Eighteen-Month Radiographic and Histologic Evaluation of Sinus Grafting with Anorganic Bovine Bone in the Chimpanzee

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Maxillary sinus grafting procedures are currently the treatment of choice when the alveolar crest of the posterior maxilla is in close approximation to the maxillary sinus. The short-term histologic and radiographic healing following sinus grafting with natural bone mineral (Bio-Oss) in the chimpanzee has been evaluated. We have previously shown by histomorphometric and radiographic analysis that the percentage of vital bone area, the vertical height, and the density of new bone in the maxillary sinus was significantly greater with anorganic bovine bone compared to bovine Type I collagen matrix. The purpose of this in vivo study was to determine the bone mineral density (BMD) of the sinus grafts, the vertical height stability, the vital bone area, and the extent of anorganic bovine bone replacement 18 months postoperatively in 4 maxillary sinuses from 4 different animals. Radiographic analysis of computed tomographic scans taken at 1.5 years revealed an average BMD of 658 mg/mL, which was not significantly different from the values found at 6.5 months. The radiographic vertical height was maintained between the 6.5- and 18-month time points. On average, the grafts were found to have a height of 14 mm. Lateral wall biopsy specimens at 7.5 months were compared to those at 18 months. With the anorganic bovine bone treatment, the percentage of vital bone area increased from 62 ± 3% to 70 ± 7% and the percentage of natural bone mineral area decreased from 19 ± 14% to 6 ± 3%. The bovine Type I collagen matrix vital bone percentage at 7.5 months was 34 ± 21%. These results demonstrate that sinus grafting with anorganic bovine bone maintains radiographic evidence of density and height stability to 1.5 years. In addition, histologic evidence supports the hypothesis that anorganic bovine bone is replaced by vital bone.
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Key words: anorganic bovine bone, bone regeneration, sinus grafting

With the exponentially growing awareness and subsequent demand for dental implants, there is a concomitant demand for improved bone regeneration techniques. Contemporary bone regeneration techniques for implant dentistry consist of a variety of materials and devices and an equally diverse array of techniques to employ them. While success has been obtained for many simpler regenerative procedures, attempts at more challenging regenerative cases have been less predictable. A considerable research effort is therefore currently focused on increasing the breadth of intervention capabilities for maximizing the regenerative healing process and simplifying the entire procedure.

