Original Article - Prospective Study

Volumetric analysis of bone substitute material performance within the human sinus cavity of former head and neck cancer patients: A prospective, randomized clinical trial

Access this article online
Website: www.amsjournal.com
DOI: 10.4103/2231-0746.200344
Quick Response Code:

Jonas Lorenz, Kathrin Eichler[1], Mike Barbeck, Henriette Lerner, Stefan Stübinger[2], Catherine Seipel, Thomas J. Vogl[1], Adorján F. Kovács[3], Shahram Ghanaati, Robert A. Sader

Department for Oral, Cranio-maxillofacial and Facial Plastic Surgery, Medical Center of the Goethe University, [1]Department for Diagnostic and Interventional Radiology, Medical Center of the Goethe University, Frankfurt am Main, [3]Private Practice, Nauheim, Germany, [2]Hightech Research Center of Cranio-Maxillofacial Surgery, University of Basel, Basel, Switzerland

Address for correspondence:
Dr. Shahram Ghanaati, Department for Oral, Cranio-maxillofacial and Facial Plastic Surgery, Medical Center of the Goethe University, Frankfurt am Main, Germany.
E-mail: shahram.ghanaati@kgu.de

ABSTRACT

Background: In numerous animal and human studies, it could be detected that in bone augmentation procedures, material's physicochemical characteristics can influence the cellular inflammatory pattern and therefore the integration in the host tissue. Histological, histomorphometrical, and clinical analyses of the integration of the biomaterial in the surrounding tissue are well established methodologies; however, they do not make a statement on volume and density changes of the augmented biomaterial. **Aims:** The aim of the present study was to assess the volume and density of a xenogeneic (Bio-Oss®, BO) and a synthetic (NanoBone®, NB) bone substitute material in split-mouth sinus augmentations in former tumor patients to complete histological and histomorphometrical assessment. **Methods:** Immediately and 6 months after sinus augmentation computed tomography scans were recorded, bone grafts were marked, and the volume was calculated with radiologic RIS-PACS software (General Electric Healthcare, Chalfont St. Giles, Great Britain) to determine the integration and degradation behavior of both biomaterials. **Results:** Radiographic analysis revealed a volume reduction of the initial augmented bone substitute material (i.e. 100%) to 77.36 (±11.68) % in the BO-group, respectively, 75.82 (±22.28) % in the NB-group six months after augmentation. In both materials, the volume reduction was not significant. Bone density significantly increased in both groups. **Conclusion:** The presented radiological investigation presents a favorable method to obtain clinically relevant information concerning the integration and degradation behavior of bone substitute materials.

Keywords: Bio-Oss, bone substitute material, graft density, graft volume, NanoBone®, radiologic analysis, sinus augmentation

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Cite this article as: Lorenz J, Eichler K, Barbeck M, Lerner H, Stübinger S, Seipel C, *et al*. Volumetric analysis of bone substitute material performance within the human sinus cavity of former head and neck cancer patients: A prospective, randomized clinical trial. Ann Maxillofac Surg 2016;6:175-81.

INTRODUCTION

In a previously published clinical trial, the performance of two bone substitute materials for sinus augmentation was analyzed. In a group of patients with head and neck cancer and highly atrophic maxillary bone, sinus augmentation was performed with the xenogeneic, bovine- based bone substitute material Bio-Oss® (BO, Geistlich Biomaterials, Wolhusen, Switzerland) and the alloplastic bone substitute material NanoBone® (NB, Artoss, Rostock, Germany) followed by insertion of dental implants 6 months later.[1]

The xenogeneic BO and the alloplastic NB have been investigated histologically and histomorphometrically with a focus on inflammatory response in the host tissue, new bone formation, and biomaterial degradation. Therefore, simultaneously with the insertion of dental implants, biopsies of the augmented area were extracted and processed. It was shown that NB granules were embedded in connective tissue, originating from the covering soft tissue and newly formed bone, ingrowing from the residual alveolar crest. Analyzing the fraction of remaining bone substitute material after an observation period of 6 months, the amount of the bovine-based bone substitute material BO was significantly higher than the amount of the synthetic hydroxyapatite (HA) bone substitute material NB. This could be a sign of the degradation of the latter through a foreign body reaction, as multinucleated giant cells and macrophages were present in a high number, as supplied through connective tissue with a high vessel density. According to the different origins, types of processing, and physicochemical structures of both investigated biomaterials, two different processes of biomaterial integration in the human organism were obvious. BO, a well-researched and frequently used xenogeneic bone substitute material, exhibited good integration in the sinus cavity and the formation of a sufficient implantation bed in the above-mentioned split-mouth trial in oral cancer patients. The biomaterial induced almost no signs of a foreign body reaction with only few multinucleated giant or foreign body cells while new bone ingrowth originating from the residual maxillary bone tissue was supported.[1]

Patients with atrophic upper alveolar bone who have been successfully treated for oral cancer and who suffer from a reduced life expectance and life quality should be orally rehabilitated to restore articulation and mastication. Therefore, dental implants have been demonstrated to achieve reliable retention for fixed and removable dentures in both healthy and tumor populations.[2-4]

Due to alveolar atrophy or tumor resection, the amount of available bone for the placement of dental implants is reduced in the majority of patients, and bone augmentation becomes necessary to achieve a sufficient implantation bed.

