Histomorphometric Analysis of Natural Bone Mineral for Maxillary Sinus Augmentation

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Purpose: *Lack of bone height in the posterior maxilla often necessitates augmentation prior to or simultaneously with dental implant placement. The purpose of this clinical study was to evaluate the use of the natural bone mineral Bio-Oss alone or in combination with autogenous bone in sinus floor elevations performed as 1- or 2-step procedures.* ***Materials and Methods:*** *Thirty-eight patients required sinus augmentation. Natural bone mineral alone was used in sinus floor augmentation in 21 patients. In 13 patients, a mixture of the bone substitute and autogenous bone was used, and in 4 patients autogenous bone alone was used. In all of the patients, samples were taken for biopsy 3 to 8 months postoperatively, and bone regeneration was evaluated histologically and histomorphometrically.* ***Results:*** *In all patients, the amount of new bone significantly increased over the observation time, while marrow areas decreased. There was no statistically significant difference in the amount of new bone formation between the Bio-Oss group (new bone 29.52% ± 7.43%) and the Bio-Oss/autogenous bone group (new bone 32.23% ± 6.86%). In the 4 patients treated with autogenous bone alone, a greater amount of newly formed bone was found; however, in these cases the area volume filled was smaller than in the other 2 groups.* ***Discussion:*** *The data showed that new bone formation takes place up to 8 months after sinus floor elevation and that there is no difference in the amount of bone formation between procedures done with the bone substitute alone or with the mixture of the substitute and autogenous bone.* ***Conclusion:*** *These data suggest that predictable bone formation can be achieved with the use of Bio-Oss.* INT J ORAL MAXILLOFAC IMPLANTS 2004;19:199–207

Key words: *autogenous bone, bone substitutes, histomorphometry, maxillary sinus, sinus augmentation*

The presence of the maxillary sinus often poses problems for the placement of implants in the posterior maxillary region and therefore represents a clinical challenge for implantation. Several investigations have demonstrated the significant resorption process of the maxillary alveolar bone following tooth removal.[1,2] Crestal bone resorption, combined with the pneumatization of the maxillary sinus that occurs after posterior tooth loss, often results in inadequate bone volume for placement of endosseous dental implants.[3–5]

Several clinical reports have evaluated the maxillary sinus augmentation procedure using a variety of bone grafting materials, such as autogenous bone from the iliac crest or the oral cavity[6–14] and different bone substitutes.[9–17] Among the xenografts, the natural bone mineral Bio-Oss (Geistlich Pharma, Wolhusen, Switzerland) has shown excellent osteoconductive properties and promising results in sinus floor elevation procedures.[18–21] However, the ultimate proof of the efficacy of a bone substitute is found in human histologic samples. To date, there have been no studies that evaluated histologic data from a large amount of patients, even though questions remain as to whether there is an advantage to mixing bone substitutes like Bio-Oss with autogenous bone over the use of Bio-Oss alone.

The aim of this study was to evaluate, by means of histologic analysis at 3 to 8 months postoperatively, the use of the natural bone mineral Bio-Oss in sinus floor elevations in patients in 1- or 2-step

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procedures. Its use alone was compared to treatment with a mixture of autogenous bone/natural bone mineral. In a limited number of patients, autogenous bone alone was used, and this treatment was compared to the other 2 treatments. The aim was to determine whether the use of the substitute alone would result in bone quality comparable to that produced with a mixture of bone substitute and autogenous bone.

MATERIALS AND METHODS

The study was carried out in one private practice and involved 38 patients who had to undergo sinus floor elevation in conjunction with the placement of dental implants. Twenty patients were female (age 45 to 69 years, mean age 54 years), and 18 were male (age 35 to 67 years, mean age 50 years). All of the patients had remaining teeth, at least in the anterior region. Tooth loss or tooth extraction had taken place at least 3 months before augmentation surgery.

Nine patients were smokers (Table 1). Of these, 4 stopped smoking from 1 week before surgery until 2 weeks postoperatively.