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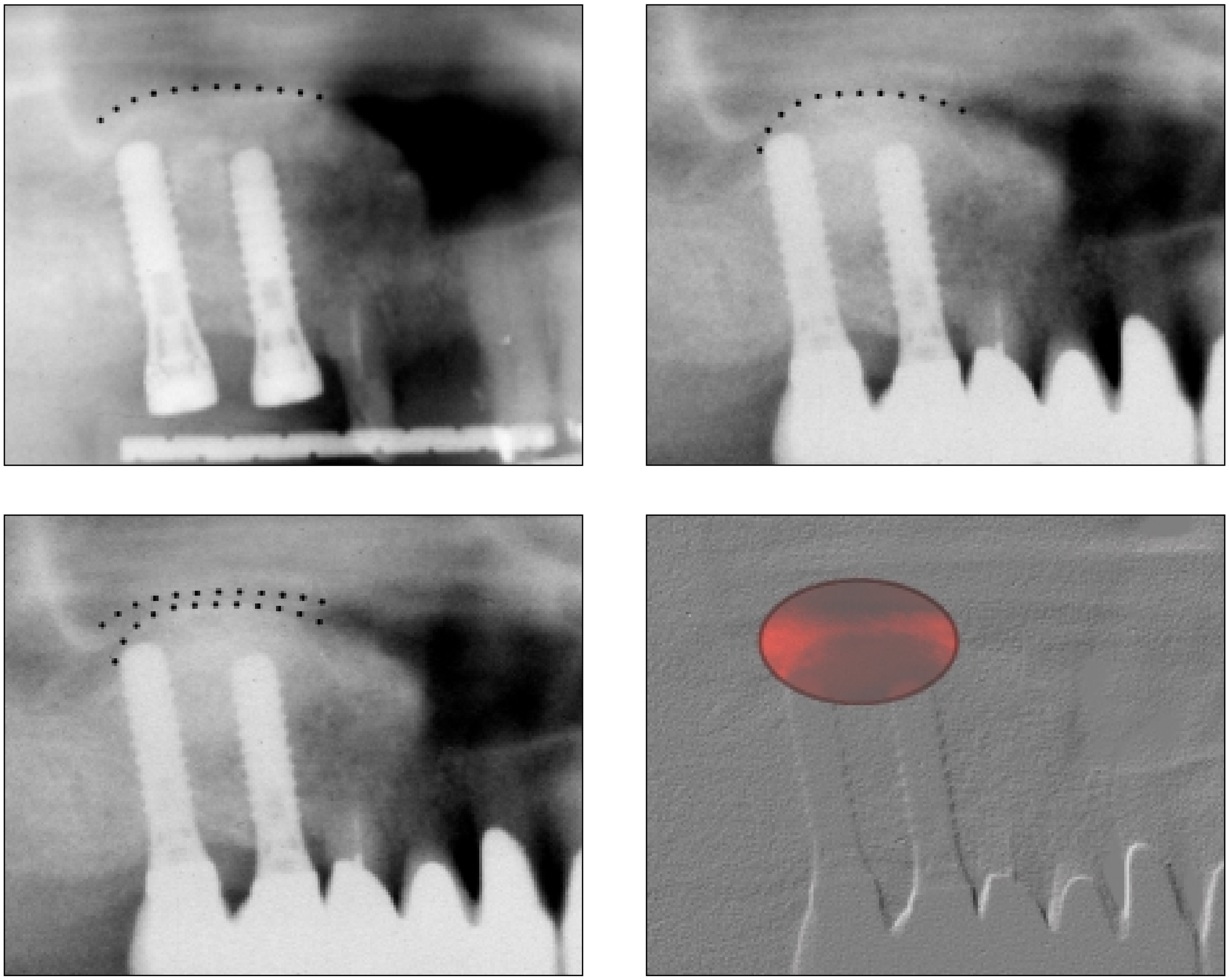

Fig 1 Radiographic example of vertical height loss, or "slumping," over time. The contrast-adjusted panoramic radiograph in Fig 1a shows the superior height of a sinus grafted with autogenous bone shortly after surgery. Fig 1b shows the superior height of the same sinus graft 9 months later. Fig 1c shows Fig 1b with the actual decrease in vertical height, or "slumping," outlined. The red area shown within the outlined region of interest on Fig 1d represents the difference in bone density over time for the digital images of Figs 1a and 1b.

One of the most challenging bone regeneration situations in the oral and maxillofacial environment is to induce bone formation following maxillary sinus augmentation for dental implant placement. This procedure was first reported by Boyne and James in 1980[1] and has since become a commonly performed procedure. While sinus grafting has many reports of success, very few studies exist to critically evaluate the long-term clinical results of this procedure.[2] One such concern that has been a subject of recent interest is the tendency of the vertical height of the sinus graft to decrease over time.[3] The sinus graft example shown in Fig 1 demonstrates the "slumping" effect that is seen in some cases.

Many different techniques are currently employed for sinus augmentation. Current data indicate a considerable amount of variation in the quality of bone attained as a result of this procedure.[4–7] In the histomorphometric data from one such study, the range in the percentage of vital bone area was from 5% to 59%.[5] In another study, the range was from 5% to 45%.[7] Previous histologic studies have been limited by a small number of biopsies and inconsistent postoperative biopsy timepoints. This makes it difficult to draw any definitive conclusions from the data; however, it is evident from these studies that in many instances very poor quality bone was realized, even after several months of healing.

