

# Histomorphometric Analysis of Maxillary Sinus Augmentation Using an Alloplast Bone Substitute

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**Purpose:** To evaluate the regenerative potential of a fully synthesized homogenous hydroxyapatite:β-tricalcium phosphate 60:40 alloplast material in sinus lift procedures.

**Materials and Methods:** Hydroxyapatite:β-tricalcium phosphate was used for sinus floor augmentation. After 9 months, 12 biopsies were taken from 12 patients. Routine histologic processing was performed and specimens were analyzed using a light microscope and a digital camera.

**Results:** Histologic evaluation showed 26.4% newly formed bone, 27.3% residual graft material, and 46.3% bone marrow. The osteoconductive index was 33.5%.

**Conclusions:** Hydroxyapatite:β-tricalcium phosphate 60:40 alloplast material was found to be biocompatible and osteoconductive in maxillary sinus augmentation procedures.

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Insufficient bone height often prevents the placement of standard dental implants in the posterior edentulous maxilla. This condition most frequently is the result of alveolar bone loss from severe periodontitis, tooth loss, sinus pneumatization, or a combination of these.<sup>1</sup> Maxillary sinus augmentation is a surgical procedure that compensates for this pathologic condition by increasing the alveolar bone height before or

simultaneous with endosseous implant placement.<sup>2,3</sup> The procedure was first presented by Tatum<sup>4</sup> in the late 1970s and was first published by Boyne and James<sup>5</sup> in 1980. The technique has been modified repeatedly.<sup>6-10</sup>

The sinus lift procedure adequately increases the vertical dimension of the resorbed alveolar process in the posterior maxilla, thus making the placement of implants of sufficient length at this site possible. Grafting materials, including autogenous bone,<sup>5,9</sup> demineralized freeze-dried bone allograft,<sup>11-14</sup> mineralized freeze-dried bone allograft,<sup>14</sup> xenografts,<sup>15-19</sup> hydroxyapatite (HA) preparations,<sup>7,15</sup> calcium sulfate preparations,<sup>20</sup> and growth factors embedded in different carrier materials,<sup>21-23</sup> have been successfully used to augment the floor of the maxillary sinus.

Although no report on disease transmission to patients undergoing augmentation procedures has appeared in the literature,<sup>24</sup> the fear of bovine spongiform encephalopathy ("mad cow disease") transferring to humans and the discovery of human immunodeficiency viruses surviving in allogenic bone after tissue processing<sup>25,26</sup> have drawn attention to the possibility of disease transmission from xenografts and allografts to humans. Therefore, the use of alloplast materials is a viable and well-accepted alternative by patients. Bioceramics made of a mixture of HA and β-tricalcium phosphate (β-TCP) have exhibited favorable bioactivity and osteoconductivity.<sup>27,28</sup> Although

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**Table 1. TISSUE COMPONENT COVERAGE AND OSTEOCONDUCTIVE INDEX 9 MONTHS AFTER SINUS LIFT**

Osteoconductive Index (%)	Total Mineralized Tissue (%)	Residual Graft (%)	Newly Formed Bone (%)	Length/Width	Implant Position	Side	Gender	Age (yr)
29.1	54.3	27.9	26.4	16/4.72*	16, 17	R	M	56
39.7	60.0	34.0	26.0	13/4.2 × 2*	26, 27	L	F	63
15.4	31.9	7.9	24.0	16/3.7, 13/4.7†	15, 16	R	F	49
25.1	51.0	34.9	16.0	13/5*	16	R	F	50
38.6	48.2	12.9	35.3	15/3.5, 15/4‡	15, 16	R	M	64
26.7	46.9	28.2	18.7	15/3.5, 15/4, 15/5‡	25, 25, 26	L	F	65
40.6	57.7	25.5	32.2	15/4, 15/5‡	16, 17	R	M	67
27.0	43.9	28.5	15.5	16/4.7†	16	L	F	61
40.4	66.6	37.0	29.6	14/4.2 × 3*	15, 16, 17	R	M	80
20.0	44.1	34.7	9.4	15/4, 15/5‡	16, 17	R	F	72
48.0	59.8	34.5	25.2	16/3.75, 16/4.2 × 3*	14, 15, 16, 17	R	F	68
51.3	79.4	21.5	57.9	15/4 × 2*, 15/5 × 2‡	24, 25, 26, 27	L	M	42
Mean 33.5	Mean 53.7	Mean 27.3	Mean 26.4			70% R	42% M	Mean 61
SD 11.2	SD 12.3	SD 9.2	SD 12.4			30% L	58% F	SD 10.6

Abbreviations: F, female; L, left; M, male; R, right; SD, standard deviation. 14,24, upper first premolar. 15,25, second premolar. 16,26, upper first molars. 17,27, upper second molars.

