CASE REPORT

Growth Factor-Mediated Sinus Augmentation Grafting With Recombinant Human Platelet-Derived Growth Factor-BB (rhPDGF-BB): Two Case Reports

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Introduction: In the following two case reports, growth factor-mediated sinus augmentation surgery is used to treat significant posterior maxillary alveolar bone deficiency. At initial examination, preexisting subsinus alveolar bone height was ≤3 mm. A composite graft of anorganic bovine bone mineral (ABBM) + mineralized bone allograft was combined with recombinant human platelet-derived growth factor-BB (rhPDGF-BB) for augmentation grafting via a traditional maxillary lateral wall osteotomy approach to the sinus. In both cases, early implant placement and loading following sinus grafting, as well as long-term clinical follow-up, document potential benefits of growth factor-mediated bone regenerative sinus augmentation procedures. The significantly abbreviated durations seen in these two cases between sinus augmentation grafting and implant placement and prosthetic restoration, to the best of our knowledge, have not been previously reported in the literature.

Case Presentations: Two adult males presented with severe posterior maxillary alveolar bone atrophy, with a maximum subsinus bone height of 3 mm in patient #1 and <1 mm in patient #2. For each patient, a 50:50 particulate composite graft of ABBM and mineralized allograft was hydrated with 1 mL of 0.3 mg/mL rhPDGF-BB. Four and one-half (4.5) and 3.5 months following grafting in patient #1 and #2, respectively, implants were placed and core biopsy specimens obtained. Histologic examination of osteotomy cores demonstrated significant amounts of vital bone for each patient. Definitive implant-supported restorations in full occlusion were placed 8.5 and 7.5 months following sinus grafting for patient #1 and #2, respectively. Three (3) and 2.4 years following implant placement, all implants were well integrated, with no evidence of radiolucency at the implant-to-bone interface.

Conclusion: The addition of tissue-engineered proteins, i.e., rhPDGF-BB, to sinus augmentation protocols may allow earlier implant placement secondary to accelerated bone formation following grafting in the severely pneumatized sinus and may provide for increased long-term positive clinical outcomes. *Clin Adv Periodontics* 2011;1:4-15.

Key Words: Bone regeneration; maxillary sinus augmentation; recombinant human platelet-derived growth factor-BB (rhPDGF-BB).

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Background

With the Sinus Consensus Conference of 1996, sinus augmentation procedures became validated as effective treatment for posterior maxillary alveolar bone volume deficiency prior to placement of osseointegrated implants.1 Today, sinus grafting has become standard-of-care treatment for the surgical management of the deficient posterior maxilla. Robust, vital bone regenerative outcomes, critical to long-term implant survival and function, help define successful surgical endpoints for sinus grafting procedures. An awareness of those procedural variables affecting vital bone regenerative outcomes in sinus grafting is a necessary requisite for surgical success. Such variables include length of time between sinus grafting and implant placement,2-11 type of graft matrix used,2,4-12 presence or absence of occlusive membranes over the lateral window osteotomy site,13-17 and the addition of bioactive signaling molecules, i.e., bone morphogenetic protein-2 (BMP-2), platelet-rich plasma, and recombinant human platelet-derived growth factor-BB (rhPDGF-BB), to osteoconductive graft matrices.18-21

Anorganic bovine bone mineral (ABBM)† has been used widely as an osteoconductive grafting matrix in sinus augmentation procedures, either alone or as a composite graft with other materials. Two systematic reviews of randomized controlled clinical trials appear to verify the therapeutic effectiveness of ABBM in sinus augmentation procedures.16,22 Implant survival rates in both reviews for 100% xenograft augmented sites are seen as equal to or better than 100% particulate autogenous bone grafts and superior to composite grafts of ABBM plus autogenous bone. Additional studies examining long-term implant survival rates in ABBM-grafted sinus further verify ABBM’s effectiveness in sinus augmentation surgery.12,23-25

In addition to implant survival, numerous published studies examine the quantity and quality of bone regeneration at various time points in ABBM-grafted sinus sites.2-4,6,7,10,11,14 Such studies are primarily small case series that tend to report a range of vital bone formation, determined in large part by the times chosen for core biopsy and varying from approximately 19% at 3 to 4 months to approximately 70% at ