Bone Regeneration of Macropore Octacalcium Phosphate–Coated Deproteinized Bovine Bone Materials in Sinus Augmentation: A Prospective Pilot Study

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Objective: *To investigate the osteogenic potential of macropore octacalcium phosphate (OCP)–coated deproteinized bovine bone materials (DBBMs) in sinus augmentation.*

Study design: *Macropore OCP-coated DBBM was manufactured from bovine bone by thermal and chemical processing. Sinus grafts of a lateral window approach with experimental bone were conducted in 10 patients. At 6 months after surgery, a total of 10 specimens were obtained from 10 patients. But, 4 of them were excluded because the amount of specimens was not enough for evaluation. Morphological investigation under scanning electron microscopy and histological evaluation were performed.*

Results: *OCP was evenly attached to the surface of the experimental graft and showed a relatively large pore size (300–400 μm) compared with Bio-Oss (100–200 μm). New bone comprised 23.49% (±0.10), and residual graft material comprised 15.39% (±0.06) in bone specimens.*

Conclusion: *A macropore-sized design and OCP coating could present a favorable environment for new bone formation in maxillary sinus grafts. (Implant Dent 2015;24:275–280)*

Key Words: sinus augmentation, octacalcium phosphate, macropore, bovine bone

Alveolar bone shortage for implant surgery has been a chronic problem for a long time. Edentulous ridges in the maxillary posterior area, in particular, have a tendency of rapid atrophy of alveolar bone after extraction of teeth after advanced periodontal disease, trauma, or retained dental caries and require special reconstructive procedures to increase the alveolar bone height through bone graft for prospective implant therapy. When a bone graft in the maxillary sinus is considered in severely compromised cases, the first surgical options become lateral approach to the maxillary sinus. Several bone graft materials can be used in maxillary sinus augmentation, such as autogenous bone, mineralized and demineralized freeze-dried allografts, coralline calcium carbonate, bioactive glass, synthetic polymers, anorganic bovine bone, and synthetic hydroxyapatite (HA).[1–8] Autogenous bone, though, is superior to other materials in infection resistance, graft success rate, abundant cellular contents, and ability to induce migration of osteogenic cells.[3,9,10] Nonetheless, autogenous bone requires additional surgical procedures that could cause donor site complications, such as hematoma and damage to adjacent anatomic structures.[11] Moreover, relatively rapid resorptions of autogenous bone grafts have been reported, particularly with severe pneumatization in maxillary sinus.[12,13]

Xenogenous and synthetic bone graft materials have been considered attractive alternatives for overcoming the shortcomings of autogenous bone graft materials. They are potentially available in unlimited amounts and can be controlled in a range of different sizes and shapes as needed and designed to deliver adjunctive molecules, such as various hormones and growth factors, to promote new bone formation.[14,15] The bone graft procedures are commonly followed by the migration of osteogenic mesenchymal cells

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and ingrowth of microcapillary cells to the defect site. The extent of these processes varies according to the shape and macro-micro size of the bone graft materials, which is controlled by a thermochemical process and surface treatment.[16,17] Synthetic HA with a controlled macropore size presents the defect site with an abundant space for the ingrowth of microvessels and the migration of osteoblasts, ensuring effective new bone formation.[18–20] The high osteoconductivity of graft bone materials promotes the new bone formation by helping the ingrowth of osteogenic cell and microvessels.[21] The modification of bone graft materials to improve osteoconductivity has also been studied.[22] Surface treatment of bone grafts is also considered to be a key factor in the promotion of new bone formation. In addition, octacalcium phosphate (OCP), an HA-based synthetic graft material, has tendency to undergo a relatively fast resorption and be promptly replaced by new bone compared with other types of synthetic bone graft, such as β-tricalcium phosphate (β-TCP) and HA.[23,24] OCP acts as a precursor for new bone formation after graft placement with excellent biocompatibility, and its physical properties can be improved by modification with additional media, allowing its use in an extensive variety of applications.[25]

