Histomorphometric Results of a Randomized Controlled Clinical Trial Studying Maxillary Sinus Augmentation with Two Different Biomaterials and Simultaneous Implant Placement

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**Purpose:** Maxillary sinus augmentation has been a predictable procedure. However, in-depth analysis of tissue healing after sinus grafting with simultaneous implant placement is limited. This study aimed to compare histologic outcomes after sinus grafting with a synthetic bone graft compared with a xenograft. **Materials and Methods:** A randomized controlled split-mouth study was conducted to compare bone formation around microimplants (2.00 mm, Dentium) placed at the time of maxillary sinus augmentation with a synthetic material (Osteon, Dentium) (OST) and deproteinized bovine bone (Bio-Oss) (BIO) as the control group. Four microimplants per subject (n = 13) were placed bilaterally for intrasubject comparison (two implants per side/patient). Bone cores with osseointegrated microimplants were harvested for histomorphometric analysis 6 to 8 months after sinus augmentation surgery. **Results:** Histologic analysis revealed newly formed bone deposited on the microimplant surface and bridging to bone graft material in both groups. Further, there was no histologic evidence of signs of inflammation in all specimens. In general, bone-to-implant contact was comparable and ranged from 6.1% to 67.0% with a mean of 38.4% ± 11.61% in OST and from 10.5% to 57.0% with a mean of 34.58% ± 12.55% in BIO. However, a significantly higher percentage of bone-to-implant contact in the first four threads of the grafted area was noted in OST compared with BIO (P = .016). **Conclusion:** The synthetic OST was found to be equivalent to BIO in new bone formation and clinical success after sinus augmentation in conjunction with microimplant placement. Although there are some statistically significant differences in the histologic outcomes, the clinical relevance of these needs to be further evaluated. Nevertheless, the findings of this study indicate that this synthetic alloplast would be a viable alternative to an allograft material. Int J Oral Maxillofac Implants 2018;33:1320–1330. doi: 10.11607/jomi.6778

**Keywords:** allografts, dental implants, sinus floor augmentation, treatment outcome, xenografts

Maxillary sinus augmentation is a procedure that aims to increase bone height of the height-deficient maxillary edentulous ridge before dental implant placement. Currently, implants placed in sites that underwent sinus augmentation show high survival rates and stable alveolar bone level over a 3-year follow-up.\textsuperscript{1} During maxillary sinus augmentation, the membrane that lines the maxillary sinus cavity (sinus membrane) is elevated from its bony surface to create space that is filled with bone replacement.

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materials to increase alveolar bone height. Different bone materials such as autogenous bone, allografts, xenografts, and alloplasts can be used for the procedure.1–3 Initially, autogenous bone was used as the most common sinus grafting material.4 Implants that were placed in augmented sites had predictable histologic5,6 and clinical outcomes.7,8 However, the need for a second surgical site prolongs the surgical intervention and increases risk and postsurgical morbidity, since healing is required in multiple sites. Therefore, alternative graft materials such as allografts, xenografts, and alloplasts have recently been used to avoid drawbacks associated with harvesting autogenous bone. Specifically, xenografts have been a commonly used material due to low resorbability9,10 and their ability to maintain bone height in the augmented sinus sites.

Bio-Oss (Geistlich Pharma) is a frequently used xenograft for sinus augmentation procedures utilizing the lateral window technique.11,12 It is a deproteinized bovine bone mineral (DBBM) that is a calcium-deficient carbon apatite and possesses osteoconductive properties.13,14 Numerous animal and clinical studies have shown that it can provide reliable treatment outcomes in sinus augmentation procedures.10,15–17 Although Bio-Oss products are processed following a high standard safety protocol, there might still be remaining safety issues due to its bovine origin.18,19 Additionally, some patients might not accept grafting materials made of animal bone because of their religious beliefs and personal preferences.20,21 Therefore, synthetic alloplasts have been studied widely over the past years.22–24 They can be fabricated in unlimited quantity with controlled quality and are without the risk of disease transmission. Overall, the use of alloplasts in sinus augmentation procedures has shown promising histologic results and implant survival rates.22,25,26 Osteon (Dentium, USA) is a biphasic calcium phosphate alloplast composed of hydroxyapatite scaffolds (HA, 70%) and coated with β-tricalcium phosphate (TCP, 30%).27 HA, with a low resorbability, could serve as a scaffold for bone formation by retaining its augmented volume. TCP as an outer layer dissolves relatively fast and releases calcium and phosphorous during dissolving, which are both suggested to stimulate bone formation.28