All patients gave their oral consent to participate in this study. The preoperative bone situation was analyzed by orthopantomograms (OPT) and computerized tomograms (CT). The remaining bone height in the maxillary sinus region was calculated from the OPT. A 1-step procedure, ie, simultaneous implantation and sinus floor elevation, was chosen if the bone height was at least 4 mm. Primary stability of the implants was also a prerequisite for a 1-step procedure. With bone height of less than 4 mm, a 2-step procedure, ie, sinus floor elevation prior to implantation, was performed.

To avoid loading in the wound area, the provisional prosthesis had to be supported by teeth and/or noninvolved soft tissue.

Sinus floor augmentation was performed in 21 patients with natural bone mineral (Bio-Oss) alone. In 13 patients a mixture of ⅔ natural bone mineral and ⅓ autogenous chin graft was used. The decision to use natural bone mineral alone or in a mixture with autogenous bone was based on the area volume that had to be regenerated; cavities covering less than approximately 2 cm^3 were treated with natural bone mineral alone. For augmentations covering a cavity size of about 3 to 4 cm^3, the mixture of bone substitute and autogenous bone was used. In 4 patients, autogenous bone graft alone was used, because only a small volume (1 to 2 cm^3) had to be augmented and therefore the amount of harvested bone was sufficient to fill the cavity.

Surgical Technique

Patients were subjected to CT as a means to objectively assess possible pathology at the sinus level and to locate possible septa and the sinus floor. Patients were prepared and draped to ensure strict asepsis. The buccal cavity and the skin of the face were disinfected with chlorhexidine. A local anesthetic agent with a vasoconstrictor (xylocaine 2%, 1:50,000; Astra, Wedel, Germany) was injected into the vestibule and at the palate. A crestal incision, slightly offset from the palatine level, was made throughout the entire length of the edentulous area. At the level of the proximal aspect of the tooth that mesially bordered the edentulous area, an anterior releasing incision was made. Posteriorly, the releasing incision was located in front of the tuberosity.

The lateral wall of the sinus was exposed by elevating a full-thickness flap. The limits of the sinus were located from the CT. With a diamond bur drill mounted on a high-speed angled piece, a rectangular window with rounded or elliptically shaped angles was made while irrigating the area. This opening measured about 8 mm in the vertical dimension and 17 mm in the mesiodistal dimension.

When the schneiderian membrane appeared, the created bony window was gently mobilized toward the interior of the sinus using the handle of a mirror and a mallet. A curette with a small radius of curvature (Sinus Elevator according to John; Stoma, Tuttlingen, Germany) was inserted at the level of the inferior border of the sinus; with this, the detachment of the membrane could be commenced. If small tears appeared, a collagen membrane (Bio-Gide; Geistlich Pharma) was used to close them. With the Sinus Elevator, the sinus membrane was gradually separated up to the medial wall of the sinus. The bony window was then positioned horizontally.

At this stage, the graft was placed. Natural bone mineral was soaked with sterile saline and mixed with tetracycline powder (Caesar & Loretz, Hilden, Germany) in a ratio of 250 mg/2 g bone substitute. In 13 patients, natural bone mineral was additionally mixed with chin bone, which was harvested during the same surgery (ratio ⅔ bone substitute to ⅓ autogenous bone). In 4 patients, chin bone was used without bone substitute and loaded into a syringe. The posterior part of the cavity was filled first, then the anterior part, and finally the central area. The superior portion of the graft was situated on the side of the medial nasal meatus in such a way that sinus drainage was not disturbed.

Table 2 provides an overview of the procedures performed.

One-Step Procedure with Simultaneous Implantation. In 22 sinus cavities, a total of 55 implants

