A Histomorphometric Comparison of Bio-Oss Alone Versus Bio-Oss and Platelet-Derived Growth Factor for Sinus Augmentation: A Postsurgical Assessment

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The purpose of this study was to assess vital bone formation at 4 to 5 months and 7 to 9 months following sinus augmentation with anorganic bovine bone matrix (ABBM) with and without recombinant human platelet-derived growth factor (rhPDGF). Twenty-four subjects received bilateral sinus elevation surgery with ABBM on one side and ABBM and rhPDGF on the contralateral side. Twelve patients had core sampling at 4 to 5 months and 12 patients at 7 to 9 months postoperatively. In subjects with cores taken at 4 to 5 months, mean vital bone, connective tissue, and residual graft were 11.8%, 54.1%, and 33.6%, respectively, with ABBM alone. Cores of sinuses filled with ABBM and rhPDGF showed mean 21.1% vital bone, 51.4% connective tissue, and 24.8% residual graft. Paired t test showed a statistically significant difference in vital bone. In cores taken at 7 to 9 months, the values for ABBM alone and ABBM + rhPDGF were 21.4% vs 19.5% vital bone, 28.4% vs 44.2% connective tissue, and 40.3% residual graft vs 35.5%. There was no statistically significant difference in vital bone at 7 to 9 months after surgery. Test and control groups showed clinically acceptable levels of vital bone both at 4 to 5 months and 7 to 9 months postsurgery. However, vital bone formation was significantly greater in the 4- to 5-month sections of ABBM + rhPDGF vs the Bio-Oss alone. In the 7- to 9-month specimens, this difference disappeared. More rapid formation of vital bone with the addition of rhPDGF may allow for earlier implant placement. (Int J Periodontics Restorative Dent 2013;33:269–279. doi: 10.11607/prd.1614)

The subantral sinus augmentation procedure is a well-known and predictable method of increasing the volume of bone in the deficient posterior maxilla for simultaneous or delayed implant placement.[1–10]

Although the original technique used autogenous bone as a graft source,[11–14] recently bone replacement graft materials have been successfully used in sinus augmentation procedures to avoid the drawbacks inherent in the harvesting of autogenous bone. These materials (allografts, xenografts, and alloplasts) have been shown to be effective and have demonstrated high implant survival rates.[15–19] The ideal augmentation material would provide both a high percentage of vital bone after a reasonable maturation

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time and implant survival rates that are equal to or better than those achieved with autogenous bone.

Anorganic bovine bone matrix (ABBM) is a bone substitute manufactured from bovine bone mineral that is processed and sterilized for use in intraoral grafting procedures. It is composed of only the mineral portion of extremity bone. This material, alone or in combination with autogenous bone, enjoys widespread use as the graft material of choice for many practitioners performing sinus augmentations procedures. In fact, 10 published evidence-based systematic reviews concluded that the results with xenografts are the most favorable, complete, and well-documented in the published literature.[1–10]

The safety standard of ABBM derives from the fact that sources include only extremity cow bone from Australia, where bovine spongiform encephalopathy (BSE) has not been detected, that has undergone chemical processing in strong alkaline solutions and subsequently subjected to heat. Examination of ABBM for protein residues using validated analyses with regard to BSE is performed on each batch. Proof of deorganification is obtained through Bio-Rad assay, SDS-Page testing, and SDS – Page + Western blotting.[20,21]

Platelet-derived growth factor (PDGF) is a wound-healing hormone that is naturally produced by the body at sites of soft tissue and bone injury. It is a well-characterized tissue growth factor long recognized for its broad wound healing effects in both soft and hard tis-sues. This growth factor, along with insulin-like growth factor-1, has been shown to be safe and effective in a series of well-controlled human clinical trials as well as in patient use for nearly 10 years.[22–30]

In periodontics, numerous studies in humans have demonstrated the effectiveness of PDGF in regenerating bone, ligament, and cementum.[22,23] Recombinant human platelet-derived growth factor BB (rhPDGF-BB) (Osteohealth, Luitpold Pharmaceuticals) was the first recombinant protein therapeutic approved for treatment of periodontal defects. It has been shown that the use of purified rhPDGF-BB mixed with bone allograft resulted in periodontal regeneration in both Class II furcations and interproximal intrabony defects.[22] Subsequently, it was shown that moderate to severe periodontal intrabony defects treated with 0.3 mg/mL rhPDGF-BB + β-tricalcium phosphate (β-TCP) had significantly greater clinical attachment level (CAL) gains and less gingival recession at 3 months and significantly greater radiographic linear bone growth and percent bone fill at 6 months compared to sites treated with the control (β-TCP + buffer).[23]

The recombinant PDGF-BB used in this study was of human origin. Tissue engineering allowed for the amplification of this human-derived protein.