As with most oral and maxillofacial regenerative procedures, a wide variety of materials have been used and reported in the literature for the sinus augmentation procedure in humans. Autografts obtained from numerous donor locations have been utilized with success.[1,4,8–10] Both the nonresorbable hydroxyapatite Interpore 200 (Steri-Oss, Yorba Linda, CA) and the anorganic bovine bone Bio-Oss (Osteohealth, Shirley, NY) have been successfully employed alone for sinus augmentation in humans.[11,12] The use of demineralized freeze-dried bone allograft alone has been reported, although results with this material alone have not always been predictable.[13,14] Numerous combinations,[9,15] including those with anorganic bovine bone (Bio-Oss), have been successfully employed.[11,14,16] Moreover, several other studies have reported promising clinical and histologic data using anorganic bovine bone in a variety of oral and maxillofacial applications.[17–19]

A model has been developed in the chimpanzee to evaluate bone formation over time clinically, radiographically, and histologically following maxillary sinus augmentation.[20–22] This model has several advantages, including a size and shape that closely approximates the human maxillary sinus. Moreover, the rate of bone metabolism is very similar in chimpanzees and humans. The overall objective of this study was to evaluate the long-term results of sinus grafting with anorganic bovine bone in the chimpanzee.

Materials and Methods

Materials. Sinus grafting was performed with commercially available purified anorganic bovine bone (Bio-Oss). Adult chimpanzees (*Pan troglodytes*) were supplied by the Southwest Foundation for Biomedical Research, San Antonio, Texas. Both sinuses were utilized on each animal, and a total of 4 animals grafted with anorganic bovine bone were evaluated 18 months after grafting. The original study groups utilized a bovine collagen Type I matrix as a control. As a result of their involvement with other research projects, only 4 animals grafted with anorganic bovine bone were available for long-term follow-up. Individual treatment assignments were determined randomly and no animal received the same treatment bilaterally.

This study was approved by the animal use committee of Oregon Health Sciences University. The animals selected were between the ages of 10 and 15 years and within a body weight range of 46 to 76 kg. Routine veterinary examinations, along with radiographic and clinical evaluation, were performed to select study animals without dental or sinus pathology. All animals had not previously participated in research. The procedures from this study did not require animal sacrifice, which allowed for long-term graft evaluation.

Surgery. Tiletamine zolazepam (10 to 15 mg/kg of body weight) and/or ketamine hydrochloride (10 to 15 mg/kg of body weight) were administered approximately 20 minutes prior to anesthesia induction either by intramuscular or intravenous injection. For anesthesia maintenance, an isoflurane/oxygen mixture was employed. A modified Caldwell-Luc procedure was performed to access the maxillary sinus from the lateral wall. An oval osteotomy was prepared with a #8 round bur using a high-speed dental handpiece. Osteotomy dimensions average 18 mm mesiodistally and 11 mm apicocoronally. Sinus membrane elevators were used to position the bony window medially and dissect the Schneiderian membrane away from the inferior wall of the sinus; the graft material was then placed in the floor of the sinus. Where small tears in the Schneiderian membrane occurred, a resorbable collagen membrane (Colla-Cote, Colla-Tec, Plainsboro, NJ) was placed to facilitate graft containment to the localized grafted area of the sinus. Two of the surgeries from this report employed a collagen membrane for small tears of less than 3 mm. The lateral wall osteotomy site was not covered with any kind of barrier membrane. The tissues were replaced and sutured (interrupted interproximal and vertical suturing) with resorbable 3-0 gut. To maximize graft containment, positive pressure was applied on the replaced flap with a moist gauze for approximately 15 minutes.

Postsurgical care consisted of the antibiotic augmentin given orally in a dosage of 500 mg 3 times daily for 10 days, the antihistamine/nasal decongestant Tavist-D (Sandoz, East Hanover, NJ) given orally 2 times daily for 7 days, and the analgesic acetaminophen with codeine as needed for pain. Postoperative procedures were performed at 1 week, 2 weeks, 2.5 months, 3.5 months, 4.5 months, 5.5 months, 6.5 months, 7.5 months, and 1.5 years.

