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Original Article

Micro-computed tomography analysis of mineral attachment to the implants augmented by three types of bone grafts: An experimental study in dogs

Mahdi Gholami[1,2], Farzaneh Ahrari[3], Hamideh Salari Sedigh[4], Christoph Bourauel[2]

[1]Oral and Maxillofacial Disease Research Center, School of Dentistry, Mashhad University of Medical Sciences, [3]Dental Research Center, School of Dentistry, Mashhad University of Medical Sciences, [4]Department of Clinical Sciences, School of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran, [2]Department of Oral Technology, School of Dentistry, University Hospital of Bonn, Bonn, Germany

ABSTRACT

Background: This study compared the effect of various grafting materials on the area and volume of minerals attached to dental implants.

Materials and Methods: In this animal study, 13 dogs were divided into three groups according to the time of sacrificing (2 months, 4 months, or 6 months). The implants were placed in oversized osteotomies, and the residual defects were filled with autograft, bovine bone graft (Cerabone), or a synthetic substitute (Osteon II). At the designated intervals, the dogs were sacrificed and the segmented implants underwent micro-computed tomography analysis. The bone-implant area (BIA) and bone-implant volume (BIV) of bone and graft material were calculated in the region of interest around the implant. The data were analyzed by two-way analysis of variance (ANOVA) at $P < 0.05$.

Results: There was no significant difference in BIA and BIV between the healing intervals for any of the grafting materials ($P > 0.05$). ANOVA exhibited comparable BIA and BIV between the grafting materials at 2 and 4 months after surgery ($P > 0.05$), although a significant difference was observed after 6 months ($P < 0.05$). Pairwise comparisons revealed that BIA was significantly greater in the autograft-stabilized than the synthetic-grafted sites ($P = 0.035$). The samples augmented with autograft also showed significantly higher BIV than those treated by the xenogenic ($P = 0.017$) or synthetic ($P = 0.002$) particles.

Conclusion: All graft materials showed comparable performance in providing mineral support for implants up to 4 months after surgery. At the long-term (6-month) interval, autogenous bone demonstrated significant superiority over xenogenic and synthetic substitutes concerning the bone area and volume around the implant.

Key Words: Autograft, dental implant, micro-computed tomography, osseointegration, synthetic bone graft, xenograft

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Address for correspondence:
Dr. Farzaneh Ahrari,
Dental Research Center,
School of Dentistry,
Mashhad University of
Medical Sciences, Vakilabad
Blvd, Mashhad, Iran.
E-mail: farzaneh.ahrari@
gmail.com,
ahrarif@mums.ac.ir

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INTRODUCTION

The request for replacing partial or complete edentulous dentitions with implants is ever-increasing. The optimal quantity and quality of the host bone are influential factors in the survival of endosseous implants. However, the bone condition may be inadequate in some cases such as those requesting immediate implant placement in large extraction sockets, patients with atrophied alveolar ridges as a result of old extractions or developmental anomalies, and subjects with localized infections or periodontal diseases. Bone augmentation with a grafting material is generally planned under these conditions to minimize the gap between the implant surface and the bone walls and thus increasing the success rate of treatment.[1-3]

Various types of grafting materials have been proposed and applied for esthetic and regenerating purposes in medicine and dentistry. Bone substitutes may be autogenic, xenogenic, or synthetic (alloplastic), based on the origin of production.[4,5] Autogenous bone is generally considered the gold standard for bone augmentation because of the cellular viability to provide osteoconductive, osteoinductive, and osteogenic features. However, the application of autograft is generally limited by the quantity of bone that could be harvested from the patient's skeleton, and by the associated morbidity due to the two surgical procedures (donor and recipient sites).[4,6,7] Xenografts are obtained from the inorganic portion of the bone of other species than the host, and provide osteoconductive properties.[8-10] The bovine-derived xenograft has gained remarkable popularity in recent years as a suitable replacement for autograft. Cerabone (Botiss Biomaterials GmbH, Zossen, Germany) is an osseous matrix obtained from the bovine trabecular bone after removing organic portions through heating above a temperature of 1200°C.[11] Synthetic (alloplastic) bone substitutes are produced from calcium phosphate and present osteoconductive potential as well.[12] They have interesting features such as unlimited supply and eliminating the risk of immunologic reactions or disease transmission. Osteon II (Genoss, Seoul, Korea) is an alloplastic bone substitute that consists of 70% hydroxyapatite and 30% β-tricalcium phosphate (β-TCP).[13-15]