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clinical observations in humans using radiology and macromorphometry are valuable and noninvasive, the most effective ways of evaluating the density, organization, structure, and quality of the newly formed bone are histology and histomorphometry.<sup>29</sup>

For osseointegration maintenance, the minimal requirement of vital bone within the graft is believed to be 25% to 35% by volume.<sup>11</sup> The aim of the present study was to evaluate the regenerative potential of a fully synthesized homogenous HA:β-TCP 60:40 alloplast material (4Bone SBS, Biomatlane, Vigneux de Bretagne, France) in sinus lift procedures and to show the potential of current technologies to improve the assessment of new grafting materials.

## Materials and Methods

### PATIENT SELECTION

Twelve adult patients (5 men and 7 women; age range, 42 to 80 years; mean age for men, 61.8 yr; mean age for women, 61.1 years) comprised the study population (Table 1). The patients presented no systemic disorders that would prevent implant placement.

All participants were informed about alternative treatment plans, but preferred maxillary sinus elevation followed by the placement of endosseous implants. All patients presented with a large pneumatized sinus, a moderate or severe atrophic posterior maxilla, and a residual alveolar bone height no greater than 5 mm—a factor that may preclude the achievement of primary implant stability during installation and cause a high failure rate.<sup>2,11</sup> Exclusion criteria included long-term steroid therapy, uncontrolled dia-

betes, long-term use of bisphosphonates, irradiation of the head and neck in the previous year, smoking at least 10 cigarettes per day during the study period or 3 months before the study, and maxillary sinus cysts or active chronic sinusitis. All participants signed an informed consent form in which the procedure was explained in detail according to the institutional review board of Clalit Sick Fund Israel. Procedures were planned after a careful evaluation of the medical history, intra- and extraoral examinations, panoramic radiographs, and relevant computed tomographic (CT) scans. The ethics committee of Tel Aviv University (Tel Aviv, Israel) approved the study protocol. Patients were treated by initial periodontal therapy, including oral hygiene instructions and training, scaling, and root planning. Whenever necessary, additional periodontal therapy was administered to achieve adequate periodontal health and satisfactory oral hygiene. A staged approach was carried out at 12 sites, ie, sinus lift grafting procedures were followed by implant placement 9 months later. All sites were grafted with a fully synthesized homogenous HA:β-TCP 60:40 alloplast material with a particle size of 0.5 to 1 mm (4Bone SBS). Several histologic studies<sup>2,30-33</sup> have reported that similar percentages of vital bone can be achieved in bone replacement grafts and in grafts with an autogenous component, provided the bone replacement grafts are allowed a longer maturation period. Biopsies were harvested at the time of implant placement, 9 months after the sinus lift procedure.

CT scans were taken preoperatively and before implant placement. Six months after implantation, the implants were exposed and restored with fixed

crowns or bridges. The implants were considered successful if they fulfilled the criteria defined by Albrektsson et al,<sup>34</sup> namely immobility, lack of peri-implant radiolucency, bone loss not exceeding 0.2 mm after the first year of service, and an absence of persistent and/or irreversible signs and symptoms, such as pain, infections, and neuropathies.

The patients' oral health was maintained by a trained oral hygienist at 2 to 4 periodic appointments per year. Treatment included periodontal charts, oral hygiene instructions, scaling, and root planning, if needed.

#### SURGICAL TECHNIQUE

Patients were premedicated 1 hour before surgery with dexamethasone 8 mg (Rekah Pharmaceutical Products Ltd, Holon, Israel)<sup>35</sup> and amoxicillin-clavulanate potassium 875 mg (Augmentin-GlaxoSmithKline, Brentford, UK). Local anesthesia included 3% lidocaine HCl (2 to 6 mL) and base norepinephrine 0.04 mg (Novocol Pharmaceutical of Canada, Inc, Cambridge, Canada). The patients rinsed their mouths with 0.2% chlorhexidine gluconate solution (Tarodent mouthwash, Taro Pharm Ind Ltd, Haifa, Israel) for 1 minute, immediately preoperatively, to obtain a better surgical antiseptic environment.