Radiographic Evaluation. Animals were scanned with a HiSpeed Advantage helical computed tomography (CT) scanner (General Electric Medical Systems, Milwaukee, WI). A standard scanning technique was developed and reproduced on all subsequent CT scans. A QCT Phantom (Image Analysis, Columbia, KY) (hydroxyapatite for tissue equivalent calibration) was employed to allow for standardization of the bone mineral density measurements.

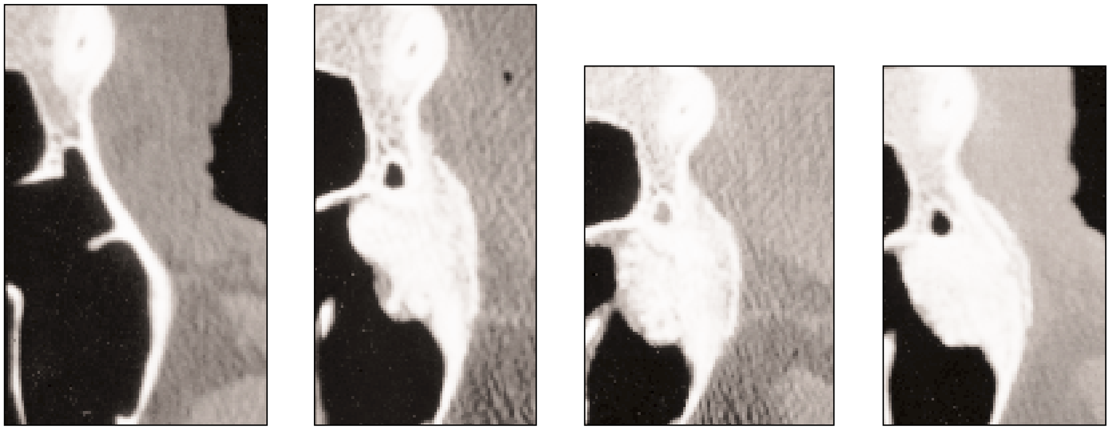

Fig 2 Computed tomographic axial scan series of the superior aspect of a representative anorganic bovine bone treatment, demonstrating stability in the sinus graft mineral content over time (*left to right:* preoperatives, 2.5 months, 4.5 months, and 1.5 years).

The CT scan data were transferred to a systems disk and then networked to a HiSpeed Advantage Windows workstation (General Electric). Regions of interest (ROI) were measured in mean Hounsfield units (standard CT measure of density relative to water). Two sets of 3 ROI measurements were performed for each sinus to evaluate both the peripheral and the central aspects of the sinuses. The ROI measurement of the central aspect of the sinus was performed on the slice approximately 2 mm superior to the landmark slice, and the ROI measurement of the peripheral aspect of the sinus was performed on the slice approximately 3 mm superior to the landmark. These heights were utilized to minimize influences from the biopsy sites. The landmark slice was typically 2 to 3 mm above the floor of the sinus. The QCT Phantom has 3 different known densities, allowing for the development of a linear regression curve to standardize each CT scan. This was used for calibration of BMD values from the CT Hounsfield units. Hounsfield units can vary from CT scan to CT scan, and the use of QCT Phantom allowed for a more accurate comparison between the different CT scans taken on the same animal at different times and between animals.

To evaluate the overall vertical performance, a tracing of the entire sinus (ROI) was outlined to collect Hounsfield units that were 2, 4, 6, 8, 10, and 12 slices superior to the landmark slice in a manner similar to that described above. The bone mineral density (BMD) values derived for whole sinus tracing indicate the average density at levels approximately 2, 4, 6, 8, 10, and 12 mm superior to the landmark slice.

Histologic Procedures. A minor surgical procedure was performed at 3.5, 5.5, 7.5 months, and 1.5 years postsurgery to access the lateral aspect of the surgical site. A cylindric biopsy, approximately 3 mm in diameter, was taken by trephine from the original surgical site (lateral osteotomy window) utilizing a locator stent.

