The present prospective randomized split-mouth trial reports on the 3-year clinical and radiological follow-up investigation of implants placed 7 months after sinus augmentation with 2 different bone substitute materials. The aim of the study was to complete the histologic observation of cellular reactions by analyses of the implants and the volumetric changes of the augmented bone substitute materials. A sinus augmentation split-mouth trial was performed in 14 patients with the synthetic bone substitute material Nanobone (NB) and the xenogeneic Bio-Oss (BO). Changes in volume and density of the augmented biomaterials were investigated by analysis of computed tomography scans, taken immediately after augmentation and after 7 months. Clinical implant parameters were assessed after 3 years of loading. Both bone substitute materials underwent nonsignificant volume reduction and significant increase in bone density over an integration period of 7 months. No significant differences concerning volume and bone density were observed between the groups. Three years after loading, 51 of 53 implants were in situ with no peri-implant infections, and only a few soft-tissue variations were present. The present prospective randomized study showed that no differences could be observed clinically and radiologically. Accordingly, it seems that both biomaterials, independent of their physicochemical composition, enable clinical success and long-time stability for dental implants. Interestingly, the histological results showed distinct differences in cellular reactions: While the xenogeneic BO induced a mild tissue reaction with only few multinucleated giant cells and comparably low vascularization, the synthetic NB induced a multinucleated giant cell-triggered tissue reaction with an increase of vascularization. Thus, the present study showed that a combination analysis—histological, clinical, and radiological—is necessary for a detailed assessment of a biomaterial's quality for clinical application.

Key Words: sinus augmentation, randomized controlled trial, Bio-Oss, Nanobone, volumetric analysis

INTRODUCTION

In cases of tooth loss, oral rehabilitation with dental implants has become a reliable intervention for replacing missing teeth and reestablishing sufficient mastication. However, bone loss due to alveolar atrophy or resective surgery limits the available amount of bone for stable implant insertion. Because of alveolar atrophy or extremely pneumatized maxillary sinus, the maxilla molar region in particular is predisposed to local bone deficit. Various surgical techniques have been described to increase the amount of local bone in this region. Since its introduction, sinus floor elevation and augmentation has been established as a reliable augmentation technique that promises implant success rates comparable to those of implants placed in nonaugmented regions.1–3 Different materials have been investigated for augmentation of the subantral space to analyze the material-related tissue reactions and to determine the success rates depending on the augmentation material.

In general, autologous bone is known as the most promising augmentation material, as it has osteoinductive, osteoconductive, and osteogenic properties. Therefore, it is considered the gold standard for augmentation in dental, oral, and maxillofacial surgery.4 However, the limited availability, the need of a second surgical site, and the risk of donor-site morbidity are restricting factors that should be considered.5
Previously, several synthetic and xenogeneic bone substitute materials have been analyzed to investigate the integration mechanisms of the biomaterials as well as the induction of a potential inflammatory response in the host tissue. In a clinical split-mouth trial, the synthetic Nanobone (NB, Artoss, Rostock, Germany) and the xenogeneic, bovine-based bone substitute material Bio-Oss (BO, Geistlich Biomaterials, Wolhusen, Switzerland) were augmented in the sinus cavity of patients with head and neck cancer and analyzed histologically, histomorphometrically, and clinically. Analysis of new bone formation showed similar results for both groups, whereas significant differences were observed in the amount of remaining bone substitute material. In the NB group, significantly less bone substitute material and a significantly higher amount of multinucleated giant cell induction and vascularization were observed. Regarding the implant survival, both bone substitute materials could form a sufficient implant bed, as only one implant from the NB group was lost 3 years after insertion.

In a further trial, a new method for analyzing volume and density changes of the augmented biomaterial by three-dimensional computerized tomography (CT) was investigated and described as a minimally invasive and technically supported analysis to complete histological and histomorphometrical assessment of the tissue-biomaterial integration and interaction in the human sinus cavity. The aforementioned study showed that for head and neck cancer patients, both bone substitute materials underwent volume decrease over an observation period of 6 months after augmentation. In addition, in both NB and BO groups, bone density increased significantly over 6 months and reached higher values than the reference zygomatic bone without significant differences between both groups.