To date, autologous bone is still postulated by clinicians and scientists to be the gold standard because of its osteoinductive, osteoconductive, and osteogenic properties.[5] However, the augmentation with autologous bone comes along with several disadvantages, such as limited amount of bone, second surgical site, and risk of donor site morbidity.[6]

To avoid the burden of an additional operation, allogeneic bone substitutes from human living or mortal donors, xenogeneic bone substitutes of bovine, porcine, or equine origin, and alloplastic bone substitute materials have been developed and well researched in recent years. In several clinical trials, the high biocompatibility, as well as the support of new bone formation after augmentation in dental and maxillofacial surgery, was demonstrated for these materials.[7-12]

Apart from xenogeneic bone substitutes, alloplastic bone substitutes, mainly originating from HA, biphasic calcium phosphate ceramics (BCP), α- and β-tricalcium phosphate ceramics, or bioactive glasses, are widespread alternatives to autologous bone transplantation.[13,14]

In recent years, alloplastic bone substitute materials have been investigated in several *in vivo* and clinical trials to analyze the tissue reaction and osseointegration of these materials in humans.[10,11,15]

In a preliminary clinical study, the potential of the same nanostructured HA-based biomaterial (NB) was assessed for sinus augmentation in humans. Qualitative histologic analysis of biopsies taken after an integration period of 6 months revealed integration of the biomaterial within the sinus cavity and a high osteoclast activity, resulting in formation of new bone at the margin of the biomaterial.[10]

In another clinical trial of sinus augmentation, the *de novo* bone formation capacity of the nanocrystalline HA bone substitute NB was assessed histologically and histomorphometrically at two time points, 3 and 6 months after implantation, in the human sinus cavity. The bone metabolism within the residual bone and augmented region was emphasized. New bone tissue formation starting from the bone-biomaterial interface could be observed in both study groups while no statistically significant difference in new bone formation could be detected after 3 and 6 months. Therefore, it was concluded that implant insertion in regions augmented with this bone substitute material could be considered already after 3 months.[11]

In the present study, the histological, histomorphometrical, and clinical results of the performed split-mouth trial were completed by a three-dimensional radiographic analysis, to determine the volumetric changes of the two different bone substitute materials, which have been augmented in the sinus cavity of patients with cancer anamnesis. Measurements were made at two time points, directly after augmentation and 6 months later at the insertion of dental implants in the augmented region. With RIS-PACS software (General Electric Healthcare, Chalfont St. Giles, Great Britain), the augmented biomaterial was marked in three-dimensional computed tomography (CT) scans in the Digital Imaging and Communications in Medicine (DICOM) format and calculated by rendering in radiographic images. Volume changes were calculated as a percentage of the inserted biomaterial fraction to determine the potential degradation of both xenogeneic and synthetic biomaterial. With this method, previously obtained histologic and histomorphometric results that analyzed the tissue reaction to both materials in the human sinus cavity could be critically reviewed. The aim was to investigate whether the above-mentioned results gained by histomorphometrical analyses can somehow be reproduced by applying the nonsurgical and thus "non-invasive" method of CT.

MATERIALS AND METHODS

Study design/patient population

The present, randomized, prospective clinical study was approved by the Ethics Committee of the University of Frankfurt am Main and conducted according to the fifth revision of the World Medical Association Declaration of Helsinki 2000. All patients gave informed consent before the sinus augmentation procedure. As previously described, eight partly or completely edentulous patients (five women and three men) with squamous cell carcinoma, affecting different sites of the oral cavity to varying extents, from the Department for Oral, Cranio-maxillofacial and Facial Plastic Surgery, Frankfurt am Main, were enrolled in the study. In all patients, the cancer was completely cured before sinus augmentation was performed in a split-mouth design with each of the bone substitute materials BO and NB inserted randomly on one side. After 6 months of healing, dental implants were inserted in the augmented regions [Table 1]. Simultaneously, bone biopsies were extracted for histological and histomorphometrical analyses.[1]

Time points of CT scan recording were set into regular cancer staging order to avoid unnecessary irradiation of the patients. Immediately after sinus augmentation, CT scans were recorded to control the augmentation results and 6 months later before implant placement to plan the implant position.