Surgical procedures were performed according to the technique described by Smiler and Holmes.<sup>7</sup> Briefly, at the edentulous region distal to the position of the first premolar, a mucoperiosteal buccal flap was elevated, exposing the lateral bony wall of the sinus antrum. A round diamond bur, 2 mm in diameter, was used to outline the demarcation of the lateral window, which was removed, thus completely exposing the underlying Schneiderian membrane. The membrane was separated from the housing bone, and a tension-free reflection exposing the sinus walls was achieved by gently pushing it away using a large flat curette (Kramer-Nevins Hu-Friedy, Chicago, IL). An inner occlusive native collagen membrane (Bio-Gide, Geistlich Pharma AG, Wolhusen, Switzerland) was placed underneath the reflected Schneiderian mem-

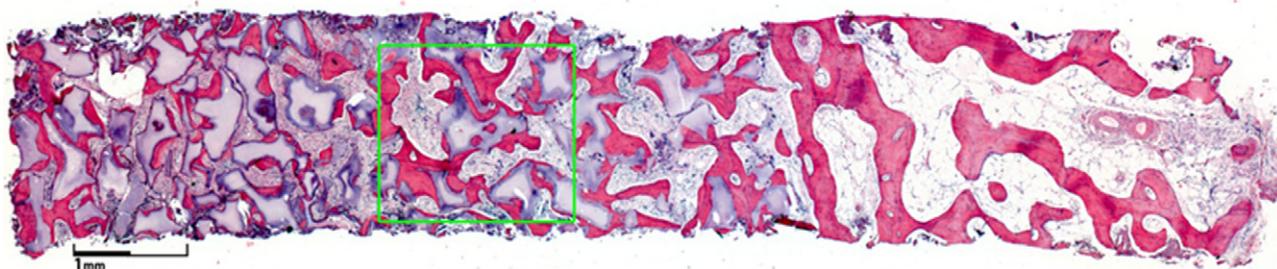
brane, serving as a "roof" to the augmented space before graft placement, as previously described.<sup>36</sup> The membrane was adapted to the Schneiderian membrane "roof," thus defining a space limited by bony walls peripherally, an osseous floor below, and an upper collagen barrier border underlying the Schneiderian membrane.

The established voids were filled with 2 to 6 mL of saline wet homogenous HA: $\beta$ -TCP grafting material (4Bone SBS), followed by sealing the open lateral window by the placement of a collagen membrane (Bio-Gide)<sup>30</sup> and primary soft tissue closure using 4-0 silk sutures (Look Surgically Specialty Corporation, Reading, PA). Postoperatively, systemic antibiotic amoxicillin-clavulanate 875 mg (Augmentin-GlaxoSmithKline) 2 times/day was prescribed for 1 week and naproxen sodium 275 mg (Narocin, Teva Pharm Ind Ltd, Petah-Tikva, Israel) 1 tablet every 6 to 8 hours for 24 hours for pain control. Dexamethasone (Rekah Pharmaceutical Products Ltd) 4 mg/day was administered for an additional 2 days<sup>35</sup> to minimize edema. Antiseptic mouthwash of 0.2% chlorhexidine gluconate (Tarodent mouthwash) was used 2 times/day (30 s each time) for 2 weeks. Sutures were removed after 14 days, followed by uneventful soft tissue healing.