The success of osseointegration around dental implants can be assessed by measuring the size of mineralized tissues attached to the implant surface. There are differences in the resorption rate and bone regenerating capability between various bone substitute materials. Micro-computed tomography (μCT) is a modern and nondestructive technology to examine bone volume and architecture around dental implants.[6,16] This technique benefits from high-resolution (6–72 μm) imaging to create numerous cross-sections from an object. The data are later employed to produce three-dimensional (3D) models without inducing detrimental effects on the original sample.[6]

There are few studies on the use of μCT to assess the effects of different bone substitutes on the osseointegration around dental implants. Therefore, the present μCT study aimed to compare the effect of various grafting materials (autograft, bovine bone graft, and synthetic graft) on the surface area and volume of bone and graft material attached to dental implants after a concurrent implantation and grafting procedure in dogs.

MATERIALS AND METHODS

Animals

This animal study was approved by the Animal Care and Use Committee at Mashhad University of Medical Sciences and coded as IR.mums.SD REC.1394.130.

Thirteen Iranian male dogs (aged 18–36 months, with body weights 20–35 kg) were collected. The dogs were housed in special-designed rooms at the Animal Center of Mashhad Dental School and fed with a standard dog feed and fresh water *ad libitum*. To ensure health and acclimation, the animals were quarantined for 2 weeks before experimentation.

Surgical procedure

The dogs were numbered and assigned to three groups based on the time of euthanasia. Five animals were sacrificed after 2 months (Group 1) whereas four dogs were sacrificed after 4 months (Group 2) and the other four after 6 months (Group 3).

The surgical procedure was conducted under general anesthesia and aseptic conditions. At first, acepromazine 1% (0.01–0.02 mg/g; Alfasan, Woerden, Netherlands) was injected intramuscularly to allow for the placement of an angiocatheter. Then, a combination of ketamine 10% (10 mg/kg; Alfasan) and diazepam 10 (10 mg/2 mL; Caspian Tamin Co, Tehran, Iran) was intravenously administered to induce general anesthesia.

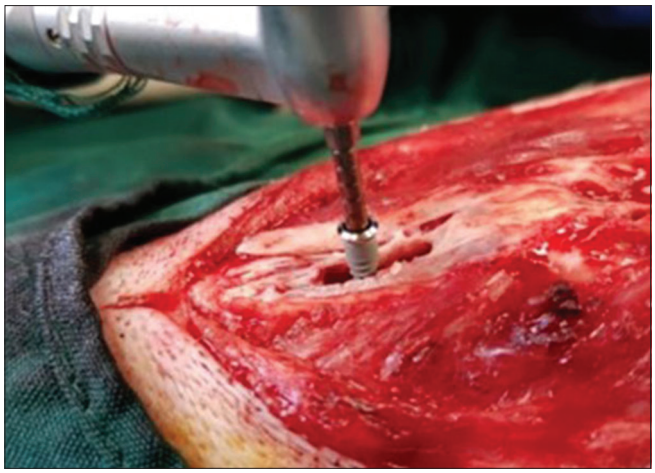

Figure 1: Placement of an implant at the center of the osteotomy defect.

The anesthesia was continued through inhalation of 2.5% isoflurane in O_2. Antibiotic therapy was started by slow intravenous injection of 1 g cefazolin (Loghman, Iran) before and after surgery. To achieve pain control, meloxicam 2.0% (0.2 mL/kg body weight; Razak, Iran) was administered during the operation.

The osteotomies were prepared in the sternum (chest bone) of dogs, which typically consists of an anterior segment (the presternum), five cylindrical segments or sternebrae (the body of the sternum), and a uniform process (the hind segment). The surgical field was shaved and disinfected with a 7.5% povidone-iodine solution. Using a number 15 surgical blade, the incision started at the site of the second rib and continued until the fifth rib. The tissues were separated layer by layer and the periosteum was reflected by a periosteal elevator.

After exposure to the sternum, 3–5 oversized defects were made in the sternebrae of each animal by trephine osteotomy. The bur was applied several times to create defects measuring 10 mm in length, 4 mm in width, and 6 mm deep, for placement of the implant and graft material.

