Maxillary sinus floor elevation with bovine bone mineral combined with either autogenous bone or autogenous stem cells: a prospective randomized clinical trial

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Abstract
Aim: To assess whether differences occur in bone formation after maxillary sinus floor elevation surgery with bovine bone mineral (BioOss®) mixed with autogenous bone or autogenous stem cells. The primary endpoint was the percentage of new bone three months after the elevation procedure.

Material and methods: In a randomized, controlled split-mouth design, in 12 consecutive patients (age 60.8 ± 5.9 years, range 48–69 years) needing reconstruction of their atrophic maxilla, a bilateral sinus floor augmentation procedure was performed. Randomly, on one side the augmentation procedure was performed with bovine bone mineral (BioOss®) seeded with mononuclear stem cells harvested from the posterior iliac crest (test group) while BioOss® mixed with autogenous bone (harvested from the retromolar area) was applied on the contra-lateral side (control group). On 14.8 ± 0.7 weeks after the sinus floor elevation, biopsies from the reconstructed areas were taken at the spots where subsequently the endosseous implants were placed. The biopsies were histomorphometrically analyzed.

Results: Significantly more bone formation was observed in the test group (17.7 ± 7.3%) when compared with the control group (12.0% ± 6.6; P = 0.026). In both the test and control group, all implants could be placed with primary stability. In one patient, not all biopsies contained BioOss®. This patient was excluded from analysis.

Conclusion: Mesenchymal stem cells seeded on BioOss® particles can induce the formation of a sufficient volume of new bone to enable the reliable placement of implants within a time frame comparable with that of applying either solely autogenous bone or a mixture of autogenous bone and BioOss®. This technique could be an alternative to using autografts.

Application of dental implants to support full dentures in edentulous patients has evolved into a viable prosthetic alternative to conventional prostheses. However, implant procedures in the posterior maxilla often pose a problem due to an insufficient bone volume [Zerbo et al. 2004]. This restriction is not only reserved to edentulous patients but also is often observed in partial dentate patients needing an implant-based prosthetic reconstruction in the posterior region of the maxilla.

The lack of bone to enable reliable placement of implants in the posterior maxilla can be solved by a maxillary sinus floor elevation procedure using autogenous bone, bone substitutes or a mixture of autogenous bone and bone substitutes as grafting materials [Hallman et al. 2002]. During this elevation procedure, the space created between the residual maxillary ridge and
the elevated Schneiderian membrane is filled with a grafting material. This way, a bone volume is created that may allow for implant placement, either simultaneously with the elevation procedure when the residual ridge allows for primary implant stability or at a second stage after healing of the grafted site.

Regarding the various augmentation materials that have been used for a sinus elevation procedure, autogenous bone, with its osteogenic, osteoinductive and osteoconductive properties, is still considered the ideal grafting material by many surgeons (Hallman & Thor 2008). However, donor site morbidity is a major problem accompanying bone-harvesting techniques and puts the patient at an inconvenience that probably can be reduced or even be avoided when using synthetic bone substitutes (Zerbo et al. 2004). To surpass donor site morbidity, bone substitutes as calcium phosphates, β-tricalcium phosphates (Cerasorb®) (Zerbo et al. 2004; Szabo et al. 2005) and bioactive glass particles (Tadoedin et al. 2000, Tadoedin et al. 2002), xenogenic substances as bovine hydroxyapatites (BioOss®) (Hallman et al. 2002; John & Wenz 2004) and allogenic substitutes as demineralized freeze-dried human bone (Wallace et al. 2005) have commonly been proposed as and shown to be adequate alternatives for autologous bone. A major drawback of these substitutes is the rather long healing time that is needed before implants can be placed (John & Wenz 2004). Moreover, these substitutes are not very suitable to be used as a sole grafting material for large reconstructions.

In addition, as clinicians often are looking for tools to speed up healing, the effect of using platelet-rich plasma (PRP) has been studied aiming to accelerate bone regeneration as it has been speculated that growth factors within PRP could enhance healing of the grafts and counteract resorption after augmentation (Thor et al. 2005; Thor et al. 2007). However, Raphoebar et al. (2005) and Schaar et al. (2008) showed that no relevant differences in healing of soft tissues and bone existed between sites reconstructed with autogenous bone and autogenous bone mixed with PRP.