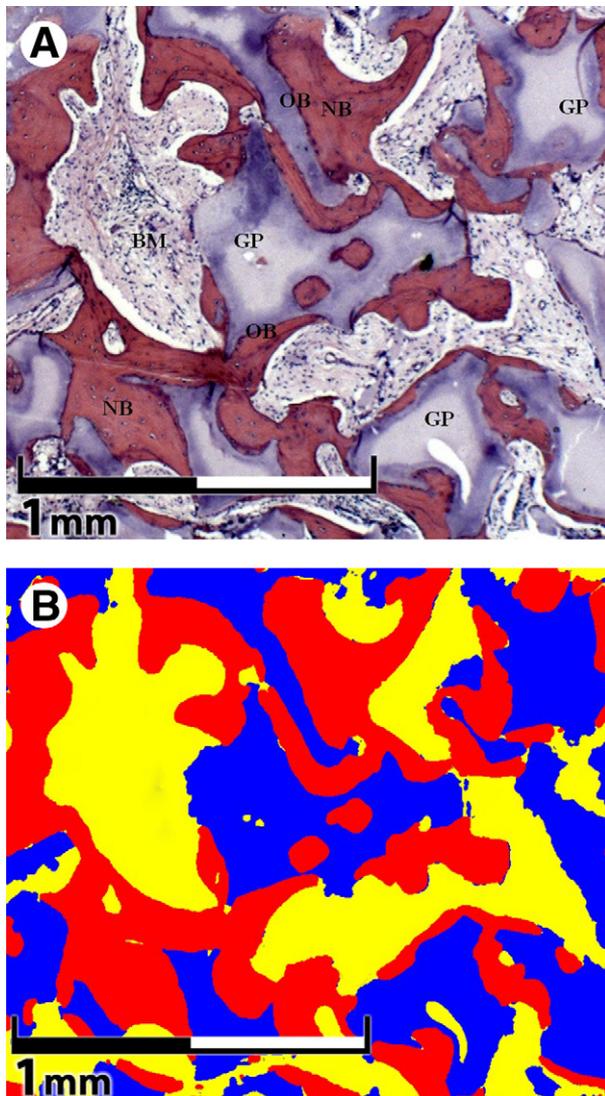
Nine months after sinus augmentation, CT scans were obtained to visualize graft material stability and the normal thickness of the Schneiderian membrane and to locate the regenerated radiopaque tissue and graft. Immediately before implant insertion, an osteotomy was performed using a trephine drill (MIS, Shlomi, Israel), and a core biopsy 2 mm in diameter and 12 to 16 mm long was harvested from the proposed implant site (Fig 1).

#### TISSUE PROCESSING

The core biopsy specimen was fixed in 10% neutral buffered formalin for 96 hours, decalcified in 5% formic acid for 14 days, and embedded in paraffin.<sup>31</sup> Blocks were cut into 5- $\mu$ m-thick slides and stained with hematoxylin and eosin.



**FIGURE 1.** A 2-mm-diameter trephine core biopsy after 9 months shows new bone associated with graft particles and connective tissue/bone marrow (hematoxylin and eosin stain; original magnification,  $\times 10$ ).



**FIGURE 2.** A, A biopsy taken 9 months after grafting with 4Bone SBS. Graft particles (GP) are surrounded by vital newly formed bone (NB) and bone marrow (BM). Lining osteoblasts (OB) are clearly observed at the interface (hematoxylin and eosin stain; original magnification,  $\times 40$ ). B, Image processing of the biopsy in identifies new bone (red), graft particles (blue), and connective tissue (yellow).

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#### HISTOMORPHOMETRIC ANALYSIS

The stained specimens were photographed under a BH-2 light microscope (Olympus, Tokyo, Japan) and a TCA-3 digital camera (Tucsen Imaging Technology Co, Province Jiangxi, Ltd, China; Fig 1). Images were processed to produce a segmented, pseudocolor image identifying different tissue components. The processed images were analyzed using custom-made software to assess the percentages of the different components and the interface between the residual graft particles and the newly formed bone (Fig 2A,B).

## Results

Twenty-eight implants were successfully placed in the study population (Table 1). CT scans after 9 months depicted an additional 6 to 18 mm of radiopaque material over the sinus floor at all sites. All implants placed were successful during the 3- to 5-year follow-up period of the study, yielding a 100% successful implant survival rate (Figs 3, 4).

#### HISTOLOGY

Biopsy specimens contained native and newly formed bone. An abrupt transition between the 2 was clearly observed (Fig 1). Graft particles were surrounded by and showed intimate contact with new bone and with the connective tissue surrounding it (Figs 1, 2A). Osteoblasts were seen lining graft particles in conjunction with newly formed bone (Fig 2A). There was no evidence of inflammatory infiltrate.

#### HISTOMORPHOMETRY

Native bone was identified according to the lack of graft material and was excluded from the analyzed data. Measurements were taken only from the core zone containing newly formed tissue and/or graft material. Graft particles were identified by their typical structure and color. New bone formation accounted for  $26.4\% \pm 12.3\%$  (mean  $\pm$  standard deviation), whereas residual graft particles averaged  $27.3\% \pm 9.2\%$  of the total surface (Table 1). Total mineralized tissue (newly formed bone plus graft particles) accounted for  $53.7\% \pm 12.3\%$  of the surface; the remaining connective tissue accounted for  $46.3\%$  (Table 1, Fig 5).