Calcified specimens were prepared for histologic analysis using the Donath technique with an Exact system (Exact, Hamburg, Germany). Following cutting and grinding, slides were stained in Stevenel's Blue (150 mL distilled water, 1 g methylene blue, and 1.5 g potassium permanganate) and counterstained in van Gieson's Picro-fuchsin (10 to 15 mL acid fuchsin [1% aqueous solution] and 100 mL saturated picric acid). This staining technique showed the host bone in a reddish-orange color and the anorganic bovine bone in a tan color. These differences allowed for the different mineralized tissues to be separated during histomorphometric evaluation. All specimens were evaluated under high power to ensure that host bone areas were vital bone.

The total area, host bone tissues, and anorganic bovine bone particles in the region of interest (original grafted area) were each quantified using greyscale detection computer-assisted histomorphometrics to evaluate changes over time and differences between treatment variables. A Quantimet 520 system was employed with the Quick software (Image Analysis).

Statistical Analysis. Student's *t* test was used to determine statistical significance. A $P < .05$ was considered to be significant. Values listed represent the mean ± 1 standard deviation.

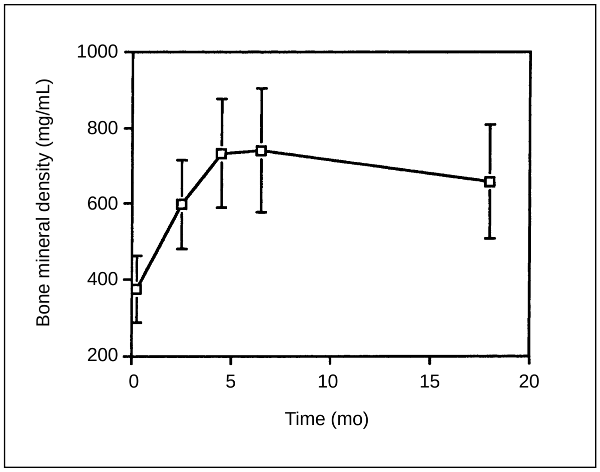

Fig 3 Graph showing increase in BMD values, as derived from CT scans, over time following sinus grafting. Average BMD values are shown for the 1-week, 2.5-month, 4.5-month, 6.5-month, and 1.5-year time points. The sites treated with anorganic bovine bone demonstrated a rapid increase in BMD from 1 week to 2.5 months, a smaller increase from 2.5 to 4.5 months, and a plateau effect through 18 months.

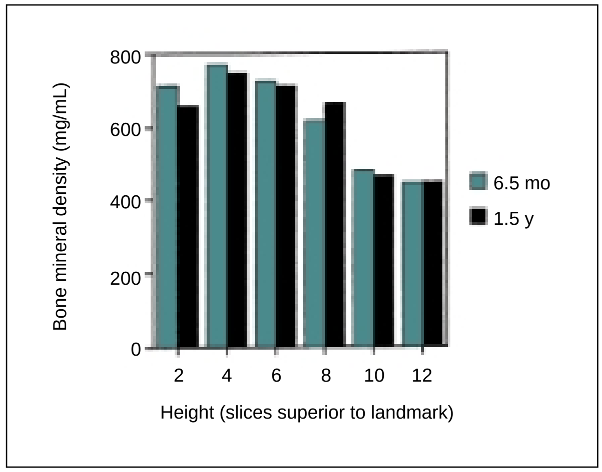

Fig 4 Graph showing average BMD values for the 6.5-month and 1.5-year CT scans evaluated at different heights relative to the landmark slice. The landmark was typically 2 mm above the floor of the maxillary sinus. Excellent bone quality (BMD of greater than 600 mg/mL) was observed to a height of 10 mm into the sinus.