Implant and graft placement

The ICX surgical kit was employed to drill the 2 mm end of each defect. Afterward, a titanium screw implant (ICX, Medentis Medical GmbH, Dernau, Germany), with a diameter of 3.45 mm and length of 6.5 mm was placed at the center of the defect [Figure 1]. A total of 3–5 implants were inserted per animal, according to the surgical conditions.

Each group of animals contained three subgroups based on the bone graft material employed. In subgroup 1 (autograft), the implant was surrounded by autogenous bone particulates (particle size: 1–2 mm). These particles were harvested during the drilling of the bone at the time of operation. In subgroup 2 (xenograft), deproteinized bovine bone mineral (particle size: 0.5–1.0 mm, Cerabone; Botiss Biomaterials GmbH, Zossen, Germany) was grafted into the osteotomy site to stabilize the implant. In Group 3 (synthetic graft), the gap surrounding the implant was filled by a synthetic biphasic calcium phosphate substitute (particle size 0.5–1.0 mm, Osteon II, Genoss, Seoul, Korea). The bone grafts were hydrated with saline solution before packing into the osteotomy site. Following excess removal, a resorbable collagen membrane (Jason Membrane, Botiss Biomaterials GmbH) was employed to cover the graft and implant.

The same order of graft placement was continued, so that each animal received all three types of graft materials. Finally, the five dogs that were planned to be euthanized at 2 months received 21 implants augmented by three types of graft materials (n = 7 per subgroup). The four dogs in Group 2 (planned to be sacrificed at 4 months) and also the four dogs in Group 3 (planned to be sacrificed at 6 months) received 18 implants supported by three bone graft materials (n = 6 per subgroup).

Wound closure was performed in four layers (periosteum, muscle, subcutaneous tissue, and skin). The first three layers were sutured by an absorbable 2-0 vicryl (Supabon, Supa Medical devices, Tehran, Iran) and the skin with a nonabsorbable 2-0 nylon (Supabon).

Postsurgical procedure

Postoperatively, the animals were transferred to a warm place. The surgical field was dressed in sterile gauze, which was changed daily for 7 days. To inhibit licking of the incision area, a cervical collar was employed. Antibiotic therapy was continued by intramuscular injection of 1 g cefazolin every 12 h for 7 days. Furthermore, a meloxicam tablet (7.5 mg, Loghman Co, Tehran, Iran) was administered every 24 h for 2 days to control pain.

The sutures were removed after 10 days in animals that showed favorable wound healing. In the presence of dehiscence, the incision area was treated by repeated suturing and antibiotic treatment.

Sample preparation for micro-computed tomography

At the designated intervals (2 months, 4 months, and 6 months), the dogs were euthanized by

an overdose of sodium pentobarbital, and the sternum was reopened. After measuring the implant stability (the result has been presented elsewhere),[10] the sternebrae containing the implant and surrounding tissues were excised by a saw. The block sections were placed in 10% neutral-buffered formalin and were sent to the Oral Technology Department at the University Hospital of Bonn for further analysis. The result of µCT testing is reported here. Three representative samples were selected from each subgroup for µCT assessment. A flowchart of the methodology is illustrated in Figure 2.

Micro-computed tomography analysis

A high-resolution µCT scanner (µCT Skyscan 1174™, Skyscan, Kontich, Belgium) was used to achieve a 3D reconstructed view of the grafted specimens. The equipment had a voxel size of 6.8 µm, an X-ray tube voltage of 50 kV, and a current of 800 µA. Altogether, 1024 µCT slices were imaged and the total scanning time was up to 300 min. The scanned data were exported in Digital Imaging and Communications in Medicine format and imported into 3D software (Amira, Visage Imaging GmbH, Berlin, Germany) for further analysis of the architecture within the region of interest (ROI) around the implant.

The ROI was established as the implant surface and the region at the 1 mm distance from the implant surface. Using the software, the superior tissue part and the 2 mm apical part of the fixture in the coronal view were considered the limit line and were excluded from the analysis. Then, the fixture, the "bone and graft material," and the soft tissues were differentiated, based on visual inspection and histogram analysis. The maximum and minimum grayscale threshold values were adopted as 70–255 for the fixture, 35–70 for the bone and graft material, and 0–35 for soft tissues.