The combination of autogenous bone and bovine bone material has been investigated in previous histological sinus floor elevation studies. Yildirim et al. (2000) examined sinus floor elevation procedures with only BioOss® in 15 sinuses of 11 patients and found 14.7 ± 5% new bone formation after a healing time of 6.8 months. In another study, Yildirim et al. (2001) evaluated the bone formation in sinus floor elevations performed with a mixture of autogenous bone and BioOss® in 13 sinus floor elevations and reported 18.9 ± 6.4% new bone formation after a 7.1-month healing period. Therefore, the addition of autogenous bone to the bovine bone material yielded an advantage of 4.2% new bone, which can be translated as a delay of a couple of months in the healing time when applying solely BioOss®.

In recent animal studies, it has been shown that seeding BioOss® with mononuclear stem cells (MSC) derived from concentrated non-mineralized tissue may result in bone-forming kinetics comparable with bone-forming kinetics in a region solely reconstructed with autogenous bone (Gutwald et al. 2009). MSCs were shown to differentiate to osteoblasts when being introduced into an environment prone to the formation of bone. In addition, in an in vitro study osteoblast-like cells were cultured on various alloplastic biomaterials used for augmentation and for reconstruction of bone defects in dental and craniomaxillofacial surgery (Schmitt et al. 2008). The latter study revealed that osteoblast-like cells attach to BioOss® and offer suitable growth and proliferation conditions. Furthermore, Gutwald et al. (2009) compared the osteogenic potential of mononuclear cells harvested from the iliac crest combined with bovine bone mineral to autogenous cancellous bone alone in a sheep model. Bilateral sinus floor augmentations were carried out. Histomorphometric analysis of biopsies taken after 8 and 16 weeks after the augmentation procedure revealed the bone-forming potential of mononuclear cells, including the mesenchymal stem cells in combination with BioOss® as biomaterial (Gutwald et al. 2009). Furthermore, Herten et al. (2009) evaluated the influence of different bone substitutes (BioOss®) on the viability of human bone marrow mesenchymal stem cells in vitro and concluded that hydroxyapatite (BioOss®) supports cell viability and allows cell proliferation.

The promising results from in vitro and animal studies (Gutwald et al. 2009) stimulated us to perform a study in human. In this randomized, controlled trial (RCT) it was assessed whether differences in bone formation occurred after a maxillary sinus floor elevation surgery with either autogenous bone in combination with BioOss® or stem cells in combination with BioOss®. The primary endpoint was the percentage of new bone 3 months after the elevation procedure.

Material and methods

This study is a joint study between the University of Freiburg and the University Medical Center Groningen. The protocol was approved by the ethics committees and the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients. All patients were treated according to the protocol for the reconstruction of bony defects with a mixture of bone substitutes and autogenous stem cells developed in Freiburg (Gutwald et al. 2009). All patients were treated with a split-mouth design.

Edentulous patients older than 18 years with need of dental implant placement in the posterior maxilla were eligible for the study if they had a maximum of 4 mm residual height of the alveolar ridge at either site of the maxilla. In addition, the patients had to be able to comply with study-related procedures including returning for follow-up examinations, exercising good oral hygiene and being able to understand the nature of the proposed surgery. Exclusion criteria were (1) smoking, (2) history of malignancy, radiotherapy or chemotherapy, (3) pregnancy or nursing, (4) medication, treatment or disease, which may have an effect on bone turnover, bone or non-mineralized tissue metabolism and (5) allergy to collagen.

Patients

The patients were referred to the Department of Oral and Maxillofacial Surgery of the University Medical Center, Groningen because of insufficient retention of their upper denture related to a severely resorbed maxilla selected on the basis of the following inclusion criteria:

- severely resorbed maxilla (class V–VI, Cawood & Howell 1991) with reduced
stability and retention of the upper denture;
- comparable bone height between the maxillary sinus and top of the maxilla on both sides;
- class IV bone quality [Lekholm & Zarb 1985];
- edentulous period of at least 1 year;
- no history of radiotherapy in the head and neck region;
- no history of reconstructive, pre-prosthetic surgery or previous oral implantology.

Orthopantomograms, lateral cephalograms and postero-anterior oblique radiographs were made to assess the height of the maxillary alveolar bone, the dimensions of the maxillary sinus and the antero-posterior relationship of the maxilla to the mandible. The radiographs were also screened for sinus pathology.