Results

Radiographic Evaluation. All sinuses were examined radiographically by taking a preoperative CT scan to screen for sinus pathology and to assist in the surgical planning. All views indicated that the sinuses were free of any evidence of pathology. The preoperative CT scan shown in Fig 2 demonstrates the lack of any radiographic evidence of pathology. The remainder of the CT scan series depicted in Fig 2 demonstrates the stability in mineralization over time, from the 2.5-month view to the 1.5-year view, in a sinus grafted with anorganic bovine bone. The 1.5-year CT scan does show a complete restoration of the lateral cortical plate.

To determine whether any long-term change in the sinus grafts' BMD had occurred, the 3 peripheral and 3 central ROIs were analyzed from the 1.5-year CT scans and compared to the BMD values previously obtained. The average of the central and peripheral BMD values for the CT scans at 1 week, 2.5 months, 4.5 months, 6.5 months, and 1.5 years are given in Fig 3. This demonstrates the rapid increase in mineralization between the 1-week and 2.5-month CT scans, the smaller increase in mineralization between the 2.5- and 4.5-month CT scans, and the plateau from 4.5 months to 1.5 years. This is in contrast to the bovine Type I collagen control, which demonstrated a delayed mineralization and a lower peak. There was no statistically significant difference found between the 4.5-month, 6.5-month, and the long-term 1.5-year BMD values for the anorganic bovine bone treatment. As was also found at the earlier time points, the 1.5-year average peripheral ROI value (694 mg/mL) was slightly elevated over the average central ROI value (622 mg/mL).

The long-term stability of the vertical bone dimension following sinus grafting has been a question of great interest. To evaluate vertical graft stability over time, the BMD values at different heights were evaluated from the 1.5-year CT scan and compared to the 6.5-month CT scan. To evaluate the graft material's performance at multiple heights, including those superior to the levels utilized for the determination of the values shown in Fig 3, entire sinus tracings were evaluated in the 6.5-month and 1.5-year CT scans. These tracings were performed for alternating slices, starting 2 slices superior to the landmark and extending to a level approximately 14 mm above the floor of the sinus. Fig 4 shows that the BMD values progressed in a superior direction for both time points. These data demonstrate that no appreciable difference exists between the BMD height values over time, suggesting vertical dimension stability (ie, a lack of "slumping") with Bio-Oss. No statistically significant differences were observed between the 6.5-month and 1.5-year BMD values for the different heights evaluated.

Histology Evaluation. To evaluate the bone histologically for changes over time, lateral wall sinus biopsies were taken, histologic specimens

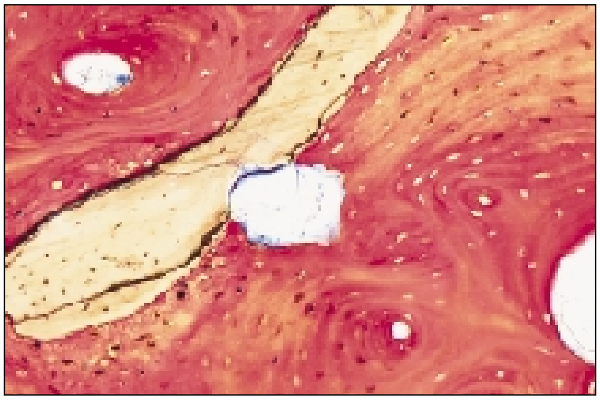

Fig 5 Biopsy of natural bone mineral after 1.5 years. This figure shows a portion of the biopsy core that was taken from the lateral wall of the grafted sinus. The anorganic bovine bone is well incorporated into vital lamellar bone (original magnification ×40).