The image was then segmented into two parts: the outside section (bone and graft tissue around the fixture) and the inside section (the segmented fixture). The 3D reconstruction of the two sections prepared by the Amira software is illustrated in Figure 3. Afterward, the surface area of the fixture was calculated by the software and considered the X parameter. Furthermore, the volume between the fixture and a zone expanded by 1 mm circumferentially around the fixture was calculated and defined as the A parameter.

To achieve the bone and graft material attached to the implant surface, the inside and outside files were combined and the noncommon points were deleted. In this way, all points in common between the two files (on the fixture surface) were retained [Figure 4]. Finally, the surface area of the common points

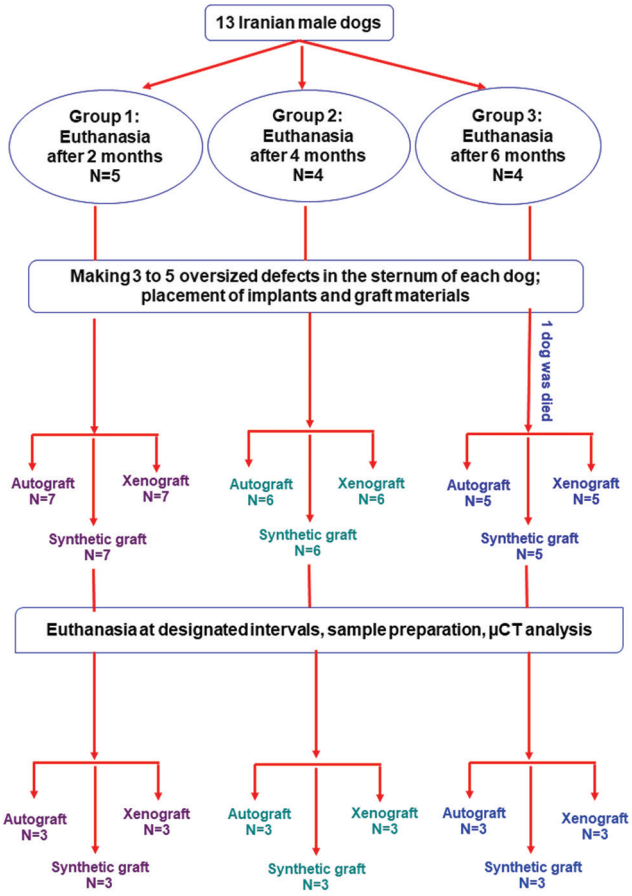

Figure 2: A flowchart of the methodology. Three representative samples were selected for micro-computed tomography (µCT).

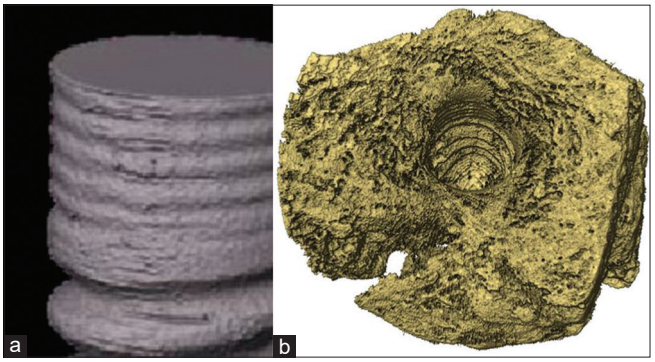

Figure 3: The three-dimensional reconstruction by micro-computed tomography for a sample retrieved after concurrent implantation and grafting procedure by deproteinized bovine bone mineral (cerabone). (a) Inside section (fixture view). (b) Outside section (bone and graft view).

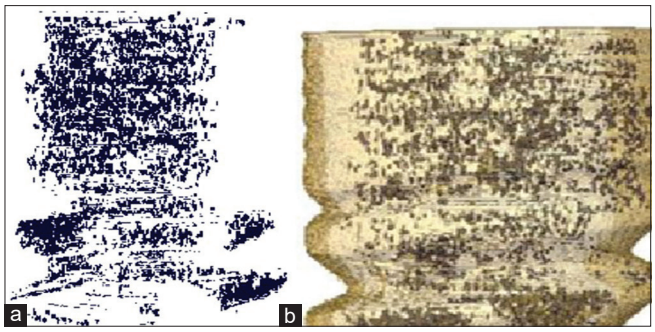

Figure 4: Micro-computed tomography analysis of a segment retrieved after concurrent implantation and grafting procedure by deproteinized bovine bone mineral (cerabone). (a) Combination of inside and outside files and deleting all noncommon points. (b) Reconstruction of the bone and graft material attached to the fixture surface.

between the inside and outside files was calculated and considered the Y parameter. In addition, the volume of bone and graft material in the ROI around the implant was measured and defined as the B parameter.