Xenogenous grafts have shown excellent osteoconductive properties and promising results in sinus floor elevation procedures. Moreover, they promote osteogenesis and show a very low resorption rate.[26,27] Xenogenous graft material is composed of natural bone mineral from other species and has extensive interconnecting pores and a high surface energy area. It acts as a framework onto which bone-forming cells and blood vessels travel to form new bone.[28,29] One type of xenogenous graft, Bio-Oss (Geistlich Pharma, Wolhusen, Switzerland), involves deproteinized bovine bone material (DBBM), which has already been proven in previous studies to be clinically stable and have superior osteogenic ability and has been commercially used in many implant surgeries.[2,12,13,26,30] However, the slow rate of resorption and its osteogenicity should be improved upon. Studies into modification of the graft, such as surface treatment and graft design, are still ongoing to overcome the limits of DBBM.[7,31,32]

In this study, the graft design of conventional DBBM was modified using thermal and chemical treatment to obtain macro-sized pores. In addition, OCP granules were attached to the surface of the graft material. Patients who had an edentulous ridge in the posterior maxilla with alveolar bone atrophy received a sinus graft through a lateral approach with macropore-sized OCP-coated DBBM in the prospective implant therapy. Graft cores were obtained 6 months after surgery to evaluate the osteogenic potential and clinical reliability of the modified DBBM.

MATERIALS AND METHODS

Preparation of OCP-Coated Macropore Bovine Bone

Macropore OCP-coated DBBM (Ti-Oss; Chiyewon, Seoul, Korea) was manufactured from bovine bone. OCP was prepared by the LeGeros method and processed to coat the surface of the experimental bone.[33] To eliminate fat and protein in general, meticulous cleansing and a thermal process were performed. During this process, the calcium core structure of trabecular bone shrinks by approximately 15%, with pore size tending to become larger as a result. This results in a significant biological advantage for bone formation because the blood is readily absorbed

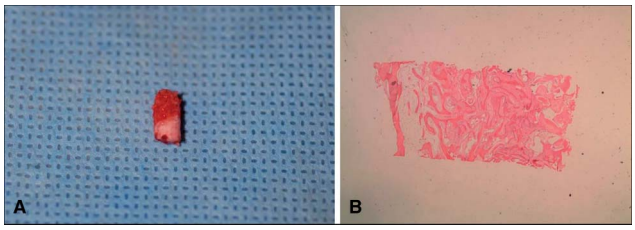

Fig. 1. A harvested bone core (**A**) and histological preparation of the specimen for assessment (**B**).

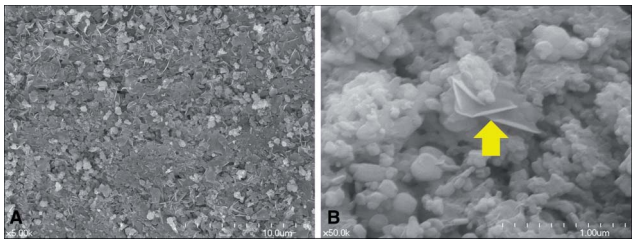

Fig. 2. OCP attached to the surface of the bovine bone. **A**, Scale-shaped OCPs were shown on the surface of the bone graft material (×5000, SEM). **B**, OCP was embedded among the round-shaped bone particles (yellow arrow ×50000, SEM). Each gradation on the scale indicates 1 μm.

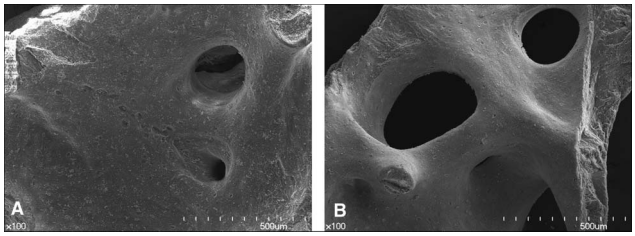

Fig. 3. Comparison of macropores on the surface of bone graft materials (×100, SEM). **A**, Bio-Oss. **B**, Ti-Oss. Each gradation on the scale indicates 50 μm.

deep inside the pore, resulting in close clot contact. The bone was selectively pulverized in the 1.2- to 1.7-mm range.