The osteoconductive index (interface between newly formed bone and graft particle surfaces) was  $33.5\% \pm 11.2\%$  of the total particle surface (Fig 6).

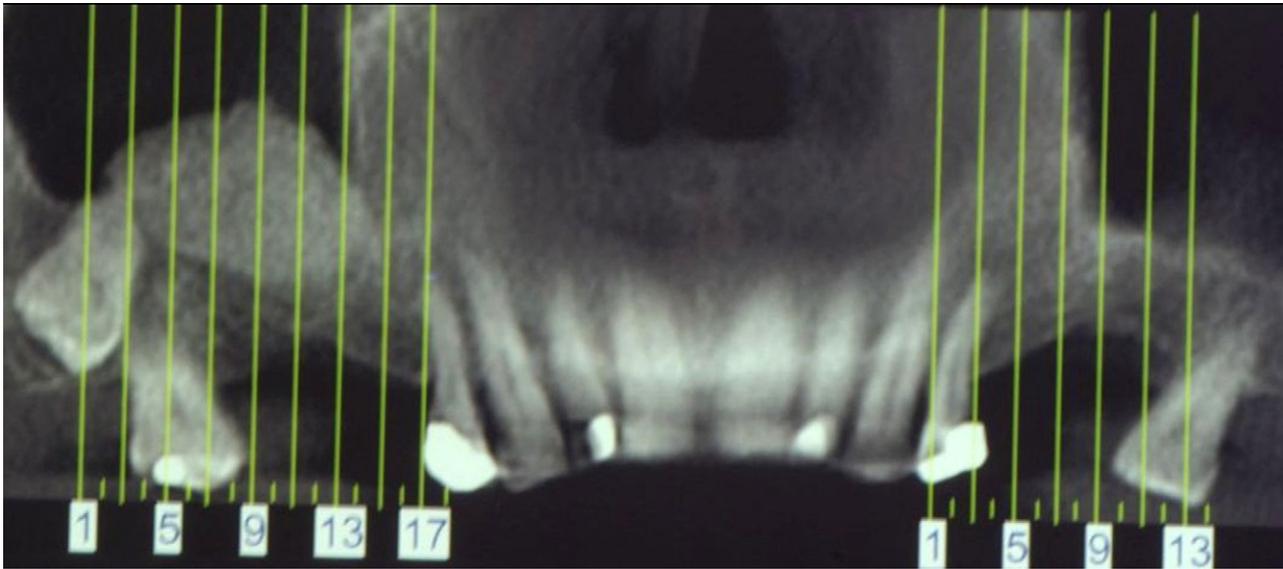
The correlation between these data and the patients' gender and age was assessed using 1-way analysis of variance and Pearson correlation, respectively. Because of sample size limitations, marginally significant results ( $P \leq .1$ ) were included.

Male subjects presented significantly higher rates of new bone formation ( $36\% \pm 12\%$  vs  $19\% \pm 6\%$ ;  $P = .01$ ; Fig 7). In addition, male subjects presented a marginally higher osteoconductive index ( $40\% \pm 7\%$  vs  $29\% \pm 11\%$ ;  $P = .088$ ) than female subjects and a larger percentage of total mineralized tissue ( $61\% \pm 12\%$  vs  $48\% \pm 10\%$ ;  $P = .067$ ; Fig 7).

The present study did not find significant correlations between age and any of the other parameters because of the limited sample size (Fig 8).

## Discussion

The gold standard material for maxillary sinus lift is cancellous autogenous bone graft. Traditionally, bone



**FIGURE 3.** Radiographic view of the implant site 9 months after sinus floor elevation showing stability of the alloplast.