At the time of the present study, PDGF-bb in sinus grafting was considered to be off-label use, as it had not been FDA-cleared. This study was approved by the New York University internal review board (IRB).

The purpose of this prospective, blinded, randomized controlled investigation was to compare the efficacy of ABBM with and without PDGF in producing vital bone at both 4 to 5 months and 7 to 9 months following sinus augmentation.

Method and materials

Twenty-four subjects were selected from those presenting to the Ashman Department of Implant Dentistry at New York University College of Dentistry, New York, New York, who desired maxillary posterior implants and did not have sufficient bone for the procedure. Each subject required bilateral subantral sinus grafting to be eligible for this study. Moreover, the subjects had to have no more than 4 to 5 mm of crestal bone below the sinus floor as determined on a computerized axial tomographic (CAT) scan (Fig 1). A panograph and a CAT scan were taken prior to patient selection and inclusion in the study as part of routine departmental diagnostic procedures. The patient was advised that a second CAT scan would be taken 1 to 2 weeks before implant placement and core sampling (Fig 2). The study exclusion criteria are listed in Table 1.

Informed consent was presented verbally and each subject who agreed to participate signed an informed consent form approved by the IRB. The use of this growth factor was off-label for sinus augmentation.

Fig 1 (left) *Presurgical measurements were obtained using a CAT scan.*

Fig 2 (right) *CAT scan of sinus in Fig 1 (test group) after a 5-month healing period and just prior to core removal.*

Table 1	Exclusion criteria
Patients requiring antibiotic prophylaxis for dental procedures	
Any sinus pathology contraindicating the graft procedure	
Patients who could not undergo standard oral surgery procedures for any reason	
Patients who smoked more than 10 cigarettes per day	
Patients with uncontrolled or poorly controlled diabetes or patients with other uncontrolled metabolic diseases	
Patients with chronic or acute sinus problems	
Women who were pregnant or who desired to become pregnant during the course of the study	
Patients under 18 years of age	

Surgical procedures

Investigators performed a standardized calibration session prior to the first surgery to ensure that the surgical technique for the sinus augmentation procedure had minimal variation between investigators. Each subject was required to take antibiotic prophylaxis using 2 g amoxicillin (Teva Pharmaceuticals) or 600 mg clindamycin (Watson Laboratories) 1 hour prior to surgery. Clinical photographs were taken prior to, during, and postsurgery. Procedures were performed with local anesthesia. The following anesthetic agents were used depending upon patient medical history and operator preference: Lidocaine HCL 2% with 1:100,000 epinephrine, Lidocaine HCL 2% with 1:50,000 epinephrine, Mepivacain/Carbocaine 3% without epinephrine, or Bupivacaine HCl 0.5% with 1:200,000 epinephrine (Abbott Laboratories).

Reflection of a full-thickness flap was performed exposing the lateral wall of the sinus.

Preparation of a hinge or complete osteotomy of the lateral sinus wall was performed using a rotary bur or piezoelectric surgery as the circumstances dictated and according to operator preference. The wall and sinus membrane were elevated. If the bony window was removed to facilitate elevation of the membrane, it was not added to the bone to be grafted.

ABBM (Bio-Oss, Osteohealth) alone was placed in one subantral compartment and ABBB + rh-PDGF was placed in the contralateral subantral compartment. The mixture material in the control sinus was composed of 2.5 g (50%) of 0.25- to 1.0-mm particle size and 2.5 g (50%) of 1.0- to 2.0-mm particle size (total, 5 g). The same ratio of small to large particles was used if any additional material was

required to fill a larger sinus. A computer-generated randomized code was used to determine the test and control sites. Depending on the sinus anatomy, a total of 4 to 7 g of material were grafted in each sinus. Two units of PDGF (0.5 mL at concentration of 0.3 mg/mL) were mixed with 1 g of ABBM. The ABBM and rh-PDGF mixture was then thoroughly combined with an additional 4 g of ABBM, yielding a total volume of 5 g of graft material to be placed in the test sinus. The same ratio of rh-PDGF to ABBM was used if any additional material was required to fill a larger sinus. The sinuses were either grafted at the same visit or no more than 6 to 8 weeks apart.