CT scans were analyzed with the RIS-PACS software from an experienced radiologist who was blinded to the surgical procedure and the distribution of the augmented biomaterials to evaluate volumetric changes of the augmented bone substitute material within the sinus cavity.

Surgical procedure

According to the previously described methods, sinus augmentation was conducted in eight patients in general anesthesia. Crestal incision and mobilization of a vestibular-based mucoperiosteal flap were performed to obtain access to the processus maxillaris.[1] With a Piezosurgery® device (Mectron, Cologne, Germany), a lateral window was extracted, and the Schneiderian membrane was exposed. Using sinus elevator instruments of different shapes and sizes, the membrane was elevated to enlarge the subantral space. Afterward, both bovine-based bone substitute material BO and alloplastic bone substitute material NB, mixed with blood extracted from the surgical site, were randomly implanted in the sinus cavities of each side. The lateral window was covered with a native collagen membrane (Bio-Gide®, Geistlich, Wolhusen, Suisse) and wound closure was achieved with single sutures.

Six months after augmentation, dental implants (CAMLOG® Screw-Line, Camlog Biotechnologies, Basel, Switzerland) were placed simultaneously with the extraction of bone biopsies for the aforementioned histological investigation.

A detailed itemization of implant numbers and sites is given in Table 1.

Bone grafting substitutes

NanoBone®

NanoBone® (NB, Artoss, Rostock, Germany), a completely synthetic bone substitute material, is composed of HA crystallites embedded in a matrix of structured silica gel. The granules, with an average size of 60 μm, are manufactured with a sol-gel technique. Thereby, sintering can be avoided. The manufacturing process results in a pore size within the bone substitute material of 100–1000 μm (macropores) or 2–10 μm (micropores), an internal surface of up to 84 m^2/g, and a material porosity of 60%–80%.[16,17]

Bio-Oss®

Bio-Oss® (BO, Geistlich Biomaterials, Wolhusen, Switzerland), a xenogeneic deproteinized bone mineral with bovine origin, is processed by sintering in a highly alkaline solution and sterilized by gamma radiation. Organic components are removed by a chemical extraction process to avoid disease transmission. Bone substitute granules have a diameter from 0.25 to 1.0 mm, pore sizes ranging from a few nanometers to 1500 nm, and a material porosity of 70%–75%.[8,18,19]

Radiographic analysis

Radiographic images

Images were recorded for preoperative diagnostics and planning, postoperative augmentation control, and 6 months before implant placement with standardized low-dose CT (Sensation 16 and Volume Zoom, Siemens Healthcare, Erlangen, Germany) and an effective dose of 110 mA. The following settings were used: tube voltage: 120 kV, scan time: 3–10 s, layer thickness: 2 mm (0.75 mm) with sagittal and coronal reconstruction, and table movement/pitch: 0.9. Patients participating in this study were all enrolled in clinical and radiological aftercare due to head and neck cancer anamnesis. CT images were recorded in agreement with the regular radiologic tumor aftercare to avoid unnecessary radiation.

Table 1: Detailed overview of the number and sites of placed implants in the augmented and nonaugmented regions. The content of this figure has already been published by the author in a different form[1]

Patient	Number of implants and sites (upper jaw)	Number of implants and sites (lower jaw)	Implants placed in Bio-Oss® augmented regions	Implants placed in NanoBone® augmented regions
1	6: 13, 15, 16, 23, 25, 26	2: 31, 41	2	2
2	6: 13, 15, 16, 21, 23, 26	4: 32, 33, 42, 43	1	1
3	6: 13, 15, 16, 23, 25, 26	0	2	2
4	6: 13, 14, 16, 23, 24, 26	4: 32, 33, 42, 43	1	1
5	6: 11, 15, 16, 24, 25, 26	4: 31, 32, 41, 42	2	2
6	6: 14, 15, 16, 24, 25, 26	2: 31, 32	2	2
7	Refused implantation	Refused implantation	Refused implantation	Refused implantation
8	6: 13, 15, 17, 23, 25, 26	0	2	2
Total	42 implants	16 implants	12	12

Analyzing software

CT scans were analyzed with the software RIS-PACS AW Suite 2.0 (General Electric Healthcare, Chalfont St. Giles, Great Britain) to determine the augmentation volume immediately after biomaterial insertion and 6 months later. The RIS-PACS system is suitable for visualizing and processing multidimensional images from different equipment (magnetic resonance tomosynthesis, CT, etc.,) and allows analysis and processing images in the DICOM format.