Depending on the height of the residual ridge, implants can be placed simultaneously at the time of sinus augmentation or in a second step at a later time point. However, there is only limited information from human histologic studies about bone formation and remodeling around implants placed simultaneously in an augmented sinus.29,30 This could be partially due to ethical problems that arise when retrieving osseointegrated regular-sized dental implant for histologic analysis. Therefore, retrievable microimplants that present with the same surface characteristics (sandblasted, large-grit, acid-etched [SLA]) as regular-sized implants have been used as a substitute for evaluating the impact of different bone grafting modalities and implant surface topographies.30,31 Although microimplants were placed for research purposes in this study, microimplants have been successfully used as transitional or permanent implants to support dental prostheses. Therefore, histologic outcomes around microimplants can be representative of the biologic healing phase of regular-sized implants.32

The present study aimed to systematically evaluate bone formation and remodeling around microimplants placed at the time of sinus augmentation with two different biomaterials, DBBM (Bio-Oss) and biphasic calcium phosphate material (Osteon). This is the first study comparing the histologic outcomes of these two materials after being used in a sinus augmentation procedure with simultaneous implant placement.

MATERIALS AND METHODS

Study Population and Subject Selection

The study was registered (ClinicalTrials.gov Identifier: NCT02174198) and conducted following the CONSORT guidelines. It was approved by the Institutional Review Board of Columbia University Medical Center. Subjects were recruited from patients who presented to the Division of Periodontics, College of Dental Medicine, Columbia University and wanted to have maxillary posterior implants requiring bilateral sinus augmentation surgery prior to implant placement. Subjects participating in the study provided written informed consent and agreed to participate throughout the entire study period.

Only subjects 18 years of age or older were included in the study. Subjects were selected to participate when future implant sites had at least 6 mm of buccal-palatal crestal bone width as determined by cone beam computed tomography (CBCT). The CBCT scan was taken prior to enrolling the patient in the study as part of the standard procedure for surgical treatment planning.

There were generally no limitations by sex, race, ethnicity, or health status of the subject except those listed under the exclusion criteria. Exclusion criteria for participants included the following: subjects with the need for antibiotic prophylaxis for subacute bacterial endocarditis or late prosthetic joint infection; patients with chronic or acute sinus problems and sinus pathology contraindicating the graft procedure (i.e., oral anterior fistula, purulence, evidence of sinus polyps); patients who smoke more than 10 cigarettes per day; patients with uncontrolled or poorly controlled diabetes or subjects...
with other uncontrolled metabolic diseases; women of childbearing age who expressed the intent of becoming pregnant during the course of the study and were pregnant or nursing a child; and patients who cannot undergo a standard oral surgery procedure for any reason.

Study Design and Randomization
A randomized, controlled split-mouth study design was applied to compare bone formation around microimplants (2 × 10 mm implant, Dentium) with a SLA surface placed at the time of maxillary sinus floor augmentation. The microimplants are designed for clinical use and have the same implant surface and topography as the regular-sized implants that were used for permanent restorations in the present study. Sinus augmentation was performed with a small particle size (0.5 to 1.0 mm) synthetic material (Osteon, Dentium) (OST) on one side and a small particle size (0.25 to 1.0 mm) deproteinized bovine bone (Bio-Oss) (BIO) as the control group for the other side.

The primary outcomes of the study were percentage of bone-to-graft contact, and the secondary outcomes were bone-to-implant contact (BIC). The hypothesis was that there would be a difference between study and control material in these parameters.