A resorbable porcine collagen membrane (BioGide, Osteohealth) was hydrated in sterile saline prior to insertion and placed over the lateral window. The membrane extended at least 3 mm beyond

the limits of the prepared window and was adapted to the surrounding bone. Primary flap closure was achieved with silk, polyglactin 910, chromic gut (Ethicon), or expanded polytetrafluoroethylene (Goretex) sutures. A postoperative panoramic radiograph was taken to ensure that all the graft material was in place.

Temporary fixed or removable appliances positioned over the surgical sites were relieved prior to reinsertion.

Subjects were placed on 7 to 10 days of antibiotic coverage depending on their history of drug allergy and appropriate analgesics (Tylenol with Codeine #3 or #4, Ortho-McNeil-Jansen Pharmaceuticals) or Motrin 600 mg (Ortho-McNeil-Jansen Pharmaceuticals). Rinses with 0.12% chlorhexidine digluconate for 2 weeks were also prescribed. Subjects returned to the clinic 7 to 14 days postsurgery for suture removal, if required, and a postoperative site evaluation. A postoperative evaluation was also performed at 1 to 2 months following surgery. Core sampling was performed at 4 to 5 months for the first 12 patients enrolled in the study. The second patient cohort had core samplings performed at 7 to 9 months.

At stage-one surgery when implants were placed, a trephine core sample (10 mm in length and 2.7 to 4.0 mm in diameter) was retrieved from the distal and most superior area of the previous window site. If a patient chose not to continue with implant therapy, a core sample was still taken from the appropriate site. Uniformity of core harvest location ensured that the cores were taken through the previously drilled window and in the most apical area of the graft, which was considered to be the least mature due to the greater width of the sinus in this area.[31]

The cores, obtained from both test and control sites, were harvested by the listed investigators in a manner that did not compromise the implant receptor sites. The timing of core harvesting with the respective study maturation periods was strictly adhered to.

Data analysis and evaluation technique

Specimens were fixed in 10% buffered formalin, embedded undecalcified in polymethyl methacrylate (Polysciences), sectioned to 60-μm thickness along the full midline longitudinal length of the core with a Isomet low-speed saw (Buehler), and ground/polished using an automated 400 CS Grinding System (Exakt Technologies). Sections were stained with Stevenel blue and Van Gieson picro fuchsin. High-resolution image montages were acquired with a ScanScope Digital Scanner (Aperio) and analyzed using in-house algorithms developed for the Quantimet image analysis system (QWin version 3.0, Leica Microsystems). The percentages areas of new bone, grafting material, fibrous connective tissue, and marrow were calculated from each image montage. Volumetric and height measurements were made on all CAT scans for comparison. Data were separated into cores taken 4 to 5 months postsurgery and those taken 7 to 9 months postsurgery and then combined to determine the results from the entire study.

Statistical analysis

A repeated-measures analysis of covariance (ANCOVA) was used to determine whether there was a statistically significant difference in percent vital bone growth. There were two main effects factors: time (baseline, core sample) and material (ABBM only, ABBM + PDGF). The interaction effect time/material was also examined. The covariate in the analysis was the time elapsed from grafting (baseline) to core sampling.

A linear mixed effects model was fit for each outcome for all subjects to assess for differences in vital bone, residual graft, and connective tissue between the treatment (ABBM + rhPDGF) and control (ABBM only) groups and to assess the effect of time of core removal. Initially, the model included fixed effects of treatment group, core time, and their interaction with a random intercept for each subject. If the interaction term was not statistically significant then the model was refit without the interaction term. If the interaction term was statistically significant then tests of simple effect were performed.