Patients

Sinus graft procedures were conducted in 10 patients. A lateral approach to the maxillary sinus cavity was used. After elevation of the sinus membrane, between 1.0 and 1.5 g of macropore OCP-coated DBBM was packed into the sinus cavity. The bony window was repositioned, and wound closure was performed with 4-0 nylon. Patients were prescribed antibiotics and analgesics for 5 days, and suture materials were removed 7 days after surgery. Cylindrical bone cores were obtained from each patient with a 3-mm trephine bur at 6 to 8 months after bone graft surgery. Implant fixtures were installed in the prepared drilling hole by a trephine bur followed by sequential drilling as part of the routine implant surgery procedure. Harvested bone cores were sent to the histology laboratory for evaluation (Fig. 1).

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol and consent form were reviewed and approved by the Institutional Review Board of the Asan Medical Center. Informed consent was obtained from all patients.

Surface Structure of the Bone Graft Material

The OCP microstructure on the surface of the bone graft material was investigated, and the macropore sizes on the surface of bone graft materials were compared with those of Bio-Oss (Geistlich Pharma) by scanning electron microscopy (S-4300; Hitachi, Tokyo, Japan).

Histological Processing and Light Microscopy Imaging

The bone cores were fixed in 10% formalin for 24 hours, dehydrated in alcohol, rinsed, embedded in paraffin, and sectioned at a thickness of 5.0 μm. The specimens were stained with hematoxylin and eosin. Histomorphometry was investigated using a light microscope. Images were captured by digital cameras and recorded to evaluate the proportions of new bone formation and residual bone graft.

Table 1. New Bone Formation and Residual Graft Materials in the Specimens

Specimen	New Bone (%)	Graft (%)
1	27.64	16.00
2	16.14	5.33
3	11.10	11.86
4	18.40	24.47
5	35.95	17.01
6	31.69	17.64
Mean	23.49	15.39

Specimens 3 and 4 had more residual bone graft material compared with newly formed bone. But, there was more newly formed bone than residual graft material in other specimens. Mean new bone formation was 23.49% (±0.10), and mean residual graft material was 15.39% (±0.06).

RESULTS

OCP Treatment

Octacalcium was successfully attached to the surface of the experimental graft. OCPs were evenly distributed on the bone surface (Fig. 2A), and they had scale-like shape embedded among the round bone particles (Fig. 2B).

Macropore Size Comparison

The macropore size of Ti-Oss was compared with that of Bio-Oss (Geistlich Pharma). Under ×100 magnification, Ti-Oss had a relatively large pore size (300–400 μm) compared with Bio-Oss (100–200 μm), showing favorable

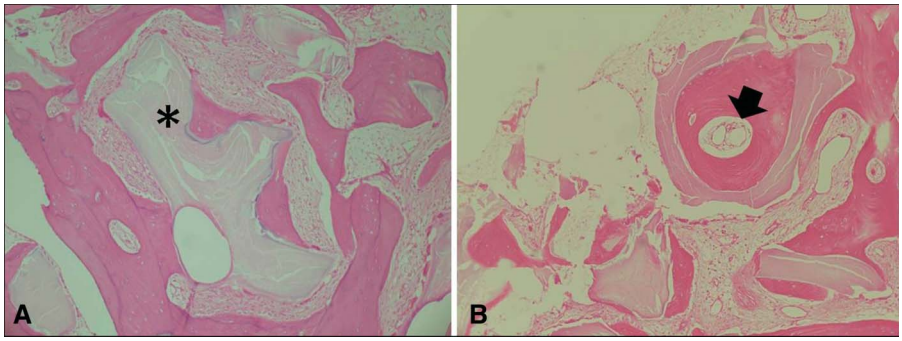

Fig. 4. New bone formation of the grafted Ti-Oss in the human maxillary sinus cavity. **A**, Residual graft material (*) was circumscribed by newly formed bone (hematoxylin and eosin stain, ×40). **B**, Ingrowth of microvessels in the newly formed bone (arrow) with lacunae in the bone lamellae (hematoxylin and eosin stain, ×100).

