Sinus Floor Elevation with Biphasic Calcium Phosphate or Deproteinized Bovine Bone Mineral: Clinical and Histomorphometric Outcomes of a Randomized Controlled Clinical Trial

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Purpose: To clinically and histomorphometrically compare a biphasic calcium phosphate (BCP) and deproteinized bovine bone mineral (DBBM) for sinus floor elevation. Materials and Methods: Sinus floor elevation procedures (lateral window) were performed randomly applying either BCP (test) or DBBM (control). At 6 months, bone biopsy specimens were harvested and dental implants were placed. The proportions of new bone, residual grafting material, and nonmineralized soft tissue were calculated. Four months after implant placement, the prosthetic reconstructions were inserted and the implant survival was assessed. Results: Fifty-one patients were treated; 25 were randomly allocated to the BCP group and 26 to the DBBM group. After 6 months in 50 patients, bone biopsy specimens could be harvested, and a total of 121 implants could be placed subsequently. The histomorphometric analysis revealed a comparable percentage of new bone in both groups (BCP 35.9%, DBBM 35.4%; P > .05). The remaining grafting material was significantly lower with BCP (25.3%) compared with DBBM (45.9%; P < .001). Nonmineralized tissue was significantly higher for the BCP group (38.1%) compared with the DBBM group (18.2%; P < .001). The implant survival rate at loading was assessed at the level of the patients (96.0% for BCP and 88.8% for DBBM; P > .05) and at the level of the implants (96.9% for BCP and 94.7% for DBBM; P > .05). Conclusion: Grafting with DBBM or BCP showed similar percentages of new bone 6 months after sinus floor elevation. Implant survival presented no significant difference until loading. Int J Oral Maxillofac Implants 2020;35:1005–1012. doi: 10.11607/jomi.8211

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Maxillary sinus floor elevation to allow the placement of endosseous implants has become a standard surgical procedure with reliable long-term results, both in clinical1–5 and experimental studies.6–8 Various grafting materials have been proposed for this kind of bone augmentation procedure.

Autogenous bone grafts (autografts) have been recommended for the purpose of acting as an osteoinductive and osteoconductive scaffold.9 In order to avoid the necessity for a second site to harvest the autogenous bone and to reduce postsurgical morbidity, bone graft substitutes were later introduced. These materials can be classified as follows: allografts (from the same species, human, but different individuals), xenografts (from different species, usually from bovine origin), and alloplastic materials (synthetic origin).4

Deproteinized bovine bone mineral (DBBM) is one of the most commonly used and documented bone substitute materials in dental surgery.4,10 The combination of DBBM and resorbable collagen membranes has been found to be effective for bone augmentation in situations where dental implants are placed.11–13 DBBM materials have also been intensely investigated for sinus floor elevation, revealing excellent long-term results.3 However, despite its good osteoconductive proprieties, DBBM does not present osteoinductive potential.14

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As an alternative, alloplastic materials can be used. Biphasic calcium phosphate (BCP), consisting of hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP), showed similar bone changes to standard graft material in a 60:40 ratio. At the same time, these allografts revealed a higher resorption rate during new bone formation. Nevertheless, the subsequently placed implants present excellent survival and success rates.

A new second generation of BCP has been developed with a 10:90 HA/TCP ratio and controlled microporosity (mean micropore diameter 1 μm), which may have an important influence on the osteoconductivity of calcium phosphate ceramics. This material has demonstrated high biocompatibility and osteoconductivity, as well as osteoinductive potential. Despite the promising preclinical studies, there is still very little data available on humans.

The aim of the present trial was to clinically and histomorphometrically analyze a second-generation BCP and DBBM 6 months after a sinus grafting procedure.

MATERIALS AND METHODS

Study Design
This study was designed as a multicenter, randomized controlled clinical study conducted at the Clinic of Restorative Dentistry, University of Zurich, Zurich, Switzerland, and in a private practice, Center of Implantology, Periodontology and 3D Head-and-Neck Imaging, Konstanz, Germany.

The clinical study protocol and all materials and procedures were approved by the respective local ethical committees (KEK-ZH-Nr. 2014-0478; F-2013-086-z). Prior to the start of the investigation, informed consent was obtained from all patients. The study was independently, externally monitored to ensure consistency and accuracy.

Subjects
Generally healthy female and male subjects, who were at least 18 years of age, with a need for either unilateral or bilateral sinus floor elevation procedures to place one or more dental implants (staged approach), were recruited.