Table 1 Overview of Patient Data

Graft type/ patient no.	Smoker?	Implant loss? (no.)	Time of biopsy (mo)	Histomorphometric results			
				Bone (%)	Marrow (%)	Nonvital bone (%)	Bio-Oss (%)
Bio-Oss							
1	No	No	3	22	66	0	12
3	No	No	8	35	53	0	12
4	No	No	4	24	52	0	24
7	No	No	3	25	67	0	8
8	Yes	Yes (1)	7	18	69	0	13
9	No	No	5	22	58	0	20
13	No	No	3	22	66	0	12
14	No	No	6	30	46	0	24
15	No	No	3	28	55	0	17
17	Yes*	No	6	39	56	0	5
20	No	No	4	25	67	0	8
22	No	No	7	39	56	0	5
25	Yes*	No	8	43	41	0	16
26	Yes	No	3	28	55	0	17
27	No	No	6	30	46	0	24
29	No	No	8	43	41	0	16
30	No	No	6	30	44	0	26
32	No	No	4	28	54	0	18
34	Yes*	Yes (1)	7	39	56	0	5
35	No	No	5	22	66	0	12
38	No	No	5	28	54	0	18
Bio-Oss + chin bone							
5	No	No	3	28	55	0	17
6	Yes	No	6	30	46	0	24
10	No	No	8	43	41	0	16
11	No	No	7	39	56	0	5
16	No	No	4	28	54	0	18
18	No	No	5	26	54	0	20
21	Yes*	No	5	30	52	0	18
24	No	No	5	30	46	0	24
28	No	No	5	32	43	0	25
31	No	No	5	25	57	0	18
33	No	No	8	43	40	0	17
36	Yes	Yes (1)	8	41	55	0	4
37	No	No	4	24	51	0	25
Chin bone							
2	Yes	No	5	51	48	1	0
12	No	Yes (1)	5	53	42	5	0
19	No	No	7	53	47	0	0
23	No	No	3	57	42	1	0

*Patient stopped smoking from 1 week preop until 2 weeks postop.

(Osseotite; 3i/Implant Innovations, Palm Beach Gardens, FL) were placed simultaneously with the graft using the manufacturer's recommended surgical protocol. Only wide-diameter (5-mm) implants were used. The flap was then replaced and sutured with horizontal mattress sutures at the level of the crestal incision and with sutures separated by the releasing incisions. Re-entry surgery was performed after 5 to 7 months.

Two-Step Procedure with Sinus Floor Elevation Prior to Implantation. A time of 5 to 7 months was allowed for healing before the implants were placed. The procedure for implantation was similar to that used in the 1-stage procedure. The implants remained submerged for 7 months before loading. A total of 48 implants were placed using the 2-step procedure.

Table 2 Overview of Procedures Performed

Type of procedure	Bio-Oss	Bio-Oss + autogenous chin bone	Autogenous chin bone
No. of 1-step procedures	14	6	2
No. of 2-step procedures	7	7	2
Total no. of sinus floor elevations	21	13	4

Postoperative Care

Postoperatively, all patients received antibiotic therapy (3 × 1 g amoxicillin per day for 1 week, starting 1 hour before the procedure). In cases of penicillin allergy, erythromycin (Erythrocine 1000, 2g/day; Abbott, Wiesbaden, Germany) was prescribed for the same period. After surgery all patients received an intravenous injection of 120 mg prednisolone (Solu-Medrol; Upjohn, Erlangen, Germany). For pain, an analgesic compound of Naproxen (Stada, Bad Vilbel, Germany; 2 × 250 mg per day) was prescribed. Topically, 0.2% oral rinsings with chlorhexidine mouthwash were prescribed starting the day after the surgery.

Implant Loading

Prosthetic treatment was not performed at the location of the investigating practice. However, in all cases, during the period of approximately 1 month necessary for soft tissue healing, the healing abutments were in place, and an existing removable temporary prosthesis was relined with a malleable resin, based on the height of the abutments. The implants were considered as loaded as soon as they became functional. All patients had regular follow-ups by the investigating surgeon at 6, 12, and 18 months after the implants became functional.

Biopsy Harvesting, Preparation, and Evaluation

Three to 8 months postoperatively, specimens for biopsy were harvested from all patients. One specimen was taken from each patient according to Froum and coworkers.[22] After a full flap was raised, a biopsy specimen was taken from the lateral aspect with the help of a trephine drill. This method allowed biopsy specimen taking independently from the second surgical intervention. The biopsy specimens were placed in 10% formaldehyde.