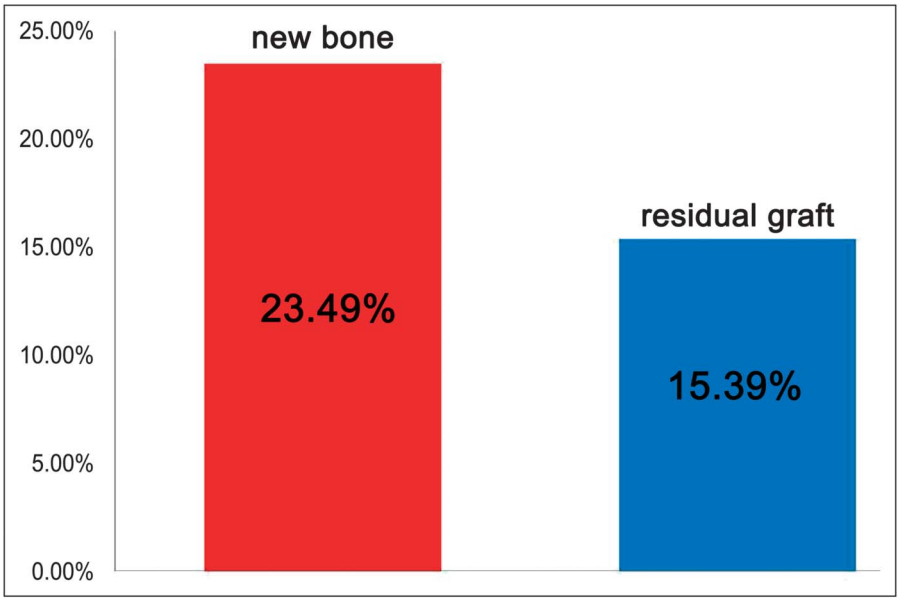

Fig. 5. Mean new bone formation and residual bone graft in the harvested cylindrical bone core.

conditions for the ingrowth of capillary and osteogenic cells (Fig. 3).

Graft Material and New Bone Formation

Four of ten specimens from 10 patients were discarded, as the harvested samples did not have sufficient bone graft material for evaluation. Therefore, 6 specimens were used for histomorphometric analysis. New bone comprised 23.49% (±0.10), and residual graft material comprised 15.39% (±0.06) (Table 1 and Figs. 4 and 5). Thus, there was more newly formed bone than residual graft material.

DISCUSSION

It is vital in implant dentistry to repair the posterior maxillary edentulous area and achieve occlusion for recovery of masticatory function. In the posterior maxillary area, fast alveolar bone resorption occurs after loss of teeth, which in most cases leads to additional surgical procedures, such as bone grafts.[34,35] Two surgical methods, generally, can be used for the reconstruction of alveolar bone in the maxillary posterior edentulous area: the lateral window approach and transalveolar bone technique.[36,37] The lateral window approach is recommended for residual alveolar bone that is less than 6 mm in height. This technique has been widely used for the reconstruction of vertical deficiencies in the maxillary posterior alveolar bone since the success of this procedure was first reported by Tantum.[37] The space acquired in the sinus cavity after elevation of the maxillary sinus mucosa can accommodate various bone graft materials, such as autogenous bone, allograft bone, xenograft bone, synthetic HA, and combinations of bone graft materials.[38–40]

The ideal bone graft materials for the maxillary sinus bone graft should be able to stabilize the space for ingrowth of new bone and osseointegration of implant fixtures and be maintained until consolidation of the bone after prosthodontic treatment. Moreover, the ideal material should show osteoconductivity for the migration of adjacent osteogenic cells. Of course, the ideal bone graft materials should also not cause patient morbidity.[34]