Histological and histomorphometrical analysis of bone biopsies from the present study population showed comparable fractions of newly formed bone, remaining bone substitute material, and connective tissue within both groups, whereas the amount of multinucleated giant cells was significantly higher in the NB group than in the BO group. Although a higher fraction of multinucleated giant cells was present in the augmented region, no significant changes in the amount of remaining bone substitute material fraction was obvious, leading to the assumption that the described multinucleated giant cells act as foreign body giant cells without osteoclastic function.

The aim of the present prospective randomized clinical trial was to investigate changes in volume and density of the augmented biomaterials Nanobone and Bio-Oss by analysis of 3D CT scans taken immediately after augmentation and after 7 months of integration. A further aim of this study was to determine the effect of the different cellular mechanisms involved in biomaterial integration on the performance of dental implants inserted 7 months after augmentation. The clinical and radiological investigation aimed to complement aforementioned results from the histological and histomorphometrical investigation. Therefore, the inserted implants were investigated clinically 3 years after placement with the primary focus on implant stability and peri-implant hard- and soft-tissue conditions.

Materials and Methods

Study design/patient population

In the present study, 14 partly or completely edentulous patients (5 men and 9 women) with an average age of 55 years (ranging from 42 to 75 years) from the Department for Oral, Craniofacial, Maxillofacial, and Facial Plastic Surgery, Frankfurt am Main, were enrolled. The study was approved by the ethics commission of the University of Frankfurt am Main and performed in accordance with the fifth revision of the World Medical Association Declaration of 2000 in Helsinki and the Consolidated Standards of Reporting Trials (CONSORT) statement of 2010. Participants of the study were informed about the study protocol and gave a written declaration of informed consent.

All patients presented with a reduced alveolar height of less than 5 mm in the maxilla molar region, were free of infection in the prospect implantation site, and had an adequate oral hygiene. Exclusion criteria were medical and general contraindications for a surgical procedure, chronic alcohol abuse, chronic liver or kidney disease, metabolic diseases (eg, uncontrolled diabetes mellitus or osteoporosis), bisphosphonate therapy, or a heavy smoking habit of more than 20 cigarettes per day.

After preoperative anamnesis and surgical planning, the two biomaterials were randomly allocated for augmentation in patient’s right and left sinuses. Thus, patients achieved augmentation of the subantral spaces of the right and left side with the synthetic nanocrystalline bone substitute NB and the xenogeneic bone substitute BO.

After a mean healing period of 7 months (ranging from 5 to 9 months), 53 dental implants (CAMLOG ScrewLine, Camlog Biotechnologies, Basel, Switzerland) were inserted in the augmented maxilla molar region. Cylinder-shaped bone biopsies of the augmented maxillary bone were extracted simultaneously with the insertion of dental implants for histological and histomorphometrical examination of the biomaterials. Because the patients were edentulous in regions other than the maxilla molar region, 75 additional dental implants were inserted in different sites but were not included in the present study.

Surgical procedure

In the present study, sinus augmentation was performed to enlarge the bone volume in the maxilla molar region to enable subsequent implant placement. Therefore, the synthetic (NB) and the xenogeneic (BO) bone substitute materials were implanted randomly in both sides (ie, left and right) of the sinus maxillaris in a split-mouth design under general anesthesia. After crestal incision and mucoperiosteal flap formation, antrostomy of the maxillary bone was made using a Piezosurgery device (Mectron, Carasco, Italy). No perforations of the Schneiderian membrane occurred. Further, the subantral space was enlarged, and the biomaterials mixed with blood from the surgical site were incorporated. No autologous bone chips or blocks were added. Finally, the antrostomy window was covered with a native collagen membrane (Bio-Gide, Geistlich), and wound margins were adapted with absorbable tension-free single sutures.
After a mean healing period of 7 months, a total 53 dental implants (CAMLOG ScrewLine, Camlog) were placed in the augmented maxilla molar region (27 in BO-grafted sites and 26 in NB-grafted sites). Simultaneous with implant placement, bone cores were extracted using trephine burs (3-mm diameter) for the histological and histomorphometrical examination.

In both surgical operations, medication consisted of penicillin-based antibiotics (started intraperatively through intravenous application and continued orally for 5 days postoperatively), chlorhexidine 0.2% mouth rinse, and 400 mg ibuprofen. Implant exposure and prosthetic restoration were performed 6 months later.