Table 2	Group A subjects							
	ABBM only				ABBM + PDGF			
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Vital bone	11.8%	9.2%	2.1%	29.3%	21.1%	11.8%	2.0%	42.7%
Connective tissue	54.1%	17.5%	26.7%	82.0%	51.4%	10.1%	33.0%	67.0%
Residual graft	33.6%	12.0%	12.5%	49.3%	24.8%	11.4%	0.2%	48.2%

Table 3	Group B subjects							
	ABBM only				ABBM + PDGF			
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Vital bone	21.4%	8.6%	8.1%	36.1%	19.5%	10.7%	0.0%	39.9%
Connective tissue	38.4%	6.6%	24.7%	46.9%	44.2%	10.4%	27.3%	60.8%
Residual graft	40.3%	6.7%	30.2%	54.5%	35.5%	9.4%	20.1%	48.9%

Table 4	All 24 subjects							
	ABBM only				ABBM + PDGF			
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Vital bone	16.6%	10.0%	2.1%	36.1%	20.3%	11.0%	0.0%	42.7%
Connective tissue	46.3%	15.2%	24.7%	82.0%	47.8%	10.7%	27.3%	67.0%
Residual graft	36.8%	10.2%	12.5%	54.5%	30.2%	11.6%	0.2%	48.9%

Results

Twenty-four patients were enrolled and all completed the study. Each subject received two sinus augmentations, one with ABBM (control) and one with ABBM + rhPDGF (treatment). The 10 female and 14 male patients had an average age of 61.2 ± 7.7 years. There were two different groups of subjects based on the time between surgery and core removal. Group A (12 subjects) had cores taken between 4

and 5 months (mean ± standard deviation, 4.25 ± 0.34 months after surgery. Group B (12 subjects) had cores taken between 7 and 9 months (mean ± SD, 8.13 ± 0.53 months) after surgery.

Table 2 shows the summary data for the 12 subjects with cores taken at 4 to 5 months, Table 3 shows the same summary data for the subjects in the 7- to 9-month core group, and Table 4 shows the summary data for all subjects combined.