Sample Size Calculation
According to a published study by Lindgren et al, the presence of contact between newly formed bone and remaining particles is $87.9\% \pm 18.2\%$ after grafting with bovine bone versus $53.9\% \pm 26.1\%$ after grafting with an alloplast. In order to detect a difference of $10\%$ with a power of $80\%$ at a significance level of .05 between control and study material, the study had to include at least 11 patients. Thirteen patients were enrolled to compensate for potential study dropouts.

Study Procedures
Bilateral maxillary sinus augmentation was performed in all patients using the lateral window approach (Fig 1). On the date of surgery, patients took 2,000 mg amoxicillin 1 hour prior to surgery. Patients allergic to amoxicillin received 600 mg of clindamycin 1 hour prior to surgery. Appropriate local anesthesia was administered before the start of the surgery. Depending on the patient medical history, operator preference, and/or surgical circumstances, the following may have been used: Lidocaine HCL 2% with 1:100,000 epinephrine, Lidocaine HCL 2% with 1:50,000 epinephrine, Mepivacain/Carbocaine 3% without epinephrine. Crestal and vertical incisions were made, and a full-thickness flap was elevated to expose the lateral wall of the sinus. A hinge or complete osteotomy of the lateral sinus wall was prepared (Fig 1a). The sinus membrane was raised from the bony floor of the maxillary sinus (Fig 1b). If the bony window was removed to facilitate elevation of the membrane, it was not added to the grafted bone.

OST and BIO were placed in the right or left subantral compartment depending on the randomization.
results using coin toss. Depending on the sinus anatomy, an appropriate amount of material was placed in each sinus. Site preparation and placement of microimplants (two per side) were done after elevating the sinus membrane and placing part of the grafting material. Microimplants were placed in the position of future dental implants (Fig 1c), and additional graft material was placed to complete augmentation (Figs 1d to 1f). Depending on the patient and complexity of the surgery, both sinuses were treated at the same time or in two consecutive appointments that were 3 weeks apart.

A synthetic resorbable collagen membrane (Collagen Membrane, GENOSS, Dentium USA) was hydrated for a few minutes in sterile saline prior to being placed over the lateral sinus window. It has been shown that covering the bony window with a membrane can improve bone growth inside the augmented sinus and clinical outcomes.34 The membranes were extended 3 mm beyond the limits of the prepared window and pressed against the bone without screw fixation. Primary closure of the flap was achieved with resorbable sutures (Chromic or polyglactin 910 [Vicryl]) (Figs 1g and 1h). The provisional fixed or removable prosthesis was relieved over the edentulous area to allow for undisturbed healing.

The subjects were placed on an appropriate analgesic, for instance, Tylenol with Codeine #3 or #4, Vicodin 500/5 mg, 1-2 tab; or Motrin 600 mg Q 6H as needed. Antibiotics were also prescribed: 875 mg Augmentin twice a day for 1 week, Azithromycin 500 mg once a day on the first day followed by 250 mg once a day from the second day to the fifth day after surgery, or clindamycin 300 mg three times a day for 1 week when the patient was allergic to penicillin. Mouthrinses with 0.12% chlorhexidine gluconate twice a day for 2 weeks were prescribed. An over-the-counter decongestant (ie, Sudafed) was sometimes prescribed following surgery to prevent nasal congestion. Sutures were removed 7 to 14 days postsurgery as part of regularly scheduled clinic visits for sinus augmentation surgery.

Six to eight months after sinus augmentation (Fig 2), patients had a second CBCT scan taken to evaluate bone height of the grafted sites and to plan final implant placement. Trephine burs were used to retrieve the microimplants and surrounding bone for histologic analysis. Afterward, final implants (diameter: 4.0 to 6.0 mm; length: 10 to 12 mm, Dentium) were placed to replace the microimplants (Fig 3). Antibiotics were prescribed following the same protocol used in the sinus augmentation procedure. Rinses with 0.12% chlorhexidine gluconate twice a day for 2 weeks were also prescribed. Sutures were removed 7 to 14 days after surgery.

Implants were loaded 2 to 4 months after placement and restored with fixed prostheses that were splinted together.