First, images, data, and patients' names were anonymized to guarantee objective, blinded analysis. The software shows the recorded CT scan as a number of two-dimensional slices, depending on slice thickness, in three different projections (coronal, axial, and sagittal). Further, a three-dimensional scan could be generated from the different two-dimensional slides.

In the present study, from the large number of software tools, "volume viewer" and "volume measurement" were used, to evaluate change of volume and density of the augmented materials directly after the augmentation and 6 months later. Furthermore, the density of the augmented bone substitute material and the zygomatic bone (reference bone) was analyzed with the software tool "density measurement."

Analysis of the graft volume and density with the above-mentioned software was performed as follows:

- Step 1: All layers of the CT in which the augmented area could be identified were chosen for analysis. With the "polygon" tool, the augmented biomaterial was marked at its margins [Figure 1]
- Step 2: The software calculated the volume of the augmented biomaterial. The transitions between the different scans were interpolated according to the appearance of the augmented biomaterial by the software
- Step 3: The volume fraction of the graft was calculated, describing the volume fraction in cm^3/mm^3
- Step 4: An area in the grafted bone substitute material and in the reference zygomatic bone was marked for the measurement of bone density [Figure 2].

Statistics

The data from the volumetric and density measurements of both biomaterial groups were compared across the study groups at different time points, immediately after augmentation and 6 months later, with analysis of variance followed by Fisher's least significant difference tests. *Post hoc* assessments were performed with GraphPad Prism software (Prism 6 V6.01, GraphPad Software Inc., La Jolla, USA). Inter- (*) and intra-individual (•) significant differences were deemed significant when $P < 0.05$ (*/•$P < 0.05$) and highly significant when $P < 0.01$ (**/••$P < 0.01$) and 0.001 (***/•••$P < 0.001$). Finally, the data were presented graphically as mean values ± standard deviations.

RESULTS

Volumetric changes of the grafts

Bio-Oss®

The radiologic analysis of the BO graft revealed volumetric reduction in all patients. The average graft volume immediately after augmentation was 2547.75 mm^3 (±1287.41 mm^3), while 6 months after augmentation, the average graft volume decreased to 1971.00 mm^3 (±1046.21 mm^3). The average percentage of the BO graft volume after 6 months was 77.36% (±11.68%) of the volume immediately after augmentation [Figures 3 and 4]. The volume reduction of the BO graft was not significant.

NanoBone®

The radiologic analysis of the NB graft revealed volumetric reduction in all patients.

The average graft volume immediately after augmentation was 2180.05 mm^3 (±670.02 mm^3), while 6 months after augmentation, the average graft volume decreased to 1621.00 mm^3 (±702.47 mm^3). The average percentage of the NB graft volume after 6 months was 75.82% (±22.28%) of the volume immediately after augmentation [Figures 3 and 4]. The volume reduction of the NB graft was not significant.

Changes in bone density of the grafts

Bio-Oss®

The radiologic analysis of the BO graft revealed increased bone density in all patients. The average density of the BO graft increased significantly from 491.00 Hounsfield units (HU) (±104.94 HU) immediately after augmentation to 859.63 HU (±211.04 HU) 6 months after augmentation (•••$P < 0.001$).

Comparison of the bone density of the region of interest immediately after augmentation and the bone density of the zygomatic bone revealed a significantly higher bone density in the zygomatic bone (average: 703.13 ± 77.79 HU; *$P < 0.05$) in all cases. Comparing the bone density of the region of interest 6 months after augmentation and the bone density of the zygomatic bone, the bone density of the region of interest was higher than the bone density of the zygomatic bone in 6 of 8 cases [Figure 5].

NanoBone®

The radiologic analysis of the NB graft revealed an increase of bone density in all patients. The average density of the NB graft increased significantly from 463.88 HU (±53.90 HU) immediately after augmentation to 771.75 HU (±172.13 HU) units 6 months after augmentation (•••$P < 0.001$).

Comparison of the bone density of the region of interest immediately after augmentation and the bone density of the zygomatic bone revealed a higher bone density in the zygomatic bone (average: 703.13 ± 77.79 HU; *$P < 0.05$) in all cases. Comparing the bone density of the region of interest 6 months after augmentation and the bone density of the zygomatic bone, the bone density of the region of interest was higher than the bone density of the zygomatic bone in 6 of 8 cases [Figure 5].