Autogenous bone is superior to other bone graft materials in terms of osteoconductivity, osteoinductivity, and biocompatibility and shows strong stability and resistance to infection after bone graft surgery. Autogenous bone has thus long been considered the gold standard material for implant surgery. An additional surgical procedure, however, is required for harvesting the graft bone, entailing damage to anatomic structures, such as the inferior alveolar nerve and maxillary sinus floor, with attendant clinical complications. Therefore, autogenous bone alternatives are sought after.[31] Synthetic bone shows no limits on supply. Moreover, the size and shape of graft materials can be controlled as needed, and they can be designed to deliver osteogenic molecules such as growth factors and hormones.[41] DBBM has commonly been used as an alternative bone graft material to autogenous bone.[2,5] Bio-Oss (Geistlich Pharma), a representative type of DBBM that is widely used in clinical setting, is a type of HA from natural bovine bone consisting of 10-μm granules with 75%–80% porosity that is processed to a completely deproteinized state.[31] Bio-Oss has excellent osteoconductivity and is slowly absorbed, enabling it to maintain the space beneath the elevated maxillary sinus membrane[42] and act as a scaffold for the ingrowth of osteogenic stem cells.[43] Forum et al[44] reported that Bio-Oss maintained augmented alveolar bone height for more than 3 years, preventing pneumatization.

The studies of Valentini et al,[45] Lee et al,[32] Hallman et al,[46] and Wallace et al[43] have reported on new bone formation and residual bone graft after sinus bone graft using DBBM, finding that the augmented alveolar bone was composed of more residual graft than new bone at the time of implant fixture installation. In contrast, Yildirim et al,[6] Lee et al,[47] Choi et al,[48] de Vicente et al,[1] and Ferreira et al[49] reported more newly formed bone than residual graft in their studies, results that are largely consistent with those of this study showing 23.49% newly formed bone and 15.39% residual material. Although the compositions of new bone and residual bone might vary according to study design and observation method, the bone cores analyzed in this study showed more new bone than the residual graft, indicating the superior new bone formation ability of the OCP-coated DBBM material.

Osteoconductivity is a key factor for new bone formation in DBBM[32] and angiogenesis should first be considered because osteogenic cells can migrate through microvessels to increase osteoconductivity.[21] The graft material should thus support the extended space and be a scaffold for angiogenesis.[16] In the scaffold design of osteoconductive material, large-sized pores can provide a central marrow space for circumferential bone formation.[31] The macropore-micropore networks of HA act as an architectural frame that induces new bone formation,[18–20] and promote bone formation because microvessels and mesenchymal cells migrate into the required space, ensuring cell adhesion and proliferation.[31]

Macropore sizes are critical for angiogenesis.[22] Herbert et al[50] found that the minimum pore size for bone regeneration was more than 100 μm. Several studies have reported that the optimal macro-level pore size of DBBM for effective bone regeneration was more than 300 μm.[51–54] The pore size affects the direct migration of osteogenic cells and microvessels, and combined micropore and macropore sizes have been found to increase macromolecule absorption, cell adhesion, and bone morphogenetic protein formation, leading to bone healing.[23,55–57] In this study, the macropore-sized DBBM showed relatively large pore sizes (300~400 μm) compared with Bio-Oss in scanning electron microscopy analysis (Fig. 3), and the composition of new bone was also higher. Dominant angiogenesis was also observed in the macropore (Fig. 4).

Synthetic HA and β-TCP are most widely used graft materials among synthetic bone graft.[58,59] These materials have excellent tissue compatibility and showed direct contact between graft material and new bone without impingement of cell contents.[60,61] OCP is a type of synthetic bone

material that is a precursor of biological apatite, which converts into biological HA under periosteal membrane.[62] The precursor transit to HA through in situ hydrolysis or dissolution of OCP followed by HA precipitation.[24,63] OCP can be applied as a coat to metallic implants, attached to microscaffold in the form of granules.[55,64] Kamakura et al[65] compared OCP with other β-TCP and HA and found that OCP was absorbed at a relatively slow rate and has active bone formation ability with a core initiating bone formation in rat calvarial defect model. Fuji et al[18] overcame the fragility of OCP using an alginate scaffold and studied the optimal OCP physical type, reporting various bone formation abilities according to pore size.

CONCLUSION

In this study, we investigated the potential for new bone formation of the macropore OCP-coated DBBMs, but clinical data were not sufficient for a definite conclusion to be obtained from statistical analysis. Further studies are needed to follow up on this pilot study. However, we found that a macropore-sized design and OCP coating could help microvascular angiogenesis and promote migration of osteogenic cells, thereby presenting a favorable environment for new bone formation in maxillary sinus grafts.

DISCLOSURE

The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the article.

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