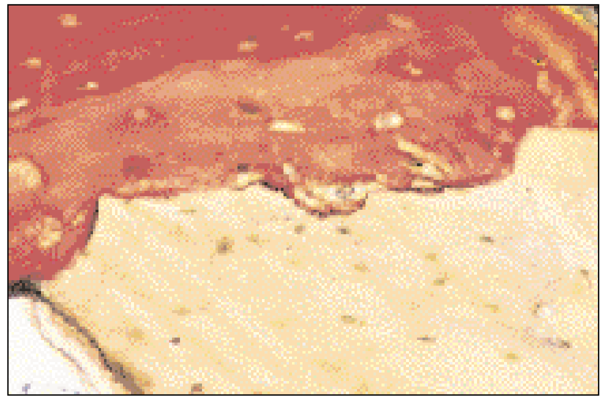

Fig 6 Biopsy of natural bone mineral after 1.5 years. This specimen shows an area of anorganic bovine bone resorption (original magnification ×100).

Table 1 Histomorphometry for Sinus Grafts with Anorganic Bovine Bone

Total mineralized percentage*	7.5 months	1.5 years
Vital bone area	62 ± 3%	70 ± 7%
Natural bone mineral area	19 ± 14%	6 ± 3%
Total mineralized area	81%	76%

*Total mineralized percentage is the sum of the average vital bone and natural bone area.

were prepared, and histomorphometry was performed to determine the percentage of vital bone area and the percentage of anorganic bovine bone area. Figure 5 shows a 1.5-year histologic specimen at 40 times original magnification, demonstrating that the graft material particles of anorganic bovine bone were completely incorporated into the mature lamellar bone. While anorganic bovine bone was still present in all 1.5-year specimens, it was present in lower amounts than typically found at the shorter time intervals. Areas of apparent resorption of anorganic bovine bone (Bio-Oss) particles and replacement with vital bone were evident (Fig 6).

The histomorphometry values for specimens taken at 7.5 months and 1.5 years are given in Table 1. An increase was seen in the percentage of vital bone area, from 63 ± 3% (mean ± SD) to 70 ± 7%, and a decrease was seen in the percentage of anorganic bovine bone area, from 19 ± 14% to 6 ± 3% over time. Yet when comparing the total percentage of mineralized tissue, the 7.5-month and the 1.5-year values are nearly identical. While a trend was evident, the increase in the percentage of vital bone area and the decrease in the percentage of anorganic bovine bone were not statistically different.

Discussion

This is the first long-term evaluation of the sinus augmentation procedure in an animal model that closely approximates the procedure in humans. Through histologic and radiographic evaluation, this study demonstrated that anorganic bovine bone provides a stable augmentation of the maxillary sinus floor. This finding is significant, since many grafting materials, including autogenous bone, have a tendency to lose density and height ("slump") over time.[2]

Three general considerations should be addressed when optimizing the vertical height of the sinus graft. First, the surgical technique can dramatically influence the overall height of the sinus graft. The goal of sinus grafting is to attain enough height to place an implant of 13 to 18 mm in length without interfering with ostium function. Implant length is influenced not only by the extent of grafting, but the height of residual host bone and the relative position compared to the occlusal plane. Second, short-term "collapse" of the graft material in the early phases of wound healing may result in a diminished overall height. Some materials do not hold up to the sinus pressure and clot fibrinolysis during the first several weeks. Third, the long-term loss in vertical height has often been attributed to a "repneumatization" of the sinus. This slumping has been shown to be related in part to the graft materials employed.[2] An additional consideration for the long-term vertical height is crestal bone loss. It appears that greater amounts of crestal bone loss occur when less than 3 mm of residual host bone exists at the time of sinus grafting.[3]

In the present study, the anorganic bovine bone sinus grafting consistently showed an excellent bone quality to a height of 10 mm into the sinus. If 5 mm of residual alveolar host bone remained, an implant at least 15 mm in length could be placed. While the quality of the bone decreased as the analysis went in a superior direction beyond 10 mm (Fig 4), the following 2 CT scan slices (slices 10 and 12) of analysis did reveal the presence of significant bone for most of the sinuses. Thus, sinus grafting typically yielded 14 mm of sinus graft height at 6.5 months, and this height remained stable to 1.5 years. For slices superior to this point, the majority of the graft sites showed little bone that could support implant placement at either of the time points of analysis.