In 12 consecutive patients (age 60.8 ± 5.93 years, range 48–69 years) needing reconstruction of their atrophic maxilla and who fulfilled the inclusion criteria, a bilateral sinus floor augmentation procedure was performed (split-mouth design). The mean vertical height of the alveolar bone on the orthopantomogram between the most caudal part of the maxillary sinus and the oral cavity were in the premolar and molar region on the right 2.1 ± 0.3 mm and on the left side 2.2 ± 0.6 mm, respectively (Table 1). Randomly, performed by envelopes, on one side the augmentation procedure was performed with bovine bone mineral (BioOss®, Geistlich Biomaterials, Wolhusen, Switzerland) seeded with MSCs harvested from the posterior iliac crest (test group) and BioOss® combined with autologous bone on the contralateral side (control group).

### Harvesting of stem cells
The patients were treated under general anesthesia. The pelvic bone was punctured about 2 cm laterocaudally from the superior posterior iliac spine with a bone marrow biopsy needle. With a 60 ml syringe flushed with heparin solution [Heparin-Natrium, 10,000 U/ml, diluted with NaCl to 1000 U/ml, both B. Braun, Melsungen, Germany] and then filled with 8 ml of citric acid (BMAC-Kit, Harvest Technologies Corporation, Plymouth, MA, USA), 52 ml of non-mineralized tissue was collected. According to the instructions of the manufacturer non-mineralized tissue was isolated directly in the operating room using the BMAC system [Bone Marrow Procedure Pack, Harvest Technologies Corporation, Plymouth, MA, USA]. The procedure of concentrating the bone marrow aspirates took about 15 min. For details of the selection procedure and characterization of the MSCs see Gutwald et al. 2009, Sauerbier et al. 2004a, 2004b). In these studies, cells from the non-mineralized tissue concentrate were amplified and differentiated into chondrogenic, adipoigenic and osteogenic cell lineages according to the methods according to Pittenger et al. [1999]. The cultured MSCs could be differentiated successfully into adipocytes, chondrocytes and osteoblasts. Flowcytrometic analysis showed a distinct population of CD 34- and CD 45-negative cells which were positive for CD44 and CD73.

Three milliliters of non-mineralized tissue concentrate and 1 ml autologous thrombine produced from venous blood [Thrombin kit, Harvest Technologies Corporation] was used to clot the non-mineralized tissue concentrate.

### Sinus augmentation and implant placement procedure
An osteotomy was prepared in the lateral wall of the maxillary sinus using the surgical procedure described by Raghoebar et al. (2001) after a pedicled mucoperiostal flap was raised to expose the lateral wall of the maxillary sinus. The floor of the maxillary sinus (test side) was augmented with BioOss® (0.25–1 mm, Geistlich Pharma AG) and enriched with mononucleated cells in thrombin according to the method of Gutwald et al. 2009] Autologous thrombine produced from venous blood (Thrombin kit, Harvest Technologies Corporation) was used to clot the non-mineralized tissue concentrate.

The control side was augmented with a mixture of 70% biomaterial and 30% autogenous bone harvested from the retromolar area as described by Capelli (2003). In addition, the width of the superior alveolar process had to be reconstructed with mandibular bone in 10 out of the 12 patients at both sides (Raghoebar et al. 2007, Raghoebar et al. 2009). All bone grafts were harvested from the retromolar region. The grafts were fixed with titanium screws. Moreover, a guide on which the planned position of the implants was marked, was used to be certain that implants will be placed in reconstructed areas.

A collagen membrane [Bio-Gide®, Geistlich Pharma AG] was used to cover the facial sinus wall defect on the surface of both grafted sites. The mucoperiostal flap was replaced and wound closure was performed using resorbable suture material Vicryl 4.0 (Ethicon, Norderstedt, Germany).