**Bone grafting substitutes**

**Nanobone**

NB is a fully synthetic bone substitute material composed of hydroxyapatite (HA) granules with an average size of 60 nm and a structured silica gel matrix with silica gel pore sizes from 5 to 50 nm. Granules are manufactured in a sol-gel procedure with temperatures below 700°C. The internal surface of the nanoporous biomaterial reaches 84 m²/g. The numerous open links of the silica gel interact with the HA granules in loose connections to form a bone substitute appearing as cones with lengths up to 2 mm, an average diameter of 0.6 mm, and a porosity of 60% to 80%.9,10

**Bio-Oss**

BO is a xenogeneic bone substitute material made from deproteinized bovine bone mineral. It is processed by different chemical and mechanical processing and preparation steps than is NB. The organic components of the original bone are removed, leaving an inorganic bone matrix. BO has a porosity of 70%–75% and pore sizes ranging from a few nanometers to 1500 nm. The granules have a diameter ranging from 0.25–1.0 mm. The xenogeneic bone substitute material seems to be chemically and physically similar to human extracellular bone matrix and has been shown to constitute an effective bone graft matrix in different human clinical trials.11–13

**Three-dimensional radiographical investigation**

To determine changes in volume and density of the augmented biomaterials, 3D CT scans were taken immediately after augmentation to control the augmentation outcome and at an average of 7 months afterward, as previous to implant placement for planning the implant placement procedure. The scans were analyzed according to a previously published methodology.7 CT scans were acquired with standardized low-dose CT (Sensation 16 and Volume Zoom, Siemens Healthcare, Erlangen, Germany) and an effective dose of 110 mAs. The following settings were used: tube voltage 120 kV, scan time 3–10 seconds layer thickness 2 mm (0.75 mm) with sagittal and coronal reconstruction, and table movement/pitch 0.9. Using the software RIS-PACS AW Suite 2.0 (General Electric Healthcare, Chalfont St Giles, UK), anonymized CT images of DICOM (digital imaging and communications in medicine) format were analyzed using the software tools “volume viewer” and “volume measurement” to evaluate volume and density of the augmented materials directly after the augmentation and 7 months later.

For analysis of the volume of the augmented bone substitute material in all layers of the CT where the augmented area could be identified, the augmented biomaterial was marked at its margins with a “polygon tool.” Subsequently, the software calculated the volume of the augmented biomaterial, and the transitions between the different scans were interpolated according to the appearance of the augmented biomaterial by the software. The volume fraction of the graft was calculated describing the volume fraction in mm³. For analysis of the bone density, areas in the augmented region and in the reference zygomatic bone were marked for the measurement.7

**Clinical follow-up investigation**

Three years after implant insertion, a clinical and radiological follow-up investigation was made at the Department of Oral and Maxillofacial Surgery, University Frankfurt, Germany, by authors T.K. and J.L. The investigators were blinded to the allocation of the biomaterial augmentation.

The following parameters were investigated at the 3-year follow-up investigation: implant survival (ie, implants being in situ); Periotest value (Medizintechnik Gulden, Modautal, Germany); presence of peri-implant osteolysis; bleeding on probing (BOP); presence of plaque; and presence of gingival recessions around the implants, which led to exposition of the implant shoulder, the abutment, or the implant windings. Further, peri-implant infection with manifestation of bone loss was investigated radiologically by standard orthopantomogram recorded at the 3-year follow-up investigation.

With these examinations, the influence of the bone substitute material on the clinical performance of the inserted implants was examined.14,15 Investigation parameters were:

- Implant being in situ
- Periotest value
- Presence of peri-implant osteolysis
- Presence of BOP
- Presence of plaque
- Presence of soft-tissue recessions around the implants

**Statistics**

The data from the volumetric and density measurements of both biomaterial groups were compared across the study groups at different time points (ie, immediately after augmentation and 7 months later) with analysis of variance (ANOVA) followed by Fisher’s least significant difference post hoc assessments (GraphPad Prism sm 6 V6.01 software, GraphPad Software Inc, La Jolla, Calif). Inter- (*) and intra-individual (**) significant differences were deemed significant when the P values were less than .05 (**/• P < .05) and highly significant when the P values were less than .01 (**/* P < .01) and .001 (***/* P < .001). Finally, the data were presented graphically as mean ± standard deviations.
RESULTS