**Processing of the Harvested Specimens**

The specimens (microimplant and surrounding bone core) were harvested and placed in 10% neutral buffered formalin to be sent to the histologic laboratory. Upon receipt, implant, bone, and soft tissue specimen were sectioned vertically in an anterior/posterior (mesial/distal) orientation according to protocol specifications. Immediately after sectioning, specimens were dehydrated with a graded series of alcohols for 9 days. Following dehydration, the specimens were infiltrated with a light-curing embedding resin (Technovit 7200 VLC, Kulzer). After 20 days of infiltration with constant shaking at normal atmospheric pressure, the specimens were embedded and polymerized by 450 nm light with the temperature of the specimens never exceeding 40°C. The specimens were then prepared by the cutting/grinding method of Donath and Breuner.35,36 The specimens were cut to a thickness of 150 µm on an EXAKT cutting/grinding system (EXAKT Technologies) and then polished to a thickness of 45 to 65 µm using a series of polishing sandpaper discs from 800 to 2,400 grit using an EXAKT micro-grinding system followed by a final polish with 0.3 micron alumina polishing paste. The slides were stained with Stevenel’s blue and Van Gieson’s picro fuchsin and cover-slipped for histologic analysis by means of bright field and polarized microscopic evaluation.

**Histomorphometric Analysis**

Histomorphometric analysis was performed by an independent examiner who did not know the site-specific randomization codes. As shown in Fig 4,
percentage of vital bone, percentage of graft, percentage of marrow space, and percentage of implant surface in direct contact with bone were measured in all histologic sections.

Area Around the Implant
The percentages of vital bone, marrow or fibrous tissue, and graft material were assessed in the whole trephined bone core excluding the microimplant (TImpC). The respective tissue components were calculated as a percentage of the whole block. Percentage of contact of bone graft to vital bone tissue in a linear relationship was analyzed in two randomly placed 8,281 pixel² boxes (CB) that were positioned in the grafted area by an independent examiner (Fig 4a).

Area Contacting Implant
The percentage of implant surface in direct contact with bone (bone-to-implant contact [BIC]), marrow tissue (marrow-to-implant contact [MIC]), and connective tissue (connective tissue-to-implant contact [CTIC]) were evaluated in the following region: total implant length (TIL) of microimplants, the first four threads at the most coronal aspect starting from the grafted area (4T), and the two threads (2T) apical to 4T. 2T was used to represent the center part of the grafted area (Fig 4b).

Data Analysis and Statistics
Summary statistics (means ± standard deviations [SD], standard error [SE]) were calculated for all measured variables in each group. Each patient served as its own control; therefore, the Wilcoxon signed rank test (paired) was used to evaluate parameters in between the control and test sites (Fig 5 and 6 and Tables 1 and 2). Further, the Mann-Whitney U test (unpaired) was used to calculate differences in the percentage of bone-to-graft linear contact. Pearson correlation coefficient was used to check for dependencies between the parameters. Differences between groups were considered statistically significant at $P < .05$.

RESULTS

Subject Characteristics and Description of the Harvested Samples
Thirteen partially maxillary edentulous patients (five women, eight men) with a mean age of 60.6 years (range: 39 to 79 years), including seven Caucasians, four Hispanics, one African American, and one other, were included in the study (Table 3). These patients were treated from 2012 to 2016. As determined on the CBCT scans, the mean initial crestal bone height was 4.32 ± 2.29 mm at the OST side and 3.90 ± 1.86 mm.
at the BIO side ($P = .75$). Six to eight months after augmentation, the mean bone height was 15.12 ± 1.94 mm and 14.69 ± 2.32 mm ($P = .80$), respectively.

As shown in Fig 7, a total of 49 specimens were available for histologic evaluation. Fifty-two microimplants had been placed; one microimplant failed during early healing because of a local infection, and one was determined to be a failure at the re-entry surgery showing fibrous encapsulation. Both microimplants were from the OST group and had been exposed during the healing phase. Among the successfully integrated 50 microimplants, 20 microimplants showed exposed platforms at the time of retrieval while other implants were completely covered by gingiva (OST: 10 exposed, 14 covered; BIO: 10 exposed, 16 covered).