For vital bone, the interaction term of the model was nearly significant ($P = .053$); therefore, tests of simple effects of group and time were performed. These simple effects are the effect of treatment group tested separately for each core time and reciprocally the effect of core time tested separately within each treatment group. Paired t tests showed a statistically significant difference in vital bone between the ABBM (mean ± SD, 11.8% ± 9.2%) (Figs 3a and 3b)
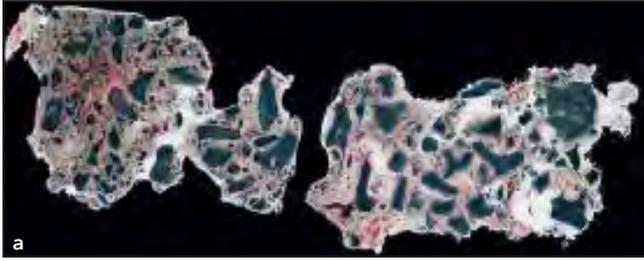
Fig 3a *Cross section of a core sample from a control site (4 months) showing bone formation of varying maturity with 10.1% vital bone (NB). Also evident are various-sized particles of Bio-Oss. The new bone formation is present between the Bio-Oss particles (B), bridging these particles and resulting in a cancellous bone pattern incorporating the Bio-Oss (Stevenel blue and van Gieson picro fuchsin; field width = 3.401 mm).*
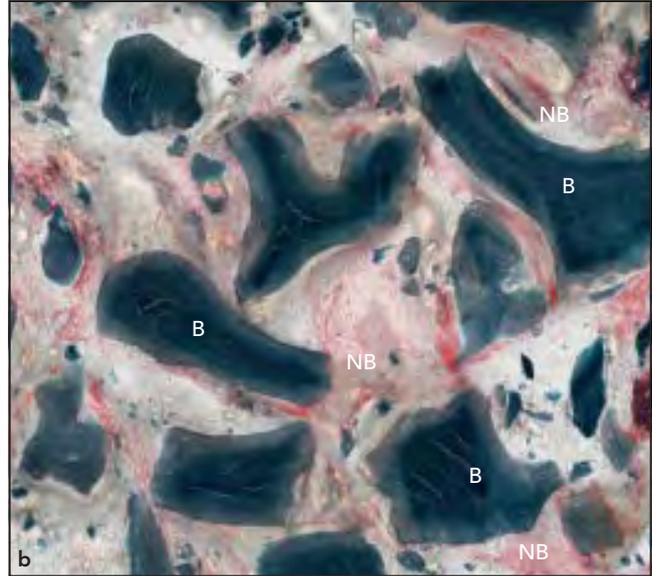
Fig 3b *High-power image showing immature, newly formed bone (NB) around particles of Bio-Oss (B). In the center of the largest particle of B, a small area of new bone is evident (Stevenel blue, van Geisson picro fuchsin; field width = 1.244 mm).*
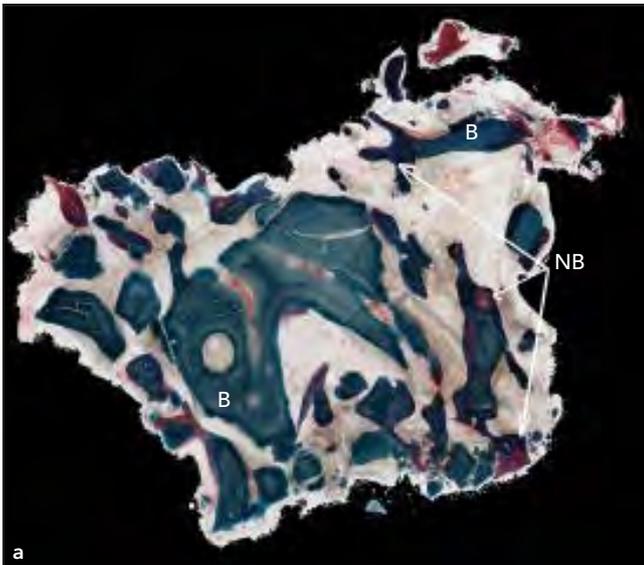
Fig 4a *Cross section of core sample from test site (4 months) showing 25.39% vital bone (NB) (Stevenel blue, van Gieson picro fuchsin; field width = 490 µm).*
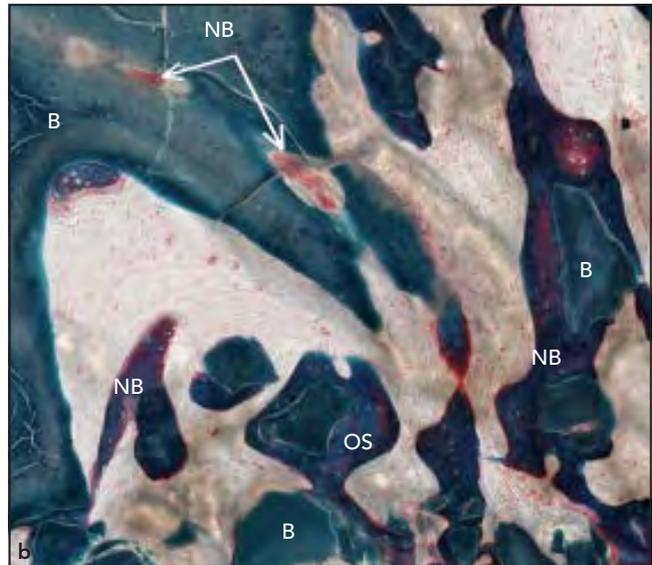
Fig 4b *High-power image showing the new bone formation (NB) bridging the particles of Bio-Oss (B), along with active osteoid (OS). In the center of the largest particle of Bio-Oss in the upper right of the image, a small area of new bone is evident (Stevenel blue, van Gieson picro fuchsin; field width = 516 µm).*