Clinical results

According to the study protocol, 7 months after sinus augmentation, a total of 53 implants were inserted in the augmented maxilla molar region in 14 patients. Of these, 27 implants were inserted in regions augmented with BO, and 26 in regions augmented with NB (Table 1). At the 3-year follow-up investigation, 51 of these 53 implants were in situ and suitable for prosthetic rehabilitation. In each, group, 1 implant failed after 3 years due to peri-implant infection. This leads to an overall survival rate of 96% for both groups, and a 96% survival rate after 3 years due to peri-implant infection. Further, no osseous peri-implant defects were obvious in either group. The radiologic analysis of the NB-augmented region also showed a volume decrease in all patients. The average volume of the BO-augmented region immediately after augmentation was 3.037 cm³ (± 0.8589 cm²), whereas 7 months after augmentation, the average volume of the augmented region decreased to 2.112 cm³ (± 0.7598 cm²; Figure 3). The average percentage volume of the BO-augmented region immediately after augmentation decreased to 2.358 cm³ (± 0.7598 cm²; Figure 3). The average percentage volume of the BO-augmented region after 7 months was 77.64% compared to the volume immediately after augmentation (stated as 100%, difference not significant; Figure 4).

Further, the accumulation of plaque at the gingival third of the implant suprastructure was noted on 12 implants of the NB group and 12 implants of the BO group (NB: 48.0%; BO: 46.2%; difference not significant). A distinct correlation between plaque accumulation and BOP could be found because plaque accumulation was also detected on most implants that presented with BOP.

Recession of the gingiva around the implants was observed on four implants (16.0%) in the NB and five implants (19.2%) in the BO group. All recessions were obvious on fixed prosthetics, which also presented plaque accumulation and BOP (Table 2).

Figure 1 shows radiographical images of patient 4 (a) after implant placement and (b) after 3 years of loading. The peri-implant bone level seems to be at a stable level, with no obvious signs of peri-implant infection.

Figure 2 shows a clinical image of patient 4 after 3 years of loading. Implants are restored with telescopic Galvano crowns. The implants are surrounded by a sufficient amount of attached gingiva, and the peri-implant soft tissue is free of infection.

Radiographical results

Results of the Volumetric Analysis

Changes in volume and density of the augmented biomaterials were analyzed by comparing CT scans taken after augmentation and before implant placement.

The radiologic analysis of the BO-augmented region showed volumetric reduction in all patients. The average volume of the BO-augmented region immediately after augmentation was 3.037 cm³ (± 0.8589 cm²), whereas 7 months after augmentation, the average volume of the augmented region decreased to 2.358 cm³ (± 0.7598 cm²; Figure 3). The average percentage volume of the BO-augmented region after 7 months was 77.64% compared to the volume immediately after augmentation (stated as 100%, difference not significant; Figure 4).