**Table 1** Mean ± SD Percentage of Bone, Marrow/Fibrous Tissue, and Remaining Bone Graft Material in TImpC in OST and BIO Groups

<table>
<thead>
<tr>
<th>Percentage of tissue component in TImpC</th>
<th>OST</th>
<th>BIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>13.35 ± 4.01</td>
<td>13.35 ± 4.83</td>
</tr>
<tr>
<td>Marrow/fibrous tissue</td>
<td>76.74 ± 5.58*</td>
<td>80.30 ± 5.13*</td>
</tr>
<tr>
<td>Graft</td>
<td>10.13 ± 3.68**</td>
<td>6.17 ± 3.73**</td>
</tr>
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</table>

TImpC = total implant core.  
* $P \leq .05$; ** $P \leq .01$; n = 23 in OST and BIO.
One bone core could not be used for histologic analysis since it became separated from the microimplant during the harvesting procedure (OST group—microimplant covered).

Bone Formation and Graft Resorption After Maxillary Sinus Augmentation

None of the analyzed cores showed histologic evidence of signs of inflammation (Fig 8). To evaluate bone formation and graft resorption in the two respective groups (OST and BIO), hard and soft tissue components in histologic sections were analyzed. As outlined in Fig 4a, TImpC describes tissue components starting at the crest and including the whole grafted area. Comparing OST with BIO, a similar percentage of bone was detected. However, there was significantly less marrow and fibrous tissue and more remaining graft material in the OST group (Fig 5; Table 1). Then, the total linear bone-to-graft contact in boxes (CB) that had been randomly selected in the grafted area was evaluated to determine how graft particles had been embedded and connected to newly formed bone. As shown in Fig 9, OST and BIO cores showed comparable bone-to-graft contact (OST 28.44% ± 13.97% vs BIO 27.41% ± 14.15%, P = .84).

Tissue Components Around Integrated Microimplants

In the second part of the histomorphometric analysis, soft and hard tissue around microimplants that had been placed at the time of maxillary sinus augmentation were analyzed. All microimplants showed initial stability after placement. The measurement TIL, total

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Medical history</th>
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<tr>
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<td>F</td>
<td>Caucasian</td>
<td>Arthritis, hyperacidity</td>
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<tr>
<td>2</td>
<td>76</td>
<td>F</td>
<td>Caucasian</td>
<td>HTN, ankle replacement, hypercholesterolemia, basal cell carcinoma, allergic to levofloxacin and codeine</td>
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<tr>
<td>3</td>
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<td>Asthma, hay fever</td>
</tr>
<tr>
<td>4</td>
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<td>Healthy</td>
</tr>
<tr>
<td>5</td>
<td>79</td>
<td>M</td>
<td>Hispanic</td>
<td>HTN, angina, colon cancer, allergy to sulfa drugs</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>M</td>
<td>Other</td>
<td>Healthy</td>
</tr>
<tr>
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<td>13</td>
<td>36</td>
<td>M</td>
<td>Caucasian</td>
<td>Healthy</td>
</tr>
</tbody>
</table>

HTN = hypertension.

**Table 3** Subject Characteristics

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The length of microimplant, provides detailed information about the direct contact of different tissues to the implant surface in both native bone and the grafted bone area. As shown in Figs 4b and 6 and Table 2, there is no significant difference between OST and BIO in all measured components that were analyzed in TIL. As a result, BIC ranged from 6.1% to 67.0% with a mean of 38.4% ± 11.61% in OST and from 10.5% to 57.0% with a mean of 34.58% ± 12.55% in BIO. Since bone formation after grafting of the maxillary sinus proceeds from the surrounding native bone,37 BIC in the 4T versus the 2T area was further evaluated to understand more about speed and pattern of tissue maturation. 4T, the first four threads within the most coronal aspect of the grafted area, reflects bone formation at the junction of native bone and the grafted area; and 2T, the two threads apical to 4T, was used to represent a more central part of the grafted area. When comparing 4T and 2T within the same bone graft group to evaluate whether there were differences between the respective areas, there was a trend of having a higher percentage of BIC in 4T; however, the difference was not statistically significant (OST—4T: 54.56% ± 15.38%, 2T: 47.32% ± 17.50%, P = .11; BIO—4T: 43.81% ± 19.39%, 2T: 40.34% ± 17.30%, P = .18). The results suggest that healing at the coronal and center part of the grafted area, regardless of the materials used, was not homogeneous given bone formation after grafting of the maxillary sinus proceeds from the surrounding native bone.