DISCUSSION

In the present study, a three-dimensional radiographic analysis was performed to determine the volumetric changes of the

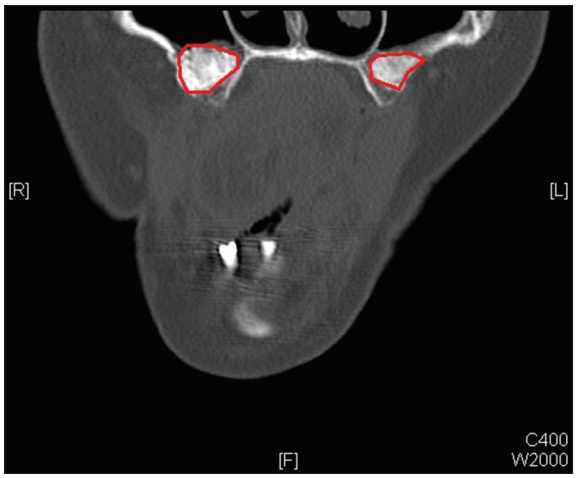

Figure 1: Coronal sequence of the analyzed computed tomography images with marked augmentation material in both sinus cavities

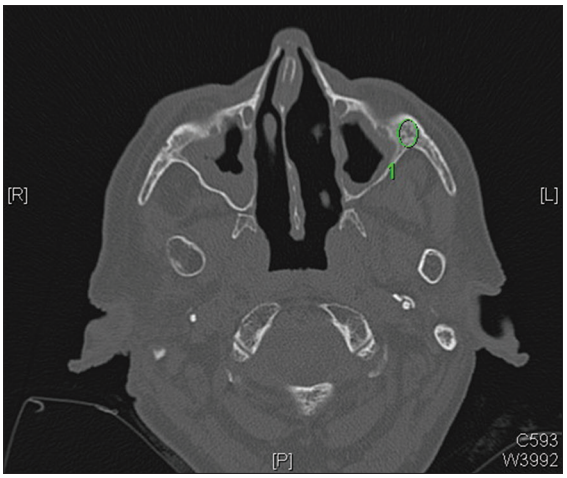

Figure 2: Transversal sequence of the analyzed computed tomography images with the marked reference zygomatic bone for bone density measurements

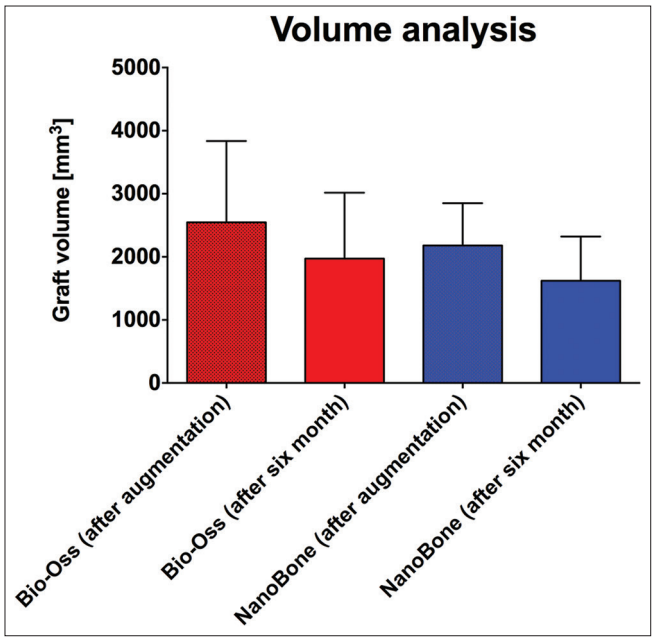

Figure 3: Graphical representation of the average volume of the Bio-Oss® and the NanoBone® grafts immediately and 6 months after augmentation (in mm³)

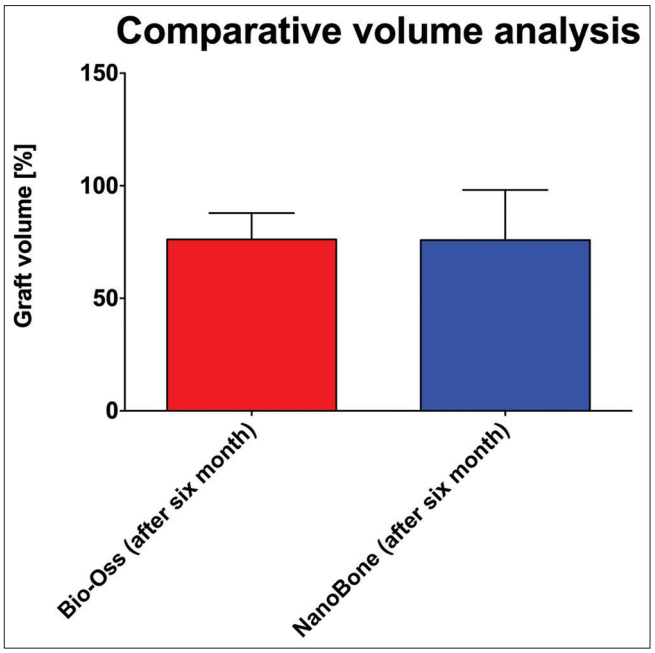

Figure 4: Graphical representation of the comparative volume analysis of the Bio-Oss® and the NanoBone® grafts 6 months after augmentation (in %)