and ABBM + rhPDGF (mean ± SD, 21.1% ± 11.8%) groups (Figs 4a and 4b) among group A subjects (*P* = .043). There was no statistically significant difference in vital bone in group B subjects between control and treatment (ABBM: 21.4% ± 8.6%; ABBM + rh-PDGF: 19.5% ± 10.7%; *P* = .645) (Figs 5 and 6). Independent sample *t* tests showed a significant difference in vital bone between group A (11.8% ± 9.2%) and group B (21.4% ± 8.6%) subjects in the ABBM group (*P* = .015), but no significant difference in the ABBM + rh-PDGF group (group A cores, 21.1% ± 11.8%; group B cores 19.5% ± 10.7%; *P* = .723).
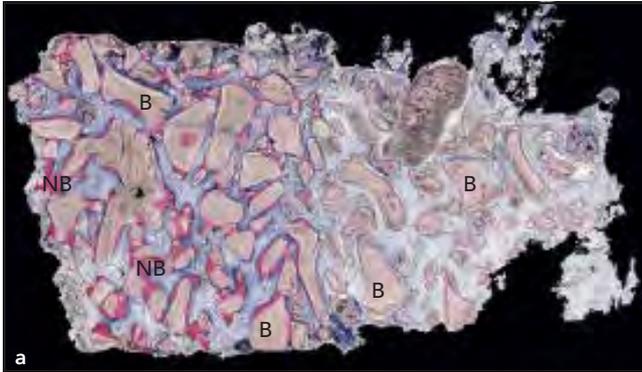
Fig 5a *A core specimen from control site at 7 months demonstrates Bio-Oss particles (B) surrounded by and interconnected with 20.85% newly regenerated bone (NB) (Stevenel blue, van Gieson picro fuchsin; field width = 5.320 mm).*
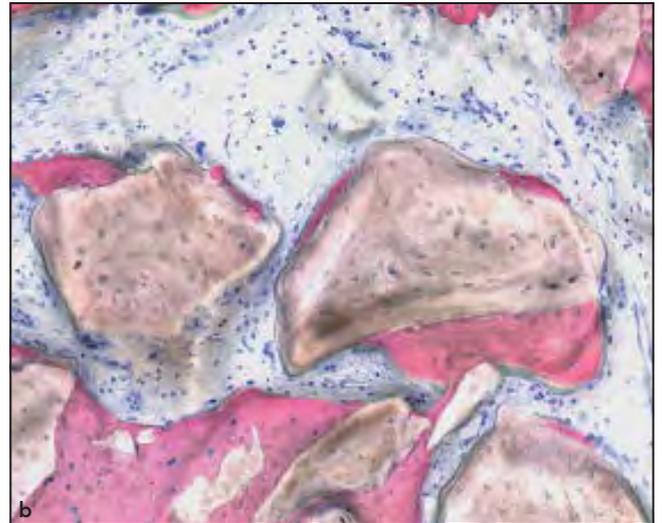
Fig 5b *High-power view showing new bone regenerated in a test site (7 months) around Bio-Oss particles (Stevenel blue, van Gieson picro fuchsin; field width = 2.262 mm).*
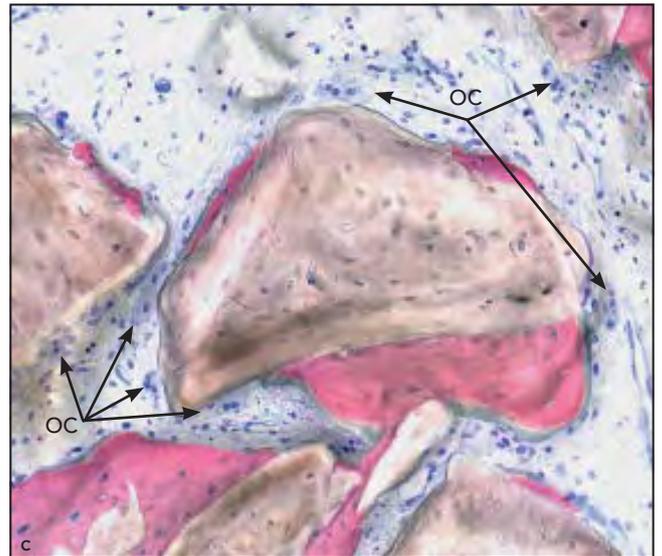
Fig 5c *High-power view showing osteoclasts (OC) around the residual graft material.*

For connective tissue, the interaction term of the initial model was not statistically significant (*P* = .218) and the model was therefore refit without the interaction. The second model showed no significant effect of ABBM treatment group (*P* = .653) but did show an effect of core timing (*P* = .001) on connective tissue. The amount of connective tissue in each treatment group was lower in group B subjects that in group A subjects.