Additionally, the different material groups using 4T and 2T measurements were compared. A significantly higher BIC in 4T in the OST group with a significantly lower percentage of MIC compared with BIO was detected (Fig 6 and Table 2). The more apically located 2T measurement revealed only a trend of having higher BIC and lower MIC measures in the OST group compared with BIO (Fig 6 and Table 2).

It has been shown that initial bone height is positively associated with implant survival38,39 and that age could affect bone healing.40 Therefore, the correlation of age/initial bone height to all the measured variables was determined in the present study.

With regard to age, the results demonstrated a significant correlation between age and the percentage of BIC (r = −0.525, P = .0059) and between age and the percentage of MIC (r = 0.525, P = .0059) in the 2T measurement of the BIO group, whereas initial bone height showed no significant correlation to any of the parameters.

**DISCUSSION**

This is the first randomized controlled split-mouth clinical study comparing a biphasic calcium phosphate alloplast material (Osteon) composed of hydroxyapatite scaffolds (HA, 70%) coated with β-tricalcium phosphate (TCP, 30%) with the bovine bone, Bio-Oss (Geistlich Pharma), commonly used in sinus augmentation procedures.41 Further, the present study also evaluated bone formation around microimplants with a SLA surface placed at the time of maxillary sinus augmentation into the two different biomaterials. Currently, clinical randomized controlled studies about sinus augmentation with simultaneous implant placement into biphasic calcium phosphate materials and subsequent healing outcomes are very limited. At present, there is only one study by Lindgren et al, which, as evident from clinical and histologic results, depicts a successful outcome with the use of an alloplast material that has a 60% HA and 40% TCP content (BoneCeramic, Straumann).29 Other studies described BoneCeramic (Straumann; 60% HA and 40% TCP) as being effective in sinus augmentation.23,24,42 However, these studies only reported the histologic results from bone cores harvested from the grafted sinus without simultaneous implant placement.

In general, the HA/TCP content ratio determines the biologic properties of a biomaterial. It can be
changed to alter its bioactivity and substitution rate during guided bone regeneration and to accommodate different clinical applications.\textsuperscript{43-45} HA and TCP have both osteoconductive properties but with HA showing a lower resorbability.\textsuperscript{46,47} Therefore, HA is commonly used to maintain space that allows for bone ingrowth,\textsuperscript{48} whereas TCP, with its faster degradability, could impact cellular activity by facilitating growth and differentiation of bone-forming osteoblasts.\textsuperscript{37} The study by Lindgren et al\textsuperscript{29} and the present study cannot be directly compared since the authors used different measurement methods and determined different parameters of interest. Nevertheless, both studies demonstrated a higher percentage of BIC in the synthetic bone graft group compared with the xenograft group. In the study by Lindgren et al, the difference in BIC between the BoneCeramic group compared with the BioOss control group did not reach statistical significance. It was hypothesized that based on the results of in vitro and clinical studies, the biphasic calcium phosphate materials that were used in both studies encompass osteoinductive properties and that these grafts might therefore stimulate bone formation at a faster rate than BioOss.\textsuperscript{49-52}

In the present study, the percentage of residual graft within the harvested bone cores was higher in the OST group than in the BIO group (Fig 5). This result is the opposite of the results of two other studies showing that the percentage of remaining biphasic calcium phosphate was lower than the percentage of remaining deproteinized bovine bone.\textsuperscript{24,29} There could be two possible explanations for this observation. First, it is impossible to standardize the amount of graft material that was used for each procedure because every patient had a different degree of sinus pneumatization at the time of surgery. Further, the three-dimensional structures of the graft materials used are different. As a result, the density of the bone material filling inside the sinus might be different and the results therefore inconsistent. Second, the HA content of the biphasic calcium phosphate (Osteon) is higher than in the two other studies.\textsuperscript{24,29} Since the degradability of HA is low, this might increase the chance of remaining graft material.