Upon receipt of the specimens in the Hard Tissue Research Laboratory (University of Oklahoma College of Dentistry, Oklahoma City, OK), the bone cores were placed in 10% neutral buffered formalin for 48 hours; this was followed by dehydration with a graded series of alcohols for 9 days at room temperature and atmospheric pressure with constant shaking. Following dehydration, the specimens were infiltrated with a light-curing embedding resin (Technovit 7200 VLC; Kulzer, Wehrheim, Germany). Following 19 days of infiltration with constant shaking at room temperature and atmospheric pressure, the specimens were embedded and polymerized by 450-nm light, with the temperature of the specimens never exceeding 40°C. All specimens were then cut vertically through the core with an Exakt cutting/grinding system (Exakt Apparatebau, Norderstedt, Germany). Following mounting on acrylic glass slides, the specimens were cut to a thickness of 150 µm with the Exakt cutting/grinding system. The specimens were then prepared to a thickness of 50 µm by the cutting/grinding method of Donath and Breuner[23] using the Exakt microgrinding system and were stained in Stevenel's blue and Van Gieson's picro-fuchsin.

Statistical Evaluation of Histomorphometric Data

The statistical evaluation was carried out by WinSTAT version 3.1 statistical software (G. Greulich Software, Staufen, Germany). Regression analysis was applied to compare the amount of new bone, marrow, and bone substitute particles observed between the different procedures for sinus floor elevation. The effect of the time of biopsy on the amount of new bone, marrow, and bone substitute observed was investigated, and the subsequent analysis was adjusted for time. The data for chin bone are included for descriptive purposes only; they could not be analyzed statistically because of the small number of patients.

RESULTS

A total of 103 implants were placed. Four implants, all placed using the 1-step procedure, were lost in 4 patients. The losses occurred at the time of re-entry surgery or shortly thereafter (within 3 weeks). In 2 cases the implants appeared to be stable at re-entry but showed slight mobility at the first subsequent wound examination. In 1 patient the provisional prosthesis had caused pressure, resulting in a buccal

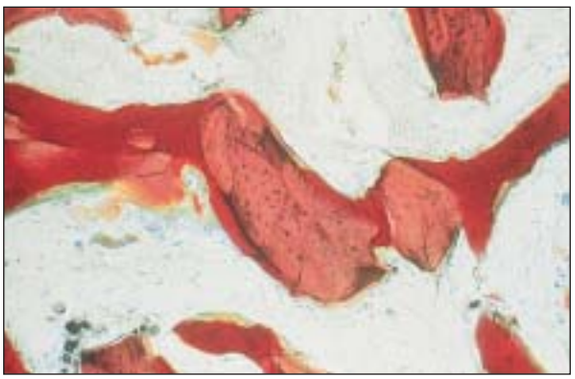

Fig 1 Histology after sinus floor elevation with natural bone mineral alone. New bone *(dark red)* is in contact with and growing among the bone substitute particles (original magnification ×25).

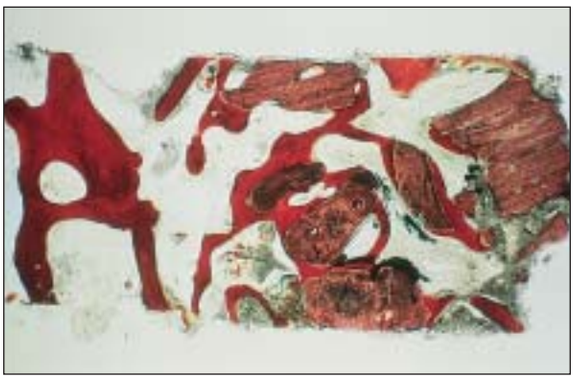

Fig 2 Histology after sinus floor elevation with natural bone mineral. The new bone *(dark red)* has formed trabeculae, which connect the bone substitute particles (original magnification ×10).

wound perforation and exposure of the cover screw at the time of re-entry. One implant showed slight mobility 3 weeks after re-entry. In none of the cases did any infection occur.

Histologic and Histomorphometric Results

Natural bone mineral particles were incorporated by new bone in the group treated with bone substitute alone (Figs 1 and 2), as well as in the group treated with a mixture of bone substitute and autogenous bone. Occasionally, lines of osteoblast-forming osteoid were found on the newly formed bone, as well as on the bone substitute surface (Fig 3). The histomorphometric results are presented in Tables 1 and 3.