For residual graft, the interaction term of the initial model was not statistically significant (*P* = .477) and the model was therefore refit without the interaction. The second model showed a significant effect of both treatment group (*P* = .016) and core timing (*P* = .004) on residual graft. Residual graft was higher in the ABBM group than in the ABBM + rhPDGF for both core times (see Tables 1 and 2). It was also higher in group B subjects than in group A subjects for both treatment groups.
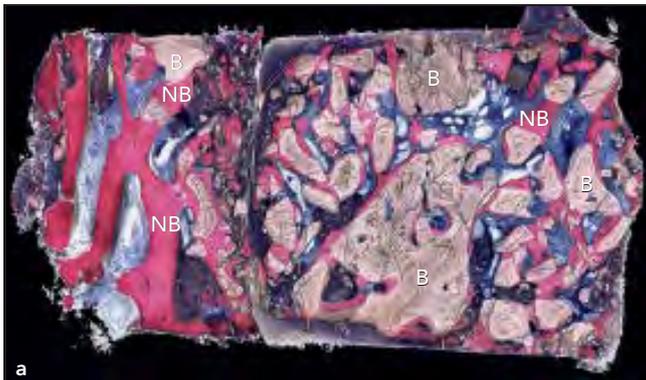
Fig 6a *Low-power view of a core showing trabeculae in which the Bio-Oss particles (B) are generally incorporated into the newly formed bone (NB) in a test site (7 months) with 19.95% of vital bone (Stevenel blue, van Gieson picro fuchsin; field width = 4.545 mm).*
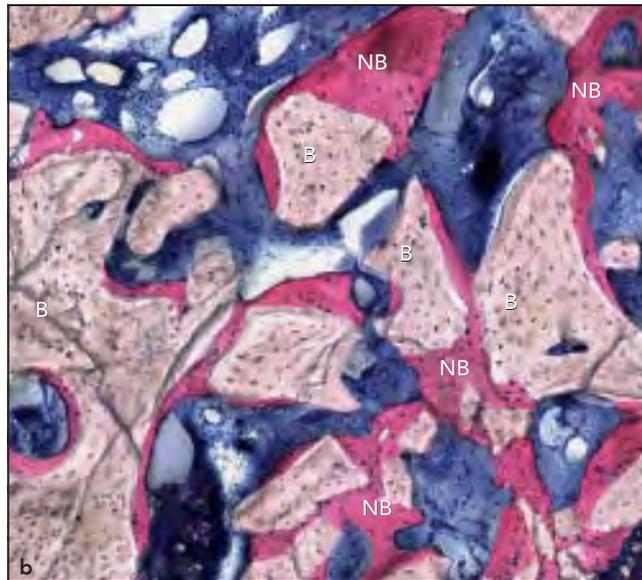
Fig 6b *High-power view of vital bone formation (NB) directly on the residual Bio-Oss particles (B) in Fig 6a (Stevenel blue, van Gieson picro fuchsin; field width = 1.292 mm).*

Discussion

An important debate topic in implant dentistry is the choice of grafting material for sinus augmentation procedures.[1–10] These graft materials include autograft,[11,12,14,16] allografts,[15] xenografts,[18,19,32] alloplasts,[16,17] bioactive agents,[33] or a combination (composite) of grafts.[34] The literature shows a wide range of results with different grafting materials.[1–10] In the review by Del Fabbro et al,[2] sinuses grafted with 100% bone replacement graft had an implant survival rate of 96.2% compared with 87.7% for sinuses grafted with 100% autogenous bone. All the reviews demonstrated equal or better implant survival rates with xenografts than those achieved with autogenous bone. The inclusion of rhPDGF-BB in the sinus grafting protocol used along with Bio-Oss has been associated with positive clinical results and may provide opportunities to improve long-term clinical outcomes for this procedure.[33]

The use of growth or differentiation factors for bone regeneration has shown significant potential. Preclinical and clinical studies have demonstrated superior outcomes in terms of the amount and rate of new bone formation when these agents were compared with traditional bone grafting materials.[33,35] These factors are present at low concentrations in bone matrix and plasma and are essential mediators of tissue repair through their stimulatory effects on angiogenesis, cell proliferation, cell differentiation, and matrix synthesis. Among the myriad growth factors, rhPDGF has received the most attention. Recombinant human platelet-derived growth factor BB is a well-characterized tissue growth factor that has been used in various human[36] and animal studies.[37,38] Ross et al[39] and Westermark[40] published comprehensive reviews of the biology of rh-PDGF. Numerous references in the periodontal literature relate to the effectiveness and mode of action of rhPDGF in periodontal regeneration,[22,23,35] ridge augmentation procedures,[36,38,41,42] and maxillary sinus elevation.[33] Results of a preclinical canine study demonstrated that purified recombinant PDGF-BB, used in combination with a deproteinized bovine block and without placement of a barrier membrane, has the potential to regenerate significant amounts of new bone in severe mandibular ridge defects.[38] A case series in humans using various combinations of ABBM and rhPDGF-BB for maxillary sinus elevation reported successful histologic results.[33]

The most effective way to evaluate the effect of rhPDGF on bone formation in a sinus graft is to use the standard bilateral study model, with the addition of rhPDGF being the only controlled variable. This is the first randomized controlled clinical trial to report on a direct comparison of an ABBM alone to an ABBM with rhPDGF in sinus augmentation. However, even in this model, factors such as differences in the size and morphology of the sinuses, the amount of residual crestal bone, and operator differences remain as potential confounding variables.