bovine-based bone substitute material BO and the synthetic bone substitute material NB, which were augmented in the sinus cavities of patients with head and neck cancer anamnesis. The aim of the investigation was to compare the changes in volume and density of the augmented regions with the previously published histological and histomorphometrical results of the performed split-mouth trial.[1] Further, it should be clarified that to what extent CT scans are suitable to determine the interaction of biomaterials within the augmentation site in the human organism.

The presented increase in bone density and decrease of the augmented volume in both groups represent the reorganization of the augmented bone substitute materials with newly formed bone and lead to the suggestion that the augmented volume reduced by condensation processes or the loss of the liquid component of the augmented volume. However, evaluation of CT scans is not able to provide an objective statement about degradation or dehydration processes. Therefore, histologic and histomorphometric analysis remains the method of choice for detailed analysis of cellular mechanisms.

The previously published histological and histomorphometrical analysis of the augmented bone substitute materials revealed good integration of the synthetic NB granules in the peri-implant tissue of the sinus cavity with formation of new bone associated with the bone substitute granules. In addition to the apposition of bone tissue, the HA granules were seeded with TRAP-positive and TRAP-negative multinucleated giant cells, which can be interpreted as an expression of an inflammatory response due to a foreign body reaction to the synthetic bone substitute material.[1]

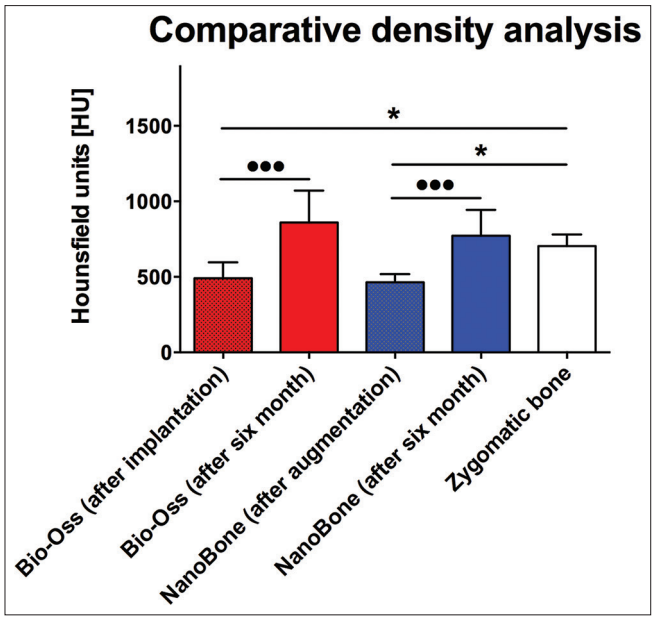

Figure 5: Graphical representation of the comparative density analysis of the Bio-Oss® and the NanoBone® grafts immediately and 6 months after augmentation compared to the density of the zygomatic bone (in Hounsfield units; *$P < 0.05$; ***$P < 0.001$)

The bovine BO granules were also well integrated in newly formed bone tissue, which seemed to originate from active osteoblasts on the surface of the bone substitute granules. In contrast to the synthetic bone substitute material, very few multinucleated giant cells were visible on the surface of the bovine-based bone substitute granules. The difference in the induction of multinucleated giant cells could be proved by histomorphometric analysis and stated as significant (number of multinucleated giant cells per mm^2: NB: 50.40 ± 7.16; BO: 16.37 ± 1.72; $P < 0.001$). In accordance with the presence of multinucleated giant cells, which are transported in the augmentation bed by a vessel-rich connective tissue, the vascularization and the ratio of connective tissue were significantly higher in the NB group (percentage vascularization: NB: 2.66% ± 0.78%; BO: 0.86% ± 0.07%; $P < 0.001$; connective tissue: NB: 53.87% ± 5.12%; BO: 34.14% ± 4.45%; $P < 0.001$). Further, the analysis of the tissue distribution in the implantation bed showed a significantly higher ratio of remaining bone substitute material in BO than that in NB group (NB: 24.28% ± 3.26%; BO: 40.13% ± 3.53%; $P < 0.01$). Interestingly, although different cellular reactions occurred in the implantation beds, no statistically significant difference in new bone formation could be observed (NB: 21.85% ± 5.96%; BO: 25.73% ± 7.94%). Although the investigated bone substitute materials induced different cellular reactions, the formation of new bone did not differ significantly.[1]