The amount of new bone was statistically significantly related to the time of biopsy (Table 4, Fig 4). In particular, a greater amount of new bone was observed when the biopsy specimen was taken at a later time ($P < .001$). In contrast, smaller areas of marrow were observed at later times (Fig 5). Regression analysis indicated no statistically significant association between the time of biopsy and the amount of bone substitute particles, but a small negative correlation was seen with smoking ($P = .08$).

Results showed that there was no statistically significant difference in the amount of new bone between the bone substitute and combined substitute/chin bone procedures. However, there appeared to be an indication that the amount of new bone was statistically significantly greater in patients treated with chin bone alone than in those treated with the bone substitute. This result should be investigated further, since the number of patients treated with chin bone was very low.

Regarding the amount of marrow observed, it appears that the percentage of marrow areas diminished over time, independent of the treatment received ($P = .03$). In the histologies of the mixture of bone substitute and autogenous bone, no remnants of nonvital bone were found. A comparison of the pre-existing bone with the regenerated areas was not possible because of the lateral direction from which the biopsy specimens were harvested.

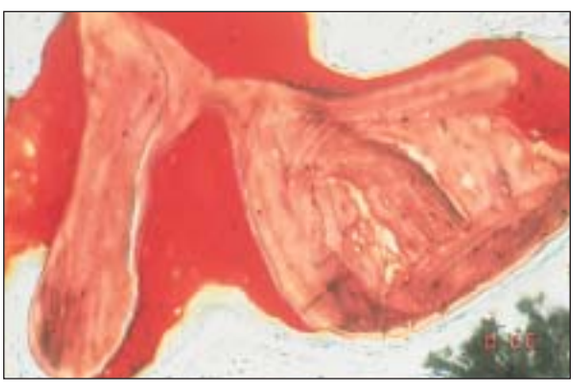

Fig 3 Histology after sinus floor elevation with natural bone mineral. The green-staining osteoid lining new bone and parts of a bone substitute particle is surfaced by osteoblasts (original magnification ×50).

DISCUSSION

The aim of this study was to evaluate in patients histologically the efficacy of natural bone mineral used alone or in combination with autogenous bone as a graft material for sinus floor elevation procedures. This study was carried out within the limits of a dental practice; therefore the overall number of patients was limited, and it was not possible to perform a randomized trial. It should be noted that the treatment procedures were chosen according to the size of the

Table 3 Histomorphometric Results (Means ± Standard Deviation)

Graft type	New bone (%)	Bio-Oss (%)	Nonvital bone (%)	Bone marrow (%)
Bio-Oss (n = 21)	29.52 ± 7.43	14.86 ± 6.54	—	55.62 ± 8.78
Bio-Oss + chin bone (n = 13)	32.23 ± 6.86	17.77 ± 6.73	0.00 ± 0.00	50.00 ± 6.01
Chin bone (n = 4)	53.50 ± 2.52	—	17.5 ± 2.22	44.75 ± 3.20

Table 4 Multiple Stepwise Regression Analysis to Assess the Effects of Time Since Surgery, Smoking, and Treatment on the Amount of Bone, Marrow, and Bio-Oss

Dependent variables	Independent variables	Constant	SEM	*P*
Bone %	Months	3.15749	0.48747	.0000
Marrow %	Months	–2.33713	0.73363	.0032
Bio-Oss %	Smoking	–2.89552	1.62663	.0846

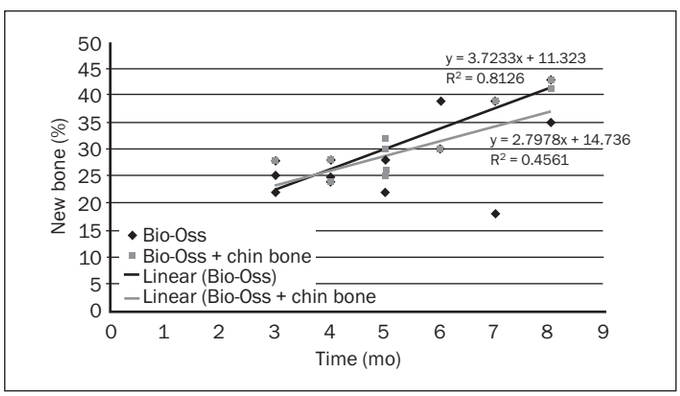

Fig 4 Percentage of new bone formation in relation to time after sinus floor elevation.