The following further inclusion criteria were applied:

- 2 to 4 mm of residual bone height, measured on a recent available radiograph (panoramic radiograph or CBCT scan, < 12 months old)
- Adequate oral hygiene (full-mouth Plaque Index < 25%)25
- Adequate inflammation control (full-mouth bleeding on probing ≤ 25%)26
- Sinus floor elevation: defects of the sinus membrane.

The defined exclusion criteria were the following:

- General contraindications for bone grafting and oral surgical procedures
- Local contraindications (eg, sinus anomalies)
- Untreated periodontitis
- Participation in other investigational drug or device studies 30 days prior to or during the conduct of the present trial
- Antibiotic therapy within 28 days prior to sinus floor elevation
- History of drug or alcohol abuse
- Smokers (> 10 cigarettes per day)
- Current pregnancy or breastfeeding

Also, there was a secondary exclusion criterion during the sinus floor elevation: defects of the sinus membrane.

Clinical Protocol
Sinus Floor Elevation Procedure. Preoperatively, patients received antibiotics and analgesics/antiphlogistics depending on the standard of care of the clinical study center. Furthermore, they rinsed with 0.2% chlorhexidine solution for 1 minute. The surgical procedure was performed using the lateral window technique, under local anesthesia.

First, a mucoperiosteal flap was elevated and a bony window was created on the lateral wall of the maxillary sinus using rotary as well as piezoelectric instruments. The sinus membrane was then carefully elevated. In case of a membrane defect, the patient was excluded from further participation in the study (secondary exclusion criterion).

At this point in time, a sealed randomization envelope was opened to allocate the sinus to either one of the two following grafting materials:

- Test group: BCP, HA/TCP 10:90 (Straumann VivOss, Institut Straumann)
- Control group: DBBM (Bio-Oss, Geistlich)

In cases with augmentation of both sinuses, one sinus was randomized as the study sinus. If the sinus was randomized into the test group, the opposite sinus was augmented with DBBM and vice versa.

The selected bone substitute material was used for grafting the obtained space beneath the elevated mucosa. In both treatment groups, the bony window was then covered with a resorbable collagen membrane (Bio-Gide, Geistlich), followed by a tension-free flap closure using nonresorbable sutures.

Patients were instructed to rinse twice a day until suture removal with 0.2% chlorhexidine solution and...
received antibiotics (750 mg amoxicillin or 300 to 600 mg clindamycin, 3 times a day, for 6 days). Analgesics were prescribed (50 mg diclofenac, max 150 mg a day, or 400 mg ibuprofen, max 1,200 mg a day).

After a healing time of 1 to 2 weeks, sutures were removed, and the wound healing was assessed (“very good,” “good,” “normal,” or “impaired”).

**Implant Placement.** After a healing time of 6 months (± 7 days), implant placement was performed.

Prior to surgery, patients rinsed with 0.2% chlorhexidine solution for 1 minute. Under local anesthesia, a mucoperiosteal flap was elevated. The implant bed preparation was performed first by means of a trephine bur with an inner diameter of 2.8 mm, in such a way that a bone biopsy specimen could be harvested at the same time. Dental implant placement (Straumann Dental Implant System, SLActive, Institut Straumann) was then completed according to the standard procedure of the clinic. The flap was closed tension-free with nonresorbable sutures. Analgesics (diclofenac, max 150 mg a day or ibuprofen, max 1,200 mg a day) and a 0.2% chlorhexidine solution (twice a day, until suture removal) were prescribed. After a healing time of 1 to 2 weeks, the sutures were removed and the wound healing was evaluated (very good, good, normal, or impaired).

Four months after implant placement, the implants were initially loaded, and the survival as well as the success rates (according to Buser et al27) were evaluated.

**Outcome Measures**

**Histomorphometry.** The primary outcome was the calculated ratio of new bone to remaining grafting material out of the histomorphometric analysis.

**Implant Survival and Success.** The secondary outcome measures were implant survival and success, which were assessed at implant loading (4 months after implant placement).

Implant success was defined using the following criteria (according to Buser et al27):

- Absence of persisting subjective discomfort, such as pain, foreign body perception, and/or dysesthesia (painful sensation)
- Absence of a recurrent peri-implant infection with suppuration (where an infection is termed recurrent if it is observed at two or more follow-up visits after treatment with systemic antibiotics)
- Absence of implant mobility on manual palpation
- Absence of any continuous peri-implant radiolucency

**Statistical Analysis**

Sample size calculations were performed for a clinically relevant difference between the test and comparator across a given range of standard deviations, with the two-sided unpaired t test under a significance level of 5% and with a power of 80%. Based on preclinical data, a difference of the means of the ratio of new bone to remaining grafting material of approximately 0.4 was expected in favor of the test treatment compared with the control. In order to show superiority, considering a common standard deviation of 0.5, 25 subjects per group were considered necessary to confirm a clinically relevant difference statistically.