The outcome variables were bone-implant area (BIA) and bone-implant volume (BIV). BIA was defined by dividing the area of bone and graft material at the implant surface (Y parameter) by the total implant surface (X parameter) and multiplying the result by 100 (BIA = Y/X ×100). BIV was also calculated, being the percentage of bone and graft volume that was present in the total volume of interest around the implant (BIV = B/A ×100; B = The volume of bone and graft material in the ROI around the implant, A = The volume between the fixture and a zone expanded by 1 mm circumferentially around the fixture, i.e. the total volume of ROI).

Statistical analysis

After confirming the normal distribution of the data by a Shapiro–Wilk test ($P > 0.05$), the data were subjected to a two-way analysis of variance (ANOVA) to denote any significant difference in BIA (the percentage of bone and graft area per total implant area) and BIV (the percentage of bone and graft volume per total volume) variables between the different grafting materials and healing intervals. As there was a significant interaction between the two factors, the differences between and within groups were analyzed separately through one-way ANOVA. The data analyses were performed through computer software (SPSS version 16.0; SPSS Inc, Chicago, IL, USA), and the level of significance was set at $P < 0.05$.

RESULTS

One dog died before the completion of the follow-up period and three inserted implants were lost. In total, 54 implants were observed until the end of the experiment ($n = 21$ implants in Group 1, $n = 18$ implants in Group 2, and $n = 15$ implants in Group 3). The success rate of implants was 83%, as 45 implants were integrated and 9 were lost. For μCT assessment, three representative samples were selected from each subgroup of animals.

Table 1 presents the mean and standard deviation of BIA (the percentage of bone and graft area per implant area) for the implants supported by the three graft materials at different follow-up periods. The data for the BIV variable (the percentage of bone and graft volume per total volume) are presented in Table 2.

The autograft-stabilized sites demonstrated the lowest BIA and BIV at the 2-month interval. Afterward, BIA and BIV increased, so that the autogenous bone was the best material concerning the area and volume of the bone graft complex at 4- and 6-month intervals. The bovine-grafted segments provided the greatest bone graft area and volume at 2 months after surgery. Both variables experienced some decrease at 4 months and then increased at the 6-month time point. The synthetic graft granules rendered small variations in BIA and BIV throughout the experiment. ANOVA revealed no statistically significant difference in BIA and BIV measurements between the different healing intervals (2 months, 4 months, and 6 months) for any of the grafting materials [$P > 0.05$; Tables 1 and 2].

ANOVA was also run to compare BIA and BIV variables between the different grafting materials at each healing interval. The results showed no significant difference in BIA and BIV among the grafting materials either at 2 or at 4 months after surgery ($P > 0.05$), although a significant difference was found at the 6-month interval [$P < 0.05$; Tables 1 and 2]. The Tukey test revealed that the surface area of bone and graft material attached to the implant surface (BIA) was significantly greater in the autograft-stabilized sites, as compared to those augmented by the synthetic graft material at 6 months [$P = 0.035$; Table 1]. Concerning BIV, the samples treated by autograft particles showed significantly higher graft and bone volume than that of the xenogenic ($P = 0.017$) or synthetic ($P = 0.002$) granules. Furthermore, BIV was significantly greater

Table 1: The mean (%) and standard deviation of the bone implant area variable (BIA = the percentage of bone and graft area per total implant area) according to the grafting materials and healing intervals

Group	Mean±SD (%)			
	2 months	4 months	6 months	Statistical significance (*P*)
Graft material				
Autograft	29±8	58±15	56±4[a]	0.123
Xenograft	39±1	28±14	46±4[a,b]	0.167
Synthetic graft	37±4	41±2	37±1[b]	0.488
Statistical significance (*P*)	0.329	0.147	0.039*	

*A statistically significant difference at $P<0.05$. Different superscript letters indicate statistical significance among the grafting materials. SD: Standard deviation

Table 2: The mean (%) and standard deviation of the bone implant volume variable (BIV = the percentage of bone and graft volume per total volume) according to the grafting materials and healing intervals

Group	Mean±SD (%)			
	2 months	4 months	6 months	Statistical significance (*P*)
Graft material				
Autograft	38±14	60±5	63±2[a]	0.127
Xenograft	43±1	31±14	52±2[b]	0.125
Synthetic graft	42±4	51±4	40±1[c]	0.121
Statistical significance (*P*)	0.819	0.078	0.002*	

*A statistically significant difference at $P<0.05$. Different superscript letters indicate statistical significance among the grafting materials. SD: Standard deviation

in the xenogenic- than in the synthetic-grafted defects ($P = 0.014$).