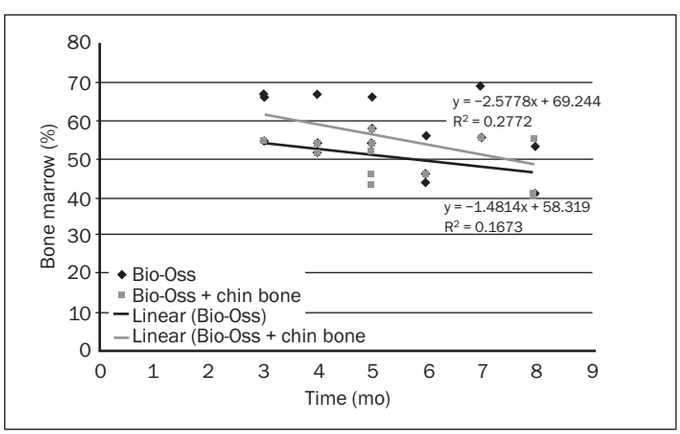

Fig 5 Percentage of marrow in relation to time after sinus floor elevation.

cavity to be augmented. These facts reflect the conditions and patient variability seen in practice but require consideration when analyzing the results.

In 38 patients, sinus floor elevation was performed with bone substitute alone, with a mixture of bone substitute and autogenous bone, or with autogenous chin graft alone. Depending on the preexisting bone height, a 1- or 2-step procedure was chosen. In patients with a pre-existing bone height of 4 mm or more, a sinus floor elevation was performed together with implant placement (1-step procedure), while in patients with less bone height, a healing period of 5 to 7 months after sinus lifting was allowed prior to implantation.

During the observation period (up to 18 months after implant loading), 4 of 55 implants placed in a

Table 5 Literature Overview of Histomorphometric Data Involving Bio-Oss

Study	Study model	New bone (%)	Bio-Oss (%)
Hürzeler et al[19]	Sinus lift, rhesus monkey	27.4	16.9
Valentini et al[26]	Sinus lift, single human explantation	28.0	28.0
McAllister et al[28]	Sinus lift, chimpanzee	62.0 (7.5 mo) 70.0 (1.5 y)	19.0 6.0
McAllister et al[29]	Sinus lift, chimpanzee	47.0	19.0
Hämmerle et al[27]	Defect filling around mandibular implants, monkey	30.0 to 33.0	13.0 to 21.0

1-step surgery were lost at or shortly after re-entry surgery. This corresponds to an overall survival rate of 93%. None of the implants placed in a 2-step surgery were lost. Jensen and Greer[8] advocated simultaneous implant placement if primary stability could be achieved in the residual bone. For this, a bone height of at least 4 to 5 mm is necessary. The advantages of this procedure are the shorter healing period and fewer surgical steps. However, histologic data from a monkey study[19] showed that the direct mineralized bone-to-implant contact in augmented sinus cavities was greater with a 2-step procedure (delayed implant placement 4 months after sinus augmentation) than for implants that had been placed simultaneously with sinus floor elevation.

Better implant osseointegration may also be the reason for the higher survival rate seen with the 2-step procedure in this clinical study. However, even if the survival rates achieved in this clinical study appear to be good, longer observation times are necessary to evaluate the long-term outcomes of the procedures described in this study.

It was possible to take biopsy specimens from the lateral aspect of the sinus of all patients for histomorphometric analysis after healing periods of 3 to 8 months. Natural bone mineral granules were incorporated and interconnected by a scaffold of newly formed bone, thereby showing high osteoconductivity. Similar results have been obtained in various other experimental and clinical studies.[18,24–26] In a monkey study, an osteoconductivity index was calculated for natural bone mineral by analyzing the direct bone-to-graft contact.[27] From these data, the authors concluded that this bone substitute is highly osteoconductive.