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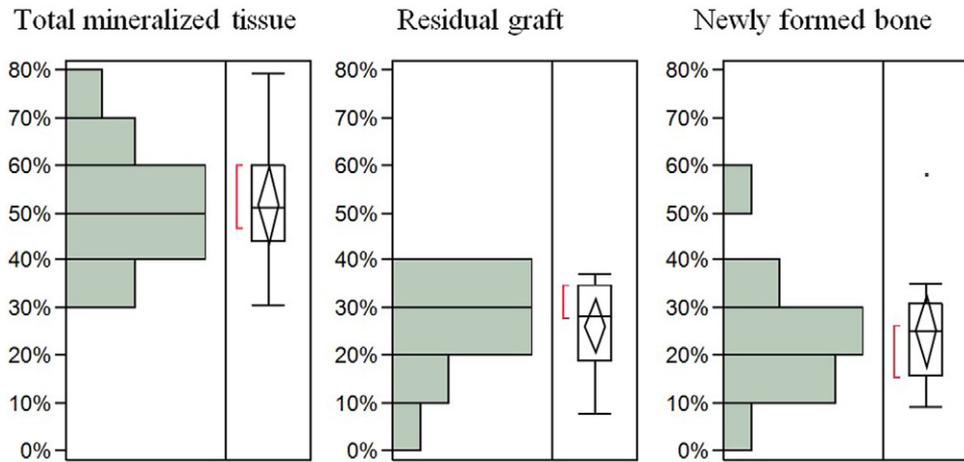
was harvested from the iliac crest or tibial plateau,<sup>37</sup> followed by intraoral and calvarial sources. Unfortunately, these procedures may present complications owing to a second surgical site. More recently, recombinant human bone morphogenetic protein-2 (rhBMP-2), which has been used for orthopedic reconstructions, was considered a valid option for dental use. A recent study on the use of rhBMP for maxillary sinus lift was performed as a multicenter, randomized, parallel evaluation of 160 patients who were assigned to the autograft population or the rhBMP-2 population.<sup>38</sup>

The study showed the safety and effectiveness of rhBMP-2: there were no adverse events in this population, whereas 17% of the autograft population developed long-term side effects related to donor-site harvesting. Bone formation was comparable between the 2 groups. In these studies,<sup>38-40</sup> an absorbable collagen sponge was used as a scaffold for rhBMP-2 administration. It had been assumed that the differences between filling materials used in sinus lift procedures would modulate the quality and quantity of newly formed bone. Therefore, the authors evaluated



**FIGURE 4.** Radiographic view of the implant site 4.5 years after implant placement.

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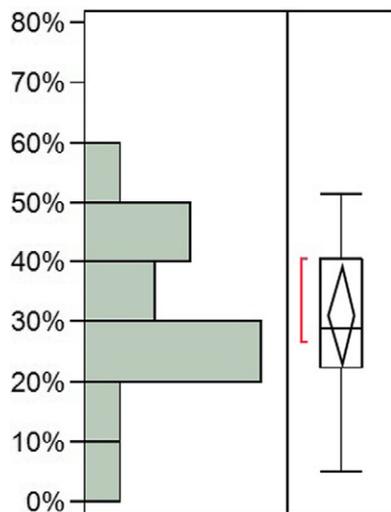
**FIGURE 5.** Distribution diagrams of the percentages of newly formed bone, residual graft, and total mineralized tissue area.

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the healing response and efficiency of fully synthesized homogenous HA: $\beta$ -TCP 60:40 alloplast material in these procedures.