### Table 1. Radiological bone height of the residual alveolar processes at the implant site (in mm)

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Bone height at baseline in mm (right side)</th>
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The bone harvesting was performed by the same surgeon from the same region with the same method. The bone was particulated using a bone mill to a grain size of 1–2 mm. Thirty percentage of bone was mixed with 70% of BBM [BioOss® 1–2 mm, Geistlich Pharma AG]. The relation was determined by volumetric measurement.
Lemgo, Germany) from the marked positions on the surgical template. On the same spot, the endosseous implants were placed. The implants were inserted at the biopsy locations after widening these holes to the required dimensions using the standard burrs for the implant system chosen. The right position of the biopsy was confirmed later by the biomaterial [BBM] content, which is clearly distinguishable in the histology. Hence, the biopsies that contained BBM, which was used in both groups must have been from the augmented area. In all cases, the bone volume was sufficient. Three months after insertion the prosthetic construction was fabricated.

**Histological evaluation**

The reference area for the histomorphometrical evaluation was the entire area in the biopsy above the old bone of the sinus floor. Values measured in % of the examined area were taken for biomaterial, old bone and newly formed bone. The value for non-mineralized tissue was gained by subtracting the values of biomaterial, old bone and newly formed bone from the total evaluated area.

The burrs with the bone biopsies inside were fixed in formalin for 48 h, rinsed in water and dehydrated in serial steps of alcohol (70%, 80%, 90% and 100%) remaining for 3 days in each concentration. After dehydration, the samples were infiltrated with resin [Technovit 7200 VLC, Heraeus Kulzer, Hanau, Germany] for 2 weeks. The resin was polymerized in a UV light chamber for 10 h. After the hardening, two sections of 300–400 μm thickness and parallel to the axis of the burr were cut using a diamante micro saw [Microslice, IBS, Cambridge, UK]. The sections were placed on an acrylic slide [Maertin, Freiburg, Germany] and reduced to a thickness of approximately 100 μm on a rotating grinding plate [Struers, Ballerup, Denmark]. The specimens were stained with Azur II and Pararosanilin, which allowed for a differentiation between BioOss® particles, preexisting and newly formed bone [Figs. 1a, 2a]. Histomorphometric examination was carried out with a light microscope [Axiovert 135, Zeiss, Kochern, Germany] [Gutwald et al. 2009]. The BioOss® particles were marked and the newly formed bone around the particles was measured [Figs. 2a, b]. The marking and measurements were performed with the computer software AnalySIS® Soft Imaging system [Olympus Europa GmbH, Hamburg, Germany]. The histologists were blinded to the samples’ groups throughout the histomorphometrical analysis.

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![Fig. 1](image_url)

Fig. 1. Biopsy taken from the experimental side [BioOss® and stem cells] at 3.1 months after grafting. In this specimen, 16.2% of new bone was present. The newly formed bone lamellae (red) connected the biomaterial particles (green) and stabilized the grafted complex. The grafted biomaterial with newly formed bone was well integrated in the surrounding host bone. There were no signs of an inflammatory reaction. The grafted bone shows signs of resorption and new bone formation; both are signs of active bone remodeling. (a) Azur II and pararosanilin staining (× 10). (b) View as used for histomorphometrical analysis. Red, newly formed bone; green, BioOss® (× 10). (c) Newly formed bone is clearly deposited around the BioOss® particles. No indication of BioOss® resorption was observed (× 50).
Statistical analysis
For the parameters NewBone (new bone formation), BioOss\textsuperscript{s} (Biomaterial) and Marrows (marrow space), values were expressed in % of the evaluated area. For statistical analysis, a nonparametric Wilcoxon’s test for paired group data was used. Eleven out of 12 patients were included for analysis as in one patient it was shown that at one side no biopsies were available from an augmented region. A \( P \leq 0.05 \) is considered as a significant result.

Results
Healing was uneventful. Loss of bone particles through the nose was not observed. A minor incision breakdown occurred in the first week in one patient at the test side. This patient was put on a regimen of rinsing with 0.12\% w/v chlorhexidine mouth rinse four times daily. The dehiscence (5 mm × 5 mm) healed uneventfully within 2 weeks.

All 12 patients were treated with a bilateral sinus floor augmentation procedure, but the results of the biopsies taken from one sinus (control side) of one patient were not included in this analysis as histological examination revealed that these biopsies were not taken from an augmented location. No BioOss\textsuperscript{s} could be identified in these biopsies (internal control as at both control and test sites BioOss\textsuperscript{s} was applied). By design (split-mouth approach), this patient was removed from the comparisons and thus the data set to be analyzed was composed of data from the 11 patients in whom biopsies (all containing BioOss\textsuperscript{s} particles) were available from both the control and test sites. Four to six cylindrical bone biopsies per patient were available (two to three of each site). All biopsies had been taken within the 13–16 weeks post-augmentation period (mean 14.8 ± 0.7 weeks, range 13.3–15.8 weeks). In Table 2, average values for the percentage of newly formed bone, BioOss\textsuperscript{s} and marrow space of the biopsies taken at a particular site are shown.