DISCUSSION

This animal study investigated the amount of bone formation after concurrent implantation and augmentation with different graft types (autogenic, xenogenic, and synthetic). The study model tried to mimic the situation when an implant is placed in a large bony defect, and thus concurrent regeneration with graft and a membrane is mandatory. All three bone substitutes were placed in the same dog to negate variations in the healing process and physiology between animals. A resorbable collagen membrane was employed to cover the defect, thus promoting guided bone regeneration by stimulating the migration of osteogenic cells and inhibiting the invasion of soft-tissue cells.[17]

μCT analysis is an accurate, useful, and nondestructive technique that allows a 3D assessment of the total circumferential space.[6,16,18] In this study, μCT analysis was employed for scanning the segmented implants. The area and volume of bone and graft material were measured in the region of interest (ROI) around the implant surface to serve as an indicator of osseointegration. The grayscale threshold for bone and graft material was considered the same in measurements, because segmentation between the two may be associated with a minor overlap in some areas.[6] Histologic studies have shown that the grafted bone undergoes the remodeling process and is partially replaced by new bone after a few weeks.[4] Therefore, the integrated parts of newly formed bone and remaining biomaterial may have similar mineral contents near the interface.[6] Despite its benefits, the μCT evaluation is associated with some limitations. It has been demonstrated that the accuracy of μCT analysis depends on the human ability to correctly determine the thresholds for different tissues. In addition, a blurred border may be observed in proximity to the implant surface in μCT data due to the occurrence of metal artifacts.[19,20]

In the autogenous group, the percentage of the bone graft area attached to the implant surface was 29% ± 8% at 2 months and then increased to 58% ± 15% and 56% ± 4% at 4 and 6 months, respectively. The ratio of bone graft volume to total volume was 38% ± 14% at 2 months, which enhanced to 60% ± 5% and 63% ± 2% at intervals of 4 and 6 months after implantation, respectively. It is believed that the viable cells in the autogenous bone provide a high potential for new bone formation and regeneration in bony defects. Despite the remarkable increase in the quantity of bone and graft material between 2 and 4 months and between 2 and 6 months, neither of the changes was statistically significant in the autogenous group.

Deproteinized bovine bone mineral (Cerabone) displayed BIA of 39% ± 1%, 28% ± 14%, and

46% ± 4% at intervals of 2, 4, and 6 months after surgery. The BIV in the Cerabone group was 43% ± 1%, 31% ± 14%, and 52% ± 2% at the corresponding intervals. The bone graft area and volume were not significantly different between the various healing intervals. The bovine bone graft is assumed to be a suitable alternative to the autograft because of its great similarity to the structure of human bone. The proteins and bone-forming cells are easily adhered to the rough surface of Cerabone, thus facilitating the integration of graft with newly formed bone. In contrast to the autogenous bone, the bovine-bone mineral shows a slow resorption rate[21-23] and may be preferred in situations when a high volume stability and preservation of the graft material are critical. On the other hand, the slow rate of resorption may cause interference with the healing process and delay bone formation in the Cerabone-grafted area.[9,24]

In the alloplastic material group (Osteon II), the ratio of bone graft area to total implant area (BIA) was 37% ± 4%, 41% ± 2%, and 37% ± 1% at intervals of 2, 4, and 6 months after implantation. The ratio of bone-implant volume to total volume was 42% ± 4%, 51% ± 4%, and 40% ± 1% at the corresponding intervals. These values demonstrated a small increase in bone graft area and volume between 2 and 4 months, which was followed by a reversal at the 6-month time point. The changes in BIA and BIV variables in the Osteone II group were small and not significant between the healing intervals. Osteon II consists of a hydroxyapatite scaffold and β-TCP at the ratio of 70/30, respectively. Hydroxyapatite has low solubility and provides a relatively firm scaffold to maintain stability, whereas β-TCP shows fast biodegradability and is rapidly remodeled and replaced by newly formed bone.[16] It is assumed that the pores in the β-TCP particles stimulate the infiltration of osteogenic cells. Furthermore, β-TCP particles are mainly degraded through the chemical dissolution of the material instead of osteoclastic resorption.[16]