**RESULTS**

A total of 56 (66% female and 34% male) patients with a mean age of 59.3 (± 10.8) years were enrolled in the two study centers (Zurich: 27; Konstanz: 29). One patient was excluded because he did not fulfill the inclusion criteria. Four further patients were excluded during the sinus floor elevation procedure because they presented defects of the sinus membrane (3 cases) or missing crestal bone (0 mm residual vertical height, 1 case). This resulted in 51 patients receiving a grafting material in the study maxillary sinus: 25 BCP (test group) and 26 DBBM (control). In addition, 15 patients were qualified for bilateral treatment, and the contralateral sinus was grafted with the opposite material. At the point in time of the sinus floor elevation, the mean residual bone height was 3.7 ± 1.4 mm in the BCP group and 3.9 ± 1.8 mm in the DBBM group. The difference between the groups was not statistically significant \( (P = .64)\).
During the healing period, one patient in the control group was excluded from further participation in the study because he refused to pay for the treatment.

No difference in the wound healing could be observed between the test and control ($P = .94$).

Six months after sinus floor elevation (6.1 ± 0.4 months overall; 6.2 ± 0.4 BCP group, 6.1 ± 0.4 DBBM group), 50 patients received a total of 121 primary stable implants. During implant bed preparation, 87 biopsy specimens were harvested (Figs 1 to 3), of which 62 could be analyzed histomorphometrically (29 in the test group and 33 in the control group).

Histomorphometry

The ratio of new bone (%) to bone grafting material (%) was calculated (Table 1). In a nonparametric significance test, the median ratio in the BCP group (1.38) was significantly higher compared with the median ratio in the DBBM group (0.67; $P < .001$). Mean values, due to the large standard deviation of BCP, were not significantly different (DBBM: 0.86 ± 0.45 vs BCP: 3.48 ± 6.76; $P = .064$).

The mean proportions of newly formed bone as well as bone graft materials and nonmineralized tissue are reported in Fig 4. New bone was comparable in both treatment groups (BCP 35.9% vs DBBM 35.4%; $P = .845$). Remaining bone grafting material was significantly lower with BCP (25.3%) compared with DBBM (45.9%; $P < .001$). The mean proportion of nonmineralized tissue in the biopsy specimens was instead significantly higher for BCP (38.1%) compared with the DBBM group (18.2%; $P < .001$).
Subgroup “Bilateral”
Bilateral sinus floor elevation was performed in 15 patients (30%). In these cases, a split-mouth design was applied. The mean proportion of new bone was not statistically significantly different between the two groups (BCP 32.6%, DBBM 28.1%; \( P = .123 \)). Remaining bone grafting material was significantly lower with BCP (24.5%) compared with DBBM (42.6%; \( P = .001 \)), while nonmineralized tissue was instead significantly higher for the BCP group (42.2%) compared with DBBM (28.9%; \( P = .003 \)).

The ratio of new bone compared with bone grafting material for this subgroup is reported in Table 2. The outcome is comparable to that of the entire cohort: The median ratio in the BCP group (1.37) was significantly higher compared with the median ratio in the DBBM group (0.59) (\( P = .017 \)). The parametric comparison of means failed to show statistical significance (\( P = .106 \)).

Implant Survival/Success
After implant surgery, no difference in wound healing could be observed between groups (\( P = .92 \)).

Implants were loaded after 5.6 ± 2.9 months (5.8 ± 3.2 BCP group, 5.4 ± 2.6 DBBM group) of healing. Out of 121 placed implants in 50 patients, 5 implants in 4 patients were lost before loading (early failures, 3.2 ± 1.5 months after placement). On the patient level, the overall implant survival rate was 92.3% (CI: 81.3 to 97.5). One patient receiving two implants in a test site lost both implants 3 weeks after insertion. In two cases, two implants were inserted into control sites; both patients lost one of these implants 3 months afterward. In another control case, an implant was lost 4 months after placement; the implant was the only one inserted (in the same region). The resulting survival rate for the test group was 96.0% (CI: 78.9 to 99.9), and for the control group, it was 88.8% (CI: 69.2 to 96.7).

On the implant base, the overall implant survival rate was 95.9% (CI: 90.4 to 98.5): 96.9% (CI: 88.7 to 99.8) for the test group and 94.7% (CI: 85.1 to 98.8) for the control group. No significant difference could be observed between the treatment groups, either patient-based or implant-based.

At loading, all implants (100%) were considered successful (according to Buser et al\(^2\)).