Accordingly, the radiologically investigated volumetric and bone density changes in the present study also did not differ significantly between both groups. Graft volumes decreased in both groups over the observation period of 6 months, while the measured bone density increased, most likely due to new bone formation in the augmented regions, also in both groups. It was concluded that the comparable increase in bone density in both groups was in accordance with the new bone formation detected by the histological analysis.[1]

A possible explanation for the fact that the augmented volume seemed to decrease and the bone density was significantly higher 6 months after augmentation in both groups, independent of the cellular reactions, is a combination of manual condensation of the augmented bone substitute material by pneumatization of the maxillary sinus and dehydration of the augmented biomaterial after its implantation with a simultaneous ingrowth of newly formed bone tissue in the intergranular space. Further, in a histological and histomorphometrical split-mouth trial, comparing the bone substitute materials NB and BO for sinus augmentation in a healthy patient collective, a significantly higher formation of multinucleated giant cells in the augmentation bed of the synthetic NB compared to the xenogeneic BO was detected while the formation of new bone as well as the ratio of remaining bone substitute showed no statistically significant difference. It could therefore be concluded that multinucleated giant cells act more as foreign body giant cells than as osteoclasts.[20] This assumption is in accordance with the results presented, as the volume reduction and density increase did not show any difference between both groups, although in histological analysis, significantly more multinucleated giant cells were found in the NB group.

The performed radiologic analysis presents a suitable supplement to the histological and histomorphometrical investigation of biomaterial integration within the human organism. Clinicians are in daily contact with bone substitute materials and are more interested in the clinical success and durability and reliability of the products they use than in the scientific details, such as cellular reactions. In comparison to the histological and histomorphometrical analysis, the radiologic analysis required less effort, both for the investigator and for the patient, as it is noninvasive and technically supported. By standard techniques, such as CT or digital volume tomography (DVT), which are commonly used in implant procedures, reliable and reproducible statements about density and volume of augmentations can be made, which are easy to understand and clearly interpretable. The ongoing development and dissemination of DVT is another factor, which facilitates the analysis of three-dimensional images at a lower exposure to radiation and makes this methodology viable for patients, clinicians, and scientists. In the planning phase of larger implantation or augmentation procedures and cases of anatomical abnormity, DVT is a standard diagnostic application. Further, it must be mentioned that two-stage sinus augmentation with implant insertion after 6 months causes a longer healing period for the patient compared to simultaneous augmentation and implant insertion. Regarding the ergonomic and patient-friendly trend toward simultaneous augmentation and implantation, it is questionable to what extent biopsies after bone augmentation can still be gained in the future, as in the case of single-stage augmentation and implantation, there is no possibility of obtaining biopsies of bone substitute materials from the augmentation site. Therefore, the analysis of CT or DVT images might become more important as it can also be performed in single-stage augmentation and implantation. The analysis of bone density and the volume of the augmented area can be an indicator of the remodeling and thus the ingrowth of new bone in the augmented bone substitute material. However, it must be mentioned that detailed conclusions about cellular reactions to different biomaterials can only be made by histological and histomorphometrical analysis. Especially, during the early phase

of research, histological analysis of biopsies is still important and will not become less relevant.

The presented methodology can prove to be a reliable and suitable technique for the analysis of graft volume and density changes and can complete histological analysis or even replace it to a certain degree. Especially for clinicians, this combination of validity and reproducibility in a noninvasive methodology presents major progress in the analysis of the interaction between bone substitute materials and the peri-implant tissue.

CONCLUSION

The presented radiologic analyses were performed to determine the changes in volume and density within the augmented human sinus cavities. Through the analysis of three-dimensional CT images that were recorded immediately after augmentation and 6 months later, changes in the volume and density of the graft over a period of 6 months were determined. In both groups, the volume of the augmented sinus cavities decreased over 6 months while the bone density increased significantly and reached higher values than the referenced zygomatic bone. Considering the results obtained from the histologic and histomorphometric investigation of the cellular response to both biomaterials, it was demonstrated that both biomaterials seemed to undergo volume reduction, while in the center of the augmented sinus cavities, bone remodeling took place, increasing the radiographically measurable bone density. It was shown that the radiologic and volumetric investigation method presented here might be a suitable, noninvasive investigation tool to complete and under certain circumstances avoid histological and histomorphometrical analysis. Moreover, this method of analysis provides suitable information for clinicians to assess the stability and predictability of augmentation procedures in an effective and minimally invasive manner.