It has been shown that the rate of bone formation and remodeling after sinus augmentation depends on the spatial location and is more pronounced closer to the previous bone crest.\textsuperscript{53} Therefore, the present study measured the histologic outcomes in different sections contacting the microimplant. When the percentage of BIC was analyzed in the whole core, the measurements were similar in both biomaterial groups. However, when BIC was analyzed only in the grafted area close to the initial bone crest (4T), OST exhibited a significantly higher BIC value than BIO. It has been shown in human and animal studies that TCP might in addition to its osteoconductive properties encompass an osteoinductive potential that can induce bone formation.\textsuperscript{49-51} whereas BIO is characterized as solely an osteoconductive material.\textsuperscript{54} A potential higher bone formation rate in the OST group could, therefore, explain the higher BIC in the area close to the bone ridge. On the other hand, no difference in BIC between BIO and OST in the center of the grafted area (2T) was detected. This might be explained by the relatively short healing time (6 to 8 months) that was available for material degradation and bone maturation in the center of the grafted area since remodeling proceeds away from the natural bone.\textsuperscript{55}

In addition to the material composition, some other variables of graft materials might have caused the differences in the histologic outcomes. It has been shown that a large particle size might improve vital bone growth in sinus augmentation compared with smaller-size particles.\textsuperscript{17} In the present study, the particle size of OST (0.50 to 1.00 mm) was only slightly larger than the particle size of BIO (0.25 to 1.00 mm). However, both are considered to be small-particle-sized bone substitutes (<1 mm) for sinus augmentation surgeries, and the influence of particle size on the histologic and clinical outcome after sinus augmentation is still debatable.\textsuperscript{16}

In the present study, age was found to be negatively correlated to the percentage of BIC in the center of the augmented area (2T) in the BIO group. Increased age is a major risk factor for delayed wound healing.\textsuperscript{56} This could indicate that, assuming bone formation was slower in the BIO group, 6 to 8 months of healing might be sufficient for bone maturation in the younger patients but not for the elders. A potential correlation between age and bone maturation in the OST group might have been overcome by faster bone remodeling and healing within the OST sites; however, this is a hypothesis and needs to be further evaluated.

It has been demonstrated that different grafting materials, including autogenous bone, xenografts, allografts, and alloplasts, do not affect the survival rate of sinus augmentation,\textsuperscript{57,58} although different grafting materials may have different histologic outcomes. Compared with other studies using calcium phosphate or deproteinized bovine bone as the grafting material in sinus augmentation,\textsuperscript{59} the present study showed a similar bone-to-graft contact to other studies but a lower vital bone proportion than other studies. These results should be interpreted with caution since healing time, measurement method, and patient characteristics were different in these studies. It is even more challenging to compare histologic results of the present study to other studies using different materials in sinus augmentation.\textsuperscript{60,61} BIC is an important parameter...
used to evaluate histologic osseointegration. Some preclinical studies showed that autogenous bone graft might improve BIC.62,63 However, the results of BIC in sinus augmentation are rarely reported in human studies,29 and the association between histologic outcomes and clinical outcomes in sinus augmentation needs to be further studied.

The present study was designed as a single center study. Although all subjects fit the selection criteria and surgeries were performed following the study protocol, it is impossible to standardize the degree of sinus pneumatization, the sites of implant placement, and the amount of graft material. Therefore, a study design in which each patient served as its own control was applied to reduce potential biases of different subject characteristics. Bilateral sinus surgeries were performed and the study sites were compared with the test sites within each individual patient, instead of enrolling different patients in a higher number into two different biomaterial groups.

CONCLUSIONS

In this randomized controlled split-mouth clinical trial, histomorphometric analysis demonstrated that OST is comparable to BIO in new bone formation when used in maxillary sinus augmentation in conjunction with simultaneous SLA microimplant placement. Although some histologic measurements were different in the two groups, the clinical relevance of this needs to be further evaluated in future studies.

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REFERENCES