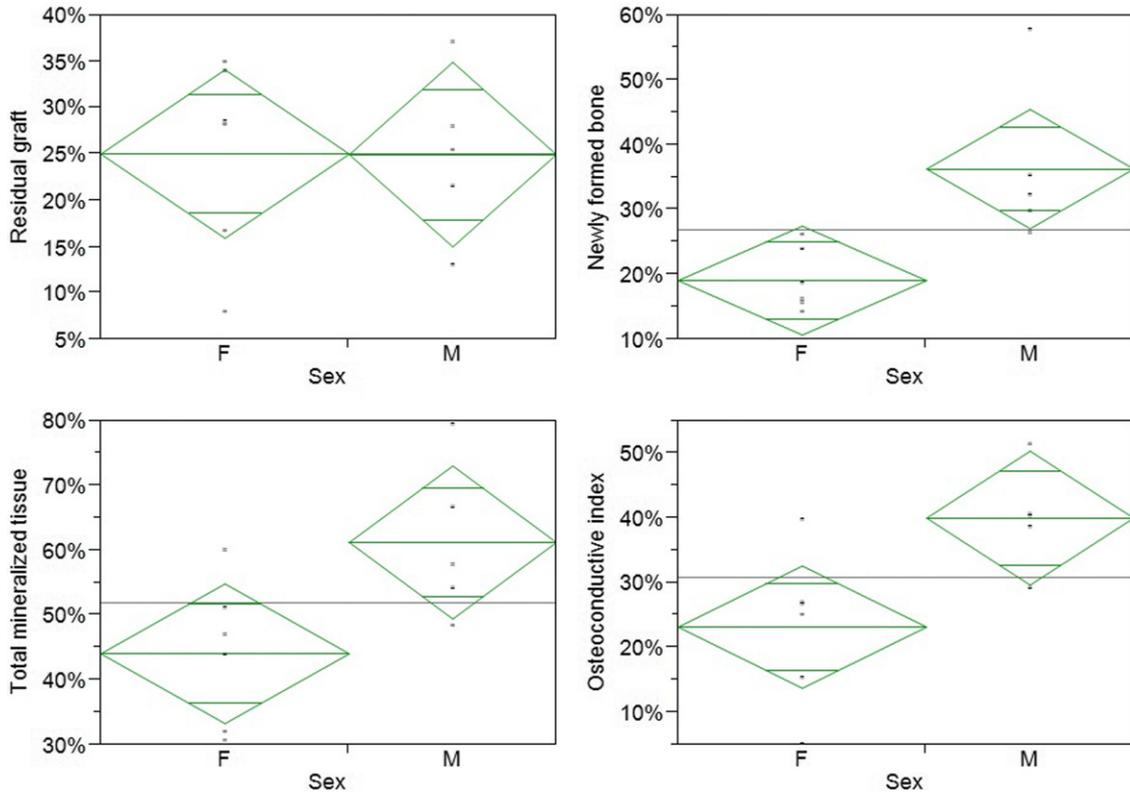
In the present study, the proportion of new bone formation was 26.4%, significantly smaller than the 41% and 36% recorded by Cammack et al<sup>14</sup> who used a mineralized freeze-dried bone allograft and a demineralized freeze-dried bone allograft, respectively, for a similar procedure, and Noubissi et al<sup>33</sup> (40.33%) who used a mineralized solvent-dehydrated bone allograft (Puros, Zimmer Dental Inc, Carlsbad, CA). The present results are, however, comparable to the proportion of new bone formation previously reported<sup>36</sup> using a mineralized freeze-dried bone allograft (Ora-graft Life Net, Virginia Beach, VA) and an internal collagen membrane for sinus augmentation procedures (29%) and to the proportion (28.3%) reported by Froum et al.<sup>32</sup> A relatively recent study<sup>41</sup> analyzing

the regenerative potential of a demineralized bone matrix paste (Orthoblast 2, Irvine, CA) used for sinus lifting presented a similar proportion (25.2%) of new bone formation after 6 months. Deproteinized bovine bone mineral (DBBM; Bio-Oss) is well documented as an augmentation material for sinus floor elevation.<sup>15,17,30-33</sup> Using DBBM, Valentini and Abensur<sup>17</sup> found that newly formed bone increased from 21.1% to 27.6% at 6 to 12 months and a decrease of graft particle components from 39.2% to 27%. These data are comparable to the 27.3% residual graft proportion reported in the present study. Valentini and Abensur<sup>17</sup> further reported that the proportion of mineralized area containing new bone and graft particles remained unchanged (about 60%). This value is comparable to the 53.7% found in the present study. It is assumed that this fraction may improve the mechanical bone properties, transforming it into a type 2 to 3 bone.<sup>2,17</sup> Ample data have been reported on new bone formation in sinus floor elevation procedures; however, very few articles have dealt with the osteoconductive values of the grafted materials.<sup>33,42,43</sup> Proussaefs et al<sup>42</sup> found that 40.17% of the DBBM particle surface was in contact with bone, whereas Tadjedin et al<sup>43</sup> found that only 34% to 38% of the DBBM surface was in contact with bone. Noubissi et al<sup>33</sup> reported similar values for DBBM (34.75%) and higher values using a mineralized solvent dehydrated allograft (Puros). These values are similar to or higher than the 33.5% achieved using 4Bone SBS. The use of biphasic calcium phosphate (HA: $\beta$ -TCP 60:40) for sinus grafting has proved to be effective in the formation of new bone.<sup>44,45</sup> Six- and 10-month biopsies have shown 38.8% and 27.3% new bone formation, respectively.<sup>44,45</sup> Another comparative study showed no significant difference in the amount of mineralized bone in sinuses grafted with biphasic calcium phosphate (Straumann Bone Ceramic, Basel, Switzerland) versus anorganic bovine bone (Bio-Oss; 21.6% vs