Financial support and sponsorship

This study was supported by a grant from the Camlog Foundation, Basel, Switzerland.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Ghanaati S, Barbeck M, Lorenz J, Stuebinger S, Seitz O, Landes C, *et al.* Synthetic bone substitute material comparable with xenogeneic material for bone tissue regeneration in oral cancer patients: First and preliminary histological, histomorphometrical and clinical results. Ann Maxillofac Surg 2013;3:126-38.
2. Kovács AF. The fate of osseointegrated implants in patients following oral cancer surgery and mandibular reconstruction. Head Neck 2000;22:111-9.
3. Javed F, Al-Hezaimi K, Al-Rasheed A, Almas K, Romanos GE. Implant survival rate after oral cancer therapy: A review. Oral Oncol 2010;46:854-9.
4. Akoglu B, Ucankale M, Ozkan Y, Kulak-Ozkan Y. Five-year treatment outcomes with three brands of implants supporting mandibular overdentures. Int J Oral Maxillofac Implants 2011;26:188-94.
5. Damien CJ, Parsons JR. Bone graft and bone graft substitutes: A review of current technology and applications. J Appl Biomater 1991;2:187-208.
6. Younger EM, Chapman MW. Morbidity at bone graft donor sites. J Orthop Trauma 1989;3:192-5.
7. Valentini P, Abensur D. Maxillary sinus floor elevation for implant placement with demineralized freeze-dried bone and bovine bone (Bio-Oss): A clinical study of 20 patients. Int J Periodontics Restorative Dent 1997;17:232-41.
8. Valentini P, Abensur DJ. Maxillary sinus grafting with anorganic bovine bone: A clinical report of long-term results. Int J Oral Maxillofac Implants 2003;18:556-60.
9. Houser BE, Mellonig JT, Brunsvold MA, Cochran DL, Meffert RM, Alder ME. Clinical evaluation of anorganic bovine bone xenograft with a bioabsorbable collagen barrier in the treatment of molar furcation defects. Int J Periodontics Restorative Dent 2001;21:161-9.
10. Stübinger S, Ghanaati S, Orth C, Hilbig U, Saldamli B, Biesterfeld S, *et al.* Maxillary sinus grafting with a nano-structured biomaterial: Preliminary clinical and histological results. Eur Surg Res 2009;42:143-9.
11. Ghanaati S, Barbeck M, Willershausen I, Thimm B, Stuebinger S, Korzinskas T, *et al.* Nanocrystalline hydroxyapatite bone substitute leads to sufficient bone tissue formation already after 3 months: Histological and histomorphometrical analysis 3 and 6 months following human sinus cavity augmentation. Clin Implant Dent Relat Res 2013;15:883-92.
12. Schlee M, Dehner JF, Baukloh K, Happe A, Seitz O, Sader R. Esthetic outcome of implant-based reconstructions in augmented bone: Comparison of autologous and allogeneic bone block grafting with the pink esthetic score (PES). Head Face Med 2014;10:21.
13. Eppley BL, Pietrzak WS, Blanton MW. Allograft and alloplastic bone substitutes: A review of science and technology for the craniomaxillofacial surgeon. J Craniofac Surg 2005;16:981-9.
14. Hoexter DL. Bone regeneration graft materials. J Oral Implantol 2002;28:290-4.
15. Ghanaati S, Orth C, Barbeck M, Willershausen I, Thimm BW, Booms P, *et al.* Histological and histomorphometrical analysis of a silica matrix embedded nanocrystalline hydroxyapatite bone substitute using the subcutaneous implantation model in Wistar rats. Biomed Mater 2010;5:35005.
16. Gerber T, Traykova T, Henkel KO, Bienengraeber V. Development and *in vivo* test of sol-gel derived bone grafting materials. J Sol-Gel Sci Technol 2003;26:1173-8.
17. Gerike W, Bienengräber V, Henkel KO, Bayerlein T, Proff P, Gedrange T, *et al.* The manufacture of synthetic non-sintered and degradable bone grafting substitutes. Folia Morphol (Warsz) 2006;65:54-5.
18. Jensen SS, Aaboe M, Pinholt EM, Hjørting-Hansen E, Melsen F, Ruyter IE. Tissue reaction and material characteristics of four bone substitutes. Int J Oral Maxillofac Implants 1996;11:55-66.
19. Norton MR, Odell EW, Thompson ID, Cook RJ. Efficacy of bovine bone mineral for alveolar augmentation: A human histologic study. Clin Oral Implants Res 2003;14:775-83.
20. Lorenz J, Kubesch A, Korzinskas T, Barbeck M, Landes C, Sader RA, *et al.* TRAP-positive multinucleated giant cells are foreign body giant cells rather than osteoclasts: Results from a split-mouth study in humans. J Oral Implantol 2015;41:e257-66.