The radiologic analysis of the NB-augmented region also showed a volume decrease in all patients. The average volume of the NB-augmented region immediately after augmentation was 2.953 cm³ (± 1.249 cm²), and 7 months after augmentation, the average volume of the augmented region decreased to 2.112 cm³ (± 1.000 cm²; see Figure 3). The average percentage volume of the BO-augmented region after 7 months was 71.52% compared to the volume immediately after augmentation (stated as 100%, difference not significant; see Figure 4).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Implants in Total</th>
<th>Implants in the Augmentation Site</th>
<th>Implants Placed in BO Augmentation</th>
<th>Implants Placed in NB Augmentation</th>
<th>Prosthetic Restoration in the Upper Jaw</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>3,4,5,10,13,14,21,27,28</td>
<td>3,4,13,14</td>
<td>13,14</td>
<td>3,4</td>
<td>f.p.</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>3,4,6,11,13,14,21,23,26,28</td>
<td>3,4,13,14</td>
<td>3,4</td>
<td>13,14</td>
<td>r.p.</td>
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<tr>
<td>3</td>
<td>47</td>
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<td>3,4</td>
<td>13,14</td>
<td>r.p.</td>
</tr>
<tr>
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<td>3,4,13,14</td>
<td>3,4</td>
<td>13,14</td>
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<tr>
<td>5</td>
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<td>13,14</td>
<td>f.p.</td>
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<tr>
<td>6</td>
<td>59</td>
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<td>14,15</td>
<td>2,3</td>
<td>f.p.</td>
</tr>
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<td>7</td>
<td>55</td>
<td>3,4,6,9,12,13,19,29,30</td>
<td>4,13</td>
<td>4</td>
<td>13</td>
<td>r.p.</td>
</tr>
<tr>
<td>8</td>
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<td>3,4,13,15</td>
<td>13,15</td>
<td>3,4</td>
<td>f.p.</td>
</tr>
<tr>
<td>9</td>
<td>51</td>
<td>2,4,14,19,28,30,31</td>
<td>2,4,14,15</td>
<td>14,15</td>
<td>2,4</td>
<td>f.p.</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
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<td>13,14</td>
<td>r.p.</td>
</tr>
<tr>
<td>11</td>
<td>75</td>
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<td>13,14</td>
<td>f.p.</td>
</tr>
<tr>
<td>12</td>
<td>63</td>
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<td>2,14</td>
<td>2</td>
<td>14</td>
<td>f.p.</td>
</tr>
<tr>
<td>13</td>
<td>58</td>
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<td>3,4,12,13,14</td>
<td>12,13,14</td>
<td>3,4</td>
<td>r.p.</td>
</tr>
<tr>
<td>14</td>
<td>46</td>
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<td>3,4,13,14</td>
<td>3,4</td>
<td>13,14</td>
<td>r.p.</td>
</tr>
<tr>
<td>Total/mean</td>
<td>61</td>
<td>128</td>
<td>53</td>
<td>27</td>
<td>26</td>
<td>7 f.p.</td>
</tr>
</tbody>
</table>

*BO indicates Bio-Oss; NB, Nanobone; f.p., fixed partial; r.p., removable prosthetics.
The decrease in the graft volume in the NB group compared to the BO group did not reach a significant level.

**Results of Bone Density Analysis**

In addition to the changes in volume, the bone density was also analyzed to determine the ossification and new bone formation within the augmented regions. Therefore, the bone density in the center of the augmented region was measured immediately after augmentation and 7 months later, before implant placement. The comparative analysis of the bone density in the augmented region and the zygomatic bone showed a significant lower bone density of the BO- and the NB-augmented region (NB: 512.8 ± 78.33 Hounsfield units [HU], BO: 506.90 ± 139.30 HU) immediately after augmentation compared to the bone density of the zygomatic bone (zygomatic bone: 604.10 ± 108.10 HU) (*P, .05). Seven months after augmentation, a highly significant increase in bone density was observed in both the BO- and the NB-augmented region (NB: 789.40 ± 55.29 HU, BO: 697.70 ± 110.50 HU) (**P < .001). Comparing the density of the BO- and the NB-augmented region immediately and 7 months after augmentation, no statistical differences were observed between the groups (Figure 5).

**TABLE 2**

Results of the 3-year clinical follow-up investigation of the implants inserted in the augmented region