**FIGURE 6.** Distribution diagram of the osteoconductive index.

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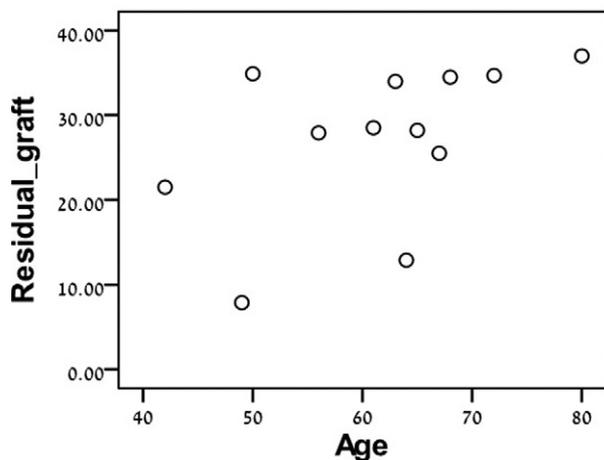
**FIGURE 7.** One-way analysis of newly formed bone, residual graft, total mineralized tissue, and the osteoconductive index by gender. F, female; M, male.

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19.8%, respectively).<sup>46</sup> In contrast, the bone-to-graft contact area was significantly larger for anorganic bovine bone compared with biphasic calcium phosphate (48.2% vs 34%).<sup>46</sup> The 34% value reported by Cordaro et al<sup>46</sup> was similar to the present finding (33.5%), although the biopsy specimens were har-

vested at different points of time (6 to 8 mo and 9 mo, respectively). The present study showed higher rates of new bone formation in male than in female subjects (36% vs 19%), and marginally significant differences were found such that male subjects presented a higher osteoconductive index (40% vs 29%) than female subjects and a larger percentage of total mineralized tissue (61% vs 48%).

The advantages of using a barrier membrane in sinus augmentation over the lateral bony window, ie, increasing the amount of vital bone formation, have been well documented.<sup>30,47,48</sup> In contradiction, Fugazzotto and Vlassis<sup>49</sup> reported a similar success rate when placing a resorbable membrane over the lateral window (98.6%) or leaving the window uncovered (99.2%). Using an internal collagen membrane underneath the Schneiderian membrane as a routine procedure has been rarely investigated.<sup>36</sup> In the present study, collagen membranes were routinely placed underneath the Schneiderian membrane and over the lateral window. The role played by Schneiderian membrane perforations in the implant success rate remains controversial.<sup>49-51</sup> The use of an internal membrane has been claimed to offer an additional biologic barrier that may help prevent the passage of



**FIGURE 8.** The correlation between age and residual graft.

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graft particles and bacterial contamination to and from the sinus cavity through potential small membrane tears.<sup>52</sup>

In the present study, collagen membrane was placed underneath the reflected Schneiderian membrane, even if the membrane appeared clinically intact. Care was taken not to cover the peripheral bony walls. The use of an internal membrane offers an additional barrier that may help prevent the passage of graft particles and bacterial contamination to and from the sinus cavity through potential small tears.<sup>49-51</sup>

It is noteworthy that the present study used modern imaging and computer processing techniques to analyze the images. The histomorphometric analysis, including the sum of a set of polygons traced on the sample, allowed the software to calculate a set of areas (ie, new bone, residual graft particles, and soft tissue), resulting in accurate measurements covering the entire specimen. This method was chosen because of the clear demarcation between the graft particles and the new bone (Figs 1, 2A). Previous reports were based on partial sampling techniques (ie, point count<sup>36</sup>) that are used widely in histomorphometric studies.<sup>36</sup> The point count is performed using a microscope with a millimeter eyepiece grid for histomorphometric measurements. The point count technique is needed in sample analysis where an allograft is used because of the similar appearance to new bone after staining.

The different histomorphometric techniques may explain in part some of the differences between the findings in the present study and similar publications.<sup>36</sup>

Within the limits of the present study, it is suggested that 4Bone SBS is a biocompatible and osteoconductive graft permitting new bone formation similar to DBBM and allograft materials when used for sinus augmentation procedures.

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