DISCUSSION
The present randomized controlled clinical study showed (1) no statistically significant difference in new bone formation between test and control groups 6 months after sinus floor elevation and (2) similar survival and success of implants placed in primary augmented sinuses after a healing period of 4 months.

The significant difference of BCP over DBBM in the ratios of new bone to bone grafting material was mainly due to the higher proportion of nonmineralized tissue (BCP 38.1% vs DBBM 18.2%) and lower percentage of remaining bone grafting material (BCP 25.3% vs DBBM 45.9%) in the BCP group, whereas newly formed bone was similar in both groups (BCP 35.9% vs DBBM
35.4%). This observation is consistent with the results of another randomized clinical trial comparing BCP with DBBM.\textsuperscript{15} In that particular study, both groups showed similar amounts of newly formed bone 6 months after augmentation (BCP 21.6% vs DBBM 19.8%), but significantly less remaining bone grafting material in the BCP group (BCP 26.6% vs DBBM 37.7%) and more soft tissue components (BCP 46.47% vs DBBM 40.4%). Another randomized controlled investigation performed a histomorphometric comparison of vital bone formation, 6 to 8 months after bilateral sinus grafting with either BCP or DBBM.\textsuperscript{17} Similar to the present study, biopsy specimens showed no significant difference in the average vital bone content (BCP 28.4% vs DBBM 22.3%). The residual graft particles were on average 28.4% in the BCP and 26.0% in the DBBM biopsy specimens, showing no statistically significant difference as well. Moreover, two recent systematic reviews confirmed the nonsignificant difference in the amount of newly formed bone after sinus floor elevation with synthetic bone substitutes vs xenografts.\textsuperscript{28,29}

As mentioned earlier, in the present investigation, BCP showed a lower percentage of remaining bone grafting material compared with DBBM. Similar results were also presented by other clinical trials.\textsuperscript{15,16} This could be explained with a higher resorption resistance of bovine bone substitutes, which has already been described in the literature.\textsuperscript{30–33} Consequently, the remaining integrated DBBM particles may contribute to the long-term volume stability of the augmented maxillary sinus. However, the clinical relevance of the remaining bone graft material is still questionable, since systematic reviews could not show any difference in implant treatment outcomes.\textsuperscript{4,28}

In this clinical investigation, a new BCP was used with an HA/TCP ratio of 10:90. This composite grafting material is similar to BCP 60:40 regarding the particle size, which varies between 500 and 1,000 \( \mu \text{m} \) for both compositions (in comparison, DBBM is 250 to 1,000 \( \mu \text{m} \)). However, the materials are different, not only in the HA/TCP ratio, but also in the preparation processes. In particular, variation of the sintering temperature could be explained with a higher resorption resistance of the materials, are different, not only in the HA/TCP ratio, but also in the preparation processes. In particular, variation of the sintering temperature and, in some cases, possibly compromise the osseointegration. One may also speculate that the lack of autogenous bone mixed with the bone substitute material may decelerate the new bone formation and, in some cases, possibly compromise the osseointegration. In order to support this speculation, an animal study including 40 minipigs showed significantly lower bone-to-implant contact 12 weeks after sinus floor elevation using DBBM alone, compared with autogenous bone in combination with DBBM.\textsuperscript{36} In contrast, a systematic review including only clinical studies comparing grafting with DBBM alone and DBBM mixed with autogenous bone (AB) revealed no statistically significant difference in the 1-year survival rates of the implants (DBBM 96% vs DBBM/AB 94%). Further, the addition of approximately 20% of autogenous bone to DBBM (80%) seemed not to improve new bone formation and bone-to-implant contact.\textsuperscript{37}

The short follow-up until implant loading can be considered the main limitation of the present
investigation. The main focus and primary outcome of the study were, however, linked to human bone biopsies and the histomorphometric analysis. Early failures during the healing phase after implant placement were also detected. However, no data have been collected on the stability of marginal bone and implant survival/success after loading. Considering the available data in the literature, comparable marginal bone levels as well as implant survival should be expected for both groups over time. Nevertheless, the clinical significance of the different soft tissue and remaining grafting material proportions on the long-term outcome cannot be evaluated.

CONCLUSIONS

Sinus floor elevation with DBBM or BCP (10:90) for staged implant therapy showed similar percentages of new bone 6 months after sinus floor elevation. No significant difference in implant survival and success until loading could be observed. Therefore, at least for an observation period of 6 months, BCP represents a valid synthetic alternative to DBBM for sinus floor elevation. The impact of different proportions of soft tissue and residual bone substitute material on the long-term implant outcome remains unknown.

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