimens in the individual groups were specific to a great extent. Even though the number of assessed specimens was limited, all the analyzed specimens showed good signs of bone regeneration. However, deproteinized bovine bone appears to be more efficient in osteoconduction when compared to β-tricalcium phosphate. Microscopic analysis of the samples revealed evidence of minimal fibrosis and minimal inflammatory reaction. There was no evidence of foreign body reaction in any of the biopsy samples in the tested groups.

Histomorphometric analysis is quantitative in nature and allows statistical evaluation of the results. In the present study, the group with β-tricalcium phosphate (group T) demonstrated 21.4% new bone formation and 39.0% residual augmentation mater-

ial. Zerbo et al in their study found 17% new bone formation after 6 months of healing with the same material.[22] Similar studies from Szabó et al and Zijderveld et al reported 29%, 36%, and 17% new bone formation, respectively.[39–41]

The deproteinized bovine bone group (group D) showed 34.2% new bone formation and 30.8% residual bone substitute. These results are comparable with the study results of Yildirim et al, who reported 14.7% new bone and 29.7% residual bone substitute in an average healing period of 6.8 months.[33] Studies from Sartori et al after 8 months of healing reported 29.8% new bone formation along with fibrovascular tissue, with 70.2% residual bone substitute.[36]

In the control group (group B), 49.2% new vital bone apposition was recorded, which is significantly higher than 4 other experimental groups. The new bone formation noticed in this study corresponds with the results of other investigators. Zerbo et al histomorphometrically compared the efficacy of sinus augmentation using β-tricalcium phosphate and chin graft in a split-mouth model.[22] They found that autogenous bone chips caused significantly higher new bone formation compared with β-tricalcium phosphate. A study by John and Wenz also arrived at a similar conclusion while comparing chin bone with deproteinized bovine bone graft.[21] This result also substantiates the use of autogenous bone as the most effective sinus graft material.

There are several studies using composite grafts in maxillary sinus augmentation surgeries. Tadjoedin et al used deproteinized bovine bone mixture with 20% to 50% autogenous bone in sinus augmentation surgeries.[25] After a healing period of 5 to 6 months, they found 30.4% to 37.3% of new bone formation and 16.2% to 26.6% residual xenograft in biopsy specimens.[25] Hallman et al used a mixture of fibrin glue with deproteinized bovine bone and 20% autogenous bone.[37] After a 6- to 8-month postoperative healing period, they observed 31.4% new bone tissue and 14.5% nonresorbed bone substitute. John and Wenz compared the effect of usage of deproteinized bovine bone and bovine bone mixed with autogenous bone at the ratio of 2:1.[21] After a 3- to 8-month postoperative healing period, they did not find any statistically significant difference in the amount of new bone formation between these groups. The results from the current study do not support a higher percentage of new bone formation with composite grafts. The validity of this statement is limited due to the relatively small study sample. The composite grafts included only 10% to 20% of the autogenous bone, which may not be sufficient to induce the significant osteogenic nature of the autogenous bone. The autogenous bone was harvested from the maxillary tuberosity in the experimental group but from chin bone in the case of the control group. The anatomical and structural difference of the autogenous graft may also be a contributory factor for the study results. Further studies are contemplated in this direction.

There are only a few studies that compare the effect of β-tricalcium phosphate and deproteinized bovine bone as sinus graft materials. Arzti et al in their studies used β-tricalcium phosphate and deproteinized bovine bone to restore the mandibular bony defects in dogs and compared bone healing at 3, 6, 12, and 24 months.[29] They noticed a significant increase in the new bone formation in the area augmented with β-tricalcium phosphate and also observed a complete resorption of β-tricalcium phosphate. However, deproteinized bovine bone particles still occupied a remarkable area fraction without significant resorption even after 6 months. In contrast, in the present study a higher proportion of new vital bone formation was found in group D ($P < .05$) compared to groups T and TB. However, a lower resorption capacity of deproteinized bovine bone when compared to β-tricalcium phosphate was not conclusively established. The possible reason could be the short 9-month healing period employed in the present study.

CONCLUSIONS

Within the limitations of the current study, after a 9-month healing period of sinus augmentation surgery, the following conclusions were drawn:

- Results of histomorphometric quantitative analysis indicated an increased amount of new bone apposition with deproteinized bovine bone rather than β-tricalcium phosphate ($P < .05$).
- The addition of 10% to 20% autogenous bone to the bone substitute did not significantly influence the new bone formation.
- When compared with β-tricalcium phosphate, deproteinized bovine bone, and composite grafts containing 80% to 90% bone substitute, the autogenous bone graft alone demonstrated a higher amount of new bone formation.

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