<table>
<thead>
<tr>
<th>Patient</th>
<th>Implants in the Augmentation Site</th>
<th>Implant Loss Total (NB/BO)</th>
<th>Perio-test Value NB</th>
<th>Perio-test Value BO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>—</td>
<td>−4, −6</td>
<td>−3, −5</td>
</tr>
<tr>
<td>2</td>
<td>3,4,13,14</td>
<td>—</td>
<td>−3, −5</td>
<td>−4, −6</td>
</tr>
<tr>
<td>3</td>
<td>3,4,13,14</td>
<td>—</td>
<td>−7, −8</td>
<td>−2, −4</td>
</tr>
<tr>
<td>4</td>
<td>3,4,13,14</td>
<td>—</td>
<td>−4, −2</td>
<td>−3, −5</td>
</tr>
<tr>
<td>5</td>
<td>3,4,13,14</td>
<td>—</td>
<td>−4, −5</td>
<td>−4, −7</td>
</tr>
<tr>
<td>6</td>
<td>2,3,14,15</td>
<td>—</td>
<td>−4, −3</td>
<td>−3, −4</td>
</tr>
<tr>
<td>7</td>
<td>4,13</td>
<td>−4</td>
<td>−4</td>
<td>−6</td>
</tr>
<tr>
<td>8</td>
<td>3,4,13,15</td>
<td>−5</td>
<td>−4, −4</td>
<td>−3, −5</td>
</tr>
<tr>
<td>9</td>
<td>2,4,14,15</td>
<td>27 (BO)</td>
<td>−3, −2</td>
<td>−3</td>
</tr>
<tr>
<td>10</td>
<td>3,4,13,14</td>
<td>−4</td>
<td>−3</td>
<td>−6, −8</td>
</tr>
<tr>
<td>11</td>
<td>3,4,13,14</td>
<td>−5</td>
<td>−7</td>
<td>−5, −6</td>
</tr>
<tr>
<td>12</td>
<td>2,14</td>
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<td>3,4,12,13,14</td>
<td>16 (NB)</td>
<td>−7</td>
<td>−3, −5, −6</td>
</tr>
<tr>
<td>14</td>
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<td>−7</td>
<td>−4, −6</td>
</tr>
<tr>
<td>Total/mean</td>
<td>53</td>
<td></td>
<td>−4,36</td>
<td>−4,69</td>
</tr>
</tbody>
</table>

*NB indicates Nanobone; BO, Bio-Oss; BOP, bleeding on probing; +, positive/present; −, negative/absent.

**FIGURES 1 and 2.** **FIGURE 1.** Radiographic images of patient 4 (a) after implant placement and (b) after 3 years of loading. The peri-implant bone level seems to be at a stable level, and no signs of peri-implant infection are obvious. **FIGURE 2.** Clinical image of patient 4 after 3 years of loading. Implants are restored with telescopic Galvano crowns. The implants are surrounded by a sufficient amount of attached gingiva, and the peri-implant soft tissue is free of infection.


The aim of the present study was to analyze the clinical performance of dental implants placed in the maxilla molar region 7 months after sinus augmentation in a split-mouth design with the synthetic HA-based bone substitute (NB) and the xenogeneic bovine-based bone substitute material (BO). Implants in the augmented regions were analyzed after a mean loading time of 3 years regarding implant survival, implant stability, and peri-implant soft- and hard-tissue conditions.

Further, the changes in the graft volume and density immediately after augmentation and 7 months later before implant placement were evaluated using 3D CT scans and software analysis.

Thus, the previously published results from the histological and histomorphometrical analysis of bone biopsies extracted simultaneously with implant placement could be complemented.

Implant survival rates in both groups (96.3% in the BO and 96.2% in the NB group) are in accordance with the survival rates of implants inserted in the augmented posterior maxilla 6 months after augmentation, as described in the literature. In addition to implant survival, implant stability was assessed by Periotest analysis. In both groups, comparable results were achieved (BO: −4.69, NB: −4.36), which are in accordance with or even better than results described in the literature. From these results, it can be concluded that both bone substitute materials could form a sufficient implantation bed to guarantee safe and long-term stable osseointegration of dental implants. Investigation of BOP, plaque accumulation, and gingival recession showed approximately the same results, leading to the conclusion that the choice of the investigated augmentation materials in the present study does not significantly influence the prevalence of peri-implantitis.

In addition to clinical investigation of the inserted dental implants, radiological analysis was performed of the 3D graft volume and the graft density immediately and 7 months after augmentation. This enabled to determine the volumetric and density changes of the grafted biomaterials within an integration period of 7 months. Both the NB and BO groups showed nonsignificant reduction of the graft volume over an integration period of 7 months. In comparison to the graft volume, the density within the grafted area increased in both groups. Immediately after augmentation, the bone density in the grafted area in both groups was significantly lower compared to the zygomatic bone; however, the bone density increased significantly compared to the bone density immediately after augmentation and reached even higher values than the zygomatic bone.

The presented increase in bone density in both bone substitute material groups seems to represent the reorganization of the graft material with newly formed bone. At the same time, the graft volume becomes reduced by condensation processes or the loss of the liquid component of the augmentation material within the 7-month period. Radiological analysis of graft volume and graft density is an interesting investigation methodology for clinicians and scientists, as it is a technically supported and minimally invasive investigation tool, especially in times of ongoing development and dissemination of digital volume tomography/cone beam computerized tomography.