Histology
The newly formed bone lamellae surrounded/enclosed the biomaterial particles and stabilized the grafted complex. The grafted material (biomaterial with newly

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Fig. 2. Biopsy taken from the control side (BioOss\textsuperscript{s} and autogenous bone) at 3.4 months after grafting. In this specimen, 11.8\% of new bone was present. The newly formed bone lamellae (red) connected the biomaterial particles (green) and stabilized the grafted complex. The grafted biomaterial with newly formed bone was well integrated in the surrounding host bone. There were no signs of an inflammatory reaction. The grafted bone shows signs of resorption and new bone formation, both are signs of active bone remodeling. [a] Azur II and pararosanilin staining (\( \times 10 \)). [b] View as used for histomorphometrical analysis. Red, newly formed bone; green, BioOss\textsuperscript{s}; yellow, autogenous bone (\( \times 10 \)). [c] Newly formed bone is deposited near BioOss\textsuperscript{s} particles and autogenous bone. No indication of BioOss\textsuperscript{s} resorption was observed, while the autogenous bone is in the process of being resorbed and replaced by newly formed bone (\( \times 50 \)).
formed bone) was well integrated in the surrounding host bone (Fig. 1).

Vital bone tissue containing osteocytes inside the bone lacunae were observed in the newly formed osseous lamellae. The biomaterial could be easily identified by its size, shape and color in comparison with newly formed bone or the pre-existing local bone. Newly formed bone appeared as a darker red than the BioOss® particles in the Azur II and pararosanilin staining (Figs. 1 and 2). Blood vessels could be detected throughout the specimens showing that blood supply is ensured throughout the whole augmentate. There were no signs of an inflammatory reaction.

**Histomorphometry**

**New bone formation**

Significantly, more new bone had been formed at the reconstructed areas at time of implant placement in the test group when compared with the control group (primary end point; Table 2; \( P = 0.026 \)).

**BioOss®**

At 3 months, post sinus floor evaluation surgery, the percentage of BioOss® present in the biopsies taken from the test and control sites was comparable (Table 2; \( P = 0.722 \)).

**Marrow space**

The percentage of the biopsies occupied by a marrow space was comparable between the test and control specimen (Table 2; \( P = 0.859 \)).

**Implants**

Comparison of the clinical features at the test and control revealed no differences with regard to wound healing and complications during or post surgery. In all augmented regions, implants could be installed with primary stability. A total of 66 nonsubmerged one-piece implants (ITI Straumann®, Institut Straumann, Waldenburg, Switzerland) was placed in the augmented maxillae.

Before the prosthetic phase, three implants (two patients) were mobile on the test side and had to be removed. In one patient, the superstructure could be made on the remaining two implants on that site, while in the other patient the two lost implants were replaced. Healing was uneventful and this patient could also be supplied with an adequately functioning implant-supported maxillary overdenture.

**Discussion**

Currently, the most reliable and well-studied grafting materials to perform sinus floor augmentation surgery are autogenous bone and mixtures of autogenous bone with BioOss® (Hallman et al. 2002). It is questionable, however, whether adding autogenous bone to biomaterials as BioOss® is necessary. Our randomized, controlled split-mouth study showed that as an augmentation material to be used for a sinus floor augmentation procedure, BioOss® seeded with stem cells was shown to be superior to BioOss® mixed with autogenous bone with respect to bone formation 3–4 months after surgery.