The present study did not assess implant survival rates; rather, it examined the percent of vital bone present after grafting bilateral sinuses with ABBM or ABBM and rhPDGF at specific time intervals. The vital bone formation was significantly greater in group A in the ABBM + rhPDGF (21.1 ± 11.8%) group vs the ABBM (11.8 ± 9.2%) alone group. However, in group B, this difference disappeared. Overall, the longer healing period showed an improved percent vital bone in the ABBM alone group. Froum et al[34] used ABBM with and without autogenous bone in nine sinuses and reported 24% mean vital bone volume at 6 to 9 months, compared with 33% vital bone volume at 12 to 15 months. Valentini et al[32] examined sinuses grafted with 100% ABBM and showed a mean percentage of vital bone of 21.08% at 6 months and 27.55% at 12 months. A similar study by Lee et al[43] also showed a correlation between mean vital bone and healing time. In 14 sinuses grafted with 100% ABBM and covered with a collagen membrane, the mean percent of vital bone was 18.3% at 6 months and 26.6% at 12 months.

The shorter healing time group (group A) was chosen to highlight any earlier benefits likely to occur for the treatment options tested. The results of the present investigation support the potential of rh-PDGF to improve bone formation in the early stage of bone healing. At 4 to 5 months, almost twice the percentage of vital bone was observed in the ABBM + rhPDGF (21.1% ± 11.8%) sinuses compared with control (11.8% ± 9.2%). However, after 7 to 9 months of healing, the vital bone percentage was similar in test and control groups. One possible interpretation for these findings is that bone formation in the ABBM + rhPDGF group is accelerated or jump-started, but that the total amount generated at the 7- to 9-month endpoint is the same. Previous studies have also reported favorable results in terms of bone formation when rhPDGF was used.[44–46] The effects of rhPDGF-BB reported in the literature appear to be most significant during the early stages of bone healing.[44,45,47,48] Sarment et al[48] reported that the highest bone turnover rate was measured at 6 weeks in rh-PDGF-BB–treated intrabony defects of humans when compared with the 24-week observational period. Thus, when a longer healing time is used, any differences in bone formation resulting from rhPDGF treatment become less obvious.

The dose level of rhPDGF used in this study (0.3 mg/mL) was higher than that reported in previous studies (40 to 50 µg/mL).[44,45,47–49] The rationale for using a higher dose level was because rhPDGF has a high clearance rate in vivo[27] and the effects of rhPDGF-BB on mitogenesis and chemotaxis of osteoblasts appear to be proportional to the concentration administered.[50,51] Nevins et al[33] used the same 0.3 mg/mL concentration in a recent sinus study. Furthermore, the 0.3 mg/mL dose level of rh-PDGF-BB is the same as used in the product GEM 21S, which is FDA-cleared for clinical use in periodontal regeneration as it has been shown to be safe in humans even with dose levels of up to 1 mg/mL.[52]

The histologic observations revealed a visible difference in the rate of graft resorption when rhPDGF was used (Table 3). This difference was greater in the earlier healing group (group A) compared to the later group (group B). Recently, an animal study showed similar results.[51] The same phenomenon of accelerated replacement–resorption of bone substitute particles saturated with rhPDGF-BB was also found in human subjects.[33] It may be speculated that the use of the growth factor accelerated the biodegradation of the graft material, a finding confirmed in the present study.

Conclusion

Within the limitations of this study, it can be concluded that *(1)* both the test and control groups showed acceptable vital bone formation at both the 4- to 5-month and 7- to 9-month maturation times; *(2)* vital bone formation was significantly greater at 4 to 5 months in the ABBM + rhPDGF group vs the ABBM alone control; however, in the 7- to 9-month cores, this difference disappeared; *(3)* the longer healing period resulted in an increased percent of vital bone in the ABBM alone group; however, this was not true in the ABBM + rh-PDGF group where the percent of vital bone was similar in the 4- to 5-month cores and 7- to 9-month cores; and *(4)* the more rapid formation of vital bone may allow for earlier implant placement. Further clinical studies using rhPDGF-BB should be performed to validate the findings of this study and to evaluate the outcome of implant survival in both standard and early loading protocols.

Acknowledgment

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