The long-term stability of the sinus graft height has been an area of great interest. With the known potential for repneumatization of the sinus, the loss of graft height is a concern, since maximal long-term success for implants placed into the grafted maxillary sinus is a goal. At the Academy of Osseointegration's Sinus Grafting Consensus Conference held in 1996, the long-term stability of the sinus graft height over time was evaluated.[2] It was found that the height decreased over time for all of the different grafting materials evaluated. The average bone loss was 2.1 ± 0.3 mm when grafting with freeze-dried bone allograft, 1.8 ± 0.4 mm when using iliac crestal bone, 0.9 ± 0.3 mm when using alloplast, and 0.8 ± 0.6 mm when using intraoral plus alloplast.

Following mandibular bone grafting with different techniques, the loss of graft height was evaluated over a 4-year period.[17] This particular study compared autogenous iliac bone with a composite graft of autograft and anorganic bovine bone at a 1:1 ratio. The study demonstrated that more than 60% of the graft was lost with autograft and only 20% of the graft was lost with the composite graft.[17] These different studies evaluating graft height over time support the use of anorganic bovine bone in the graft material mixture to enhance the long-term stability of the vertical aspect of the grafted region.

Following sinus grafting with anorganic bovine bone, the incremental increases in BMD values were greatest for the 1-week to 2.5-month interval. The peak BMD value was attained by 4.5 months. Thus it appears that the increase in BMD reached a plateau by the 4.5-month evaluation. Based on the radiographic data alone, this would imply that a healing time of 4 to 5 months would likely be acceptable for implant placement in the chimpanzee. The excellent performance of anorganic bovine bone is likely the result of the optimal osteoconductive properties of this material.

It is advantageous for the materials employed for sinus grafting to be resorbed and replaced over time with the patients' own bone. The mechanisms and time for replacement of the majority of graft materials are not known. The rate of replacement for grafts containing anorganic bovine bone in humans has also not been fully identified. A recent report by Berglundh and Lindhe demonstrated anorganic bovine bone resorption in the amount of 6% during a 4-month time span in the dog model, as determined by a histomorphometry change from 17% to 11%.[23] Another report suggests that some anorganic bovine bone is still present after 44 months in humans.[24] The present study demonstrates that while a significant amount of anorganic bovine bone is still present after 1.5 years, it is actively being replaced by vital bone. The present findings are thus in agreement with the previously discussed study in dogs.[23] Additional animal studies have also demonstrated that anorganic bovine bone is replaced by vital host bone.[25]

Anorganic bovine bone appears to be replaced at the rate of regular bone during remodeling. Therefore, the time for resorption is likely related to sigma, which is 6 months in humans and in all likelihood equivalent in the chimpanzee. It is also related to the percentage of bone undergoing remodeling in a specific location. Typically, 10 to 15% of the human skeleton is replaced each year, depending on the type of bone and its functional demands. In some regions, such as those near implants recently put into function or in recently grafted areas, an increased amount of localized bone metabolism can be found.

This presence of particulate may influence bone quality. This may be a consideration when dental implants are placed in the bone. By increasing the amount of mineralized matrix, bone density and clinical hardness may be improved. On the other hand, the goal is to maximize the surface area of vital bone–dental implant contact and not the nonvital particle–dental implant contact. Interestingly, it has been found that with anorganic bovine bone, a minimal amount of graft material is typically in contact with the implant, even when anorganic bovine bone is present in a fairly high percentage in the overall graft area.[23] This appears to be related to the fact that vital bone surrounds most of the graft particles and to the increased bone remodeling that is normal in the areas immediately adjacent to implants.

Summary

In summary, the results of this study demonstrate that: *(1)* maxillary sinus floor grafting using anorganic bovine bone (Bio-Oss) yields a stable result, with no apparent "slumping" over time; *(2)* there is significantly greater bone formation using anorganic bovine bone than bovine Type I collagen matrix; and *(3)* anorganic bovine bone is integrated and subsequently replaced with vital host bone.

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