The previously published histological and histomorphometrical analysis of bone biopsies from the augmented areas of the presented study population have shown that the synthetic NB granules were well integrated in the peri-implant tissue and were surrounded by newly formed bone tissue. The xenogeneic BO granules were integrated into the newly formed bone tissue, which seemed to originate from active osteoblasts on the surfaces of the bone substitute granules. The surface of the synthetic NB granules was clearly colonized by multinucleated giant cells, whereas the xenogeneic BO granules showed only a few multinucleated giant cells on their surface. This finding could be proved by histomorphometric analysis, which showed a significantly higher amount of multinucleated giant cells (NB: 14.23 multinucleated giant cells/mm²; BO: 8.36 multinucleated giant cells/mm², **P < .01) as an expression of the inflammatory response/foreign body reaction in the.
synthetic bone substitute group. Further, histomorphometric analysis showed significantly more blood vessels (NB: 28.69 ± 10.54 vessels/mm², BO: 10.42 ± 3.74 vessels/mm², *** P < .001) and a significantly higher vessel fraction in the synthetic study group (NB: 2.13 ± 0.82%; BO: 0.86 ± 0.33%; ** P < .01). In contrast, the differences in the percentages of connective tissue (NB: 44.20 ± 3.97 %; BO: 48.73 ± 13.43 %), remaining bone substitute (NB: 36.77 ± 4.83%; BO: 27.61 ± 11.71%), and newly formed bone (NB: 19.02 ± 7.28%; BO: 23.66 ± 7.97%) did not exhibit statistically significant differences. These histologic results highlight the different cellular reactions to synthetic and xenogeneic bone substitute materials. The data suggest that the significantly higher number of multinucleated giant cells within the NB implantation bed have no effect on its biodegradation, as the ratio of remaining bone substitute material did not reach statistically significant differences. Accordingly, the multinucleated giant cells observed within the NB implantation bed have characteristics more similar to those of foreign body giant cells than to those of osteoclasts.

The presented results from the 3-year implant follow-up
investigation underline the fact that both biomaterials, although causing different cellular reactions, could form a sufficient implantation bed for long-term stable osseointegration. Further, there were no significant differences between implant survival, implant stability, and peri-implant hard- and soft-tissue health. However, the evaluation of CT scans could not yield an objective statement about degradation or dehydration processes; therefore, histologic and histomorphometric analysis is still the method of choice for detailed analysis of cellular mechanisms. An isolated consideration of clinical and radiologic assessment could lead to the assumption that there is no difference between the investigated bone substitute materials of different origins and processing. However, histologic analysis demonstrated pronounced differences, especially in the induction of multinucleated giant cells. It can be concluded that both clinical and radiological analysis and histologic analysis are necessary to give a true statement on biomaterials’ capacity. To date, it remains unclear whether the previously published different cellular tissue reactions to these material classes (ie, the presence of multinucleated giant cells within the implantation bed of the synthetic material) has any effect on long-term implant stability. Thus, longer clinical observation periods are necessary to answer this question.

**CONCLUSION**

The presented clinical 3-year follow-up investigation of dental implants placed in the augmented maxilla molar region was performed to determine the ability of a synthetic and a xenogeneic bone substitute material to form a sufficient and long-term stable implantation bed. A three-dimensional radiologic analysis of the graft volume and the graft density immediately after augmentation and 7 months later showed that both bone substitute materials could form an implantation bed for long-term stable implant placement and peri-implant soft- and hard-tissue health with an implant survival rate of 96% and no major signs of peri-implant infection or bone loss. However, although both bone substitute materials performed almost equally, previous histologic and histomorphometric results showed that the biomaterials induce totally different tissue reactions, especially in the induction of multinucleated giant cells. Thus, the present study could demonstrate that a combination of histological, clinical, and radiological analyses is necessary for a detailed assessment of a biomaterial’s quality for the clinical application.

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**REFERENCES**


**ABBREVIATIONS**

BO: Bio-Oss
BOP: bleeding on probing
CT: computerized tomography
f.p.: fixed prosthetics
HA: hydroxyapatite
HU: Hounsfield units
NB: Nanobone
r.p.: removable prosthetics

**NOTE**

The authors declare no conflicts of interest.