As shown in our study, adding mononuclear cells, including the mesenchymal stem cell fraction, to BioOss®, can lead to more new bone formation compared with BioOss® combined with autologous bone. These results are supported by the results from various animal studies (Yildirim et al. 2000; Gutwald et al. 2009; Herten et al. 2009; Sauerbier et al. 2010a, 2010b). They showed in a sheep model the osteogenic potential of mononuclear cells and the bone-forming potential of mononuclear cells, including the mesenchymal stem cells in combination with BioOss® as the biomaterial. Pieri et al. (2008) investigated whether mesenchymal stem cells and PRP seeded on a fluorhydroxyapatite scaffold can improve bone formation and bone-to-implant contact in maxillary sinus grafting. They showed that sinus augmentation with mesenchymal stem cells may enhance bone formation and osseointegration of dental implants in minipigs. Also, McAllister et al. (2009) showed that treatment with mesenchymal stem cells has a positive effect on bone formation. The purpose of their case series was to evaluate the bone formation following sinus-augmentation procedures using an allograft cellular bone matrix containing native mesenchymal stem cells.

Next to the promising results from the application of mesenchymal stem cells, other studies also challenged whether autogenous bone still has to be considered as the grafting material of first choice. For example, Hallman et al. (2002) studied the graft/titanium implant interface in maxillary sinuses augmented with autogenous bone, bovine hydroxyapatite, or an 80–20% mixture of bovine hydroxyapatite and autogenous bone. They reported no significant differences in the healing of the augmented sites between the three groups after 6–9 months. In addition, Zerbo et al. (2004) and Szabo et al. (2005) compared the applicability of autogenous bone and β-tricalcium phosphate for sinus floor elevation surgery in a split-mouth design. In both studies, it was concluded that in the long run (i.e., > 6 months) there
was no significant difference in the healing of the augmented sites, although Zerbo et al. [2004] mentioned that the rate of bone formation was delayed by approximately 6 months in the test site when compared with the site reconstructed with autogenous bone. Finally, bioglass, a material that has been shown to be able to directly chemically bond to bone, has also been shown as a potentially applicable grafting material for reconstructive procedures as the particles. When applied in the size range of 300–355 μm, bioglass showed osteoconductive properties [Tadjoedin et al. 2000; Tadjoedin et al. 2002].

As mentioned in the previous paragraph, it is commonly known that a bovine bone mineral as BioOss® is in need of a longer healing period than autogenous bone before implants can be placed [John & Wenz 2004]. A healing time of 6 months before implant placement is recommended for BioOss®. With regard to our study, we were not allowed to compare BioOss® in combination with stem cells to treatment with BioOss® alone because the ethics committee did not allow biopsy and implant placement after 13–16 weeks in a BioOss®-only group. Adding mononuclear cells derived from a non-mineralized tissue aspirate to BioOss® has been shown to result in bone-forming kinetics comparable with autogenous bone alone [Schmitt et al. 2008]. In our study, 3.8 months after treatment all mixtures (control and test group) showed more new bone formation than other studies after a healing period of 6 up to 9 months in which patients were treated with BioOss® alone [Hallman et al. 2002; Froum et al. 2006]. Furthermore, our results are comparable with those achieved with BioOss® alone at later healing time points, 6–8 months [Froum et al. 2006]. In the latter randomized, controlled investigation, the authors histomorphometrically evaluated the formation of vital bone following bilateral grafting with two different materials – Puros, a mineralized cancellous bone allograft (MCBA) and BioOss® at 26–32 weeks. Histomorphometric analysis of 10 MCBA cores and nine BioOss® cores revealed an average vital bone content of 28.25% and 12.44%, respectively. Significantly, more bone was formed in the MCBA sites after a healing time of 6 up to 8 months.

The use of a grafting material to perform a sinus lift procedure even may become questionable as a recent study has demonstrated that the mere lifting of the sinus mucosal lining and simultaneous placement of implants also can result in bone formation [Lundgren et al. 2008]. However, currently this technique only is applied for conditions allowing for sufficient primary stability of implants during placement and a sufficient width of the alveolar crest but not for reconstruction in the horizontal and vertical direction, which was not the case in the subjects included in our trial. Moreover, for evidence whether this treatment indeed reliably will result in the induction of bone growth, well-designed studies have to be carried out in the future. Finally, in all our cases we had to both increase the height as to widen the posterior maxillary ridge.

From this study, it is concluded that mesenchymal stem cells derived from an aspirate of the posterior iliac crest seeded on BioOss® particles can induce the formation of a sufficient volume of new bone to enable a reliable placement of implants within a time frame comparable with that of applying either solely autogenous bone or a mixture of autogenous bone and BioOss®. This technique could be an alternative to autografts, in particular by surpassing their inherent donor site morbidity.

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Sinus floor elevation with autogenous stem cells