At 2 months and 4 months after surgery, the three graft materials showed comparable performance in providing mineral support for implants placed in large defects. However, at the 6-month time point, the autogenous particles exhibited significant superiority over the synthetic bone substitute concerning the bone graft area (BIA variable), and performed significantly better than both the synthetic and bovine bone granules, cornering the volume of bone and graft material (BIV variable). Furthermore, the defects treated with the bovine-derived xenograft displayed significantly higher BIV than those of the synthetic-grafted sites.

Overall, the autogenous particles performed the best, and the synthetic bone substitute demonstrated the worst performance at the long-term interval. The findings of this study implied that both xenogenic and synthetic grafts performed similarly to the autograft up to 4 months after implantation, but autograft-treated sites revealed greater amounts of bone and graft material at the 6-month time point. The superior performance of autograft particles may be related to the presence of osteogenic cells, which can lead to a higher rate of bone formation in the grafted area. In contrast, both xenogenic and synthetic bone substitutes are just osteoconductive and thus require a longer time for regeneration than autograft.[25] Comparison of xenogenic and synthetic grafts at 6 months also revealed a small but significant superiority of the xenograft concerning the bone volume around the implant, which may have some implications in the clinical situation.

Although autograft was superior in bone regeneration than other materials at the long-term interval, both bovine bone and alloplastic grafts performed well and could be considered suitable alternatives to the autogenous bone for supporting the implants placed in bony defects. This is especially important in clinical conditions when other parameters such as availability, patient morbidity, biocompatibility, or expense lead the clinician to choose a grafting material other than the autogenous bone.

The outcomes of this study are corroborated by previous studies that reported the superiority of autografts compared to other grafting materials for supporting implants placed in bone defects.[3,18] Using μCT analysis, de Faria Vasconcelos *et al.*[18] reported that autografts outperformed xenografts in maxillary sites grafted with these materials. In contrast to the outcomes of this study, Friberg[26] demonstrated that all types of graft materials (autografts, allografts, xenografts, and alloplastic materials) created comparable augmentation results, which allowed for the placement of implants in bone defects. Oh *et al.*[27] displayed similar biocompatibility and osteoconductivity for biphasic calcium phosphate and deproteinized bovine bone mineral when applied for maxillary sinus augmentation. In the study of Antunes

et al.,[19] deproteinized bovine bone mineral in the form of sponge or granules demonstrated similar or higher bone formation as compared to the autogenous bone within the defect. The controversy between the results of this study and those of previous authors could be ascribed to variations in several factors including the method of evaluation, the size of the bone defect, and the surgical procedure employed.

The limitations of this study were the small sample size, and the insertion of implants in the sternum instead of the maxillary or mandibular jaw. Another limitation was that in the measurements, bone and graft material was considered a mixture and the amount of mineralized bone was not differentiated from the residual graft material. Since bovine bone graft displays slow and superficial resorption, new bone formation and osseointegration around Cerabone may be poor and with inadequate strength.[9] Further long-term studies with larger sample sizes are warranted to assess the efficacy of various grafting materials in enhancing osseointegration around dental implants placed through concurrent implantation and grafting procedure in extensive bone defects.

CONCLUSION

Within the limitations of the present μCT study, the following conclusions can be drawn:

1. There was no significant difference in bone area and volume measurements between specimens obtained at 2 months, 4 months, and 6 months after concurrent implantation and regeneration with any of the grafting materials (autogenic, xenogenic, or synthetic).
2. The three graft materials showed comparable performance in providing mineral support for implants placed in large defects at 2 months and 4 months after surgery. However, at the 6-month interval, the defects augmented by autograft demonstrated significant superiority over the xenogenic- or synthetic-grafted sites concerning the bone area and volume around the implant surface.
3. Although autogenous bone graft particles could produce better bone regeneration than other materials at the long-term interval, both xenogenic and synthetic bone substitutes could be considered suitable alternatives for autografts to be employed in conjunction with dental implants in extensive defects.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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