Statistical evaluation of the histomorphometric data revealed that there was a statistically significant relationship between the amount of new bone and the time the biopsy specimen was taken. The amount of bone increased with time, while marrow areas decreased. Therefore, subsequent analyses were adjusted for time.

The increase in bone formation within the first 8 months of this study is consistent with findings from a recent sinus lift study in chimpanzees by McAllister and coworkers.[28] In that animal study, natural bone mineral was used for sinus floor elevation, and bone mineral density, as derived from CT, was shown to increase steadily within the first 4.5 months, later reaching a plateau.

With regard to the histomorphometric analysis, there was no statistically significant difference in new bone formation between bone substitute alone and substitute mixed with autogenous chin bone. The overall amount of new bone formation in these 2 groups was about 30% (29.5% for natural bone mineral alone and 32.2% for the mixture). Also, the amount of bone substitute particles found in the biopsies was very similar (14.9% and 17.8%, respectively). These results correspond very well to findings of other investigators who used natural bone mineral alone as a graft material in sinus floor elevation or for the filling of defects around implants (Table 5). These data from different studies suggest that predictable bone formation can be achieved with the use of natural bone mineral.

Within the limits of this clinical study it was not possible to differentiate between the maturity of newly formed bone at various time points, nor was it possible to analyze implant osseointegration. However, the data showed that new bone formation took place up to 8 months after sinus floor augmentation and that there was no difference in amount of bone between procedures done with bone substitute alone or with the mixture of substitute and autogenous bone.

There are 2 main advantages to a bone substitute, whether used alone or in combination with autogenous bone. First, harvesting of autogenous bone can be avoided completely or at least limited, thereby reducing pain and discomfort for the patient. Additionally, a slowly resorbing material such as natural bone mineral can reduce resorption of the newly formed bone.[28]

In this study, natural bone mineral was mixed with autogenous chin bone in patients with larger sinus cavity volumes (ie, more than 3 to 4 cm^3). It was anticipated that autogenous bone could add the osteogenic and osteoinductive component that is necessary to achieve complete bone formation in such defect sizes. Histomorphometrically, the amount of newly formed bone was similar to that achieved with the bone substitute alone. Whether an osteogenic, osteoinductive effect of autogenous bone was clinically necessary in these defect sizes, or whether a similar result could be achieved with the use of the bone substitute alone, could not be concluded within the limits of this clinical study. Until now, to the authors' knowledge, there have been no studies available comparing the use of natural bone mineral alone with a mixture of bone substitute and autogenous bone in similar sized defects.

In 4 patients, a chin graft alone was used to augment the sinus floor. The amount of new bone was calculated to be 53.5%, while particles identified as nonvital graft bone amounted for 1.8%. It is not clear from this study if residual graft particles could not be identified or if they already had been resorbed and replaced by newly formed bone.

There was an indication that the amount of new bone was greater in patients treated with chin bone alone than in the patients treated with the bone substitute alone. However, it should be noted that the volumes augmented with autogenous bone alone were smaller than those filled with bone substitute or the mixture of bone substitute and autogenous bone. Therefore, it can be assumed that bone regeneration in the autogenous bone group may have been achieved more easily than in the other 2 groups. Since there were only 4 patients in this group, further studies should be conducted to clarify this matter.

CONCLUSIONS

The aim of this study was to evaluate histomorphometrically whether sinus floor augmentation can predictably be performed with the help of a bone substitute. In 34 patients treated with a bone substitute (Bio-Oss) or a mixture of bone substitute with autogenous chin graft, similar results of the integration of the bone substitute particles as well as new bone formation were found. This material was found to have an excellent osteoconductivity and can be used successfully for human sinus floor augmentation.

ACKNOWLEDGMENTS

We thank Mrs Penelope Vounatsou and Mr Reto Brignoli for performing statistical evaluations and Mrs Sara Burch for her excellent secretarial work. We also thank Dr Thomas Ràsonyi for his contributions to this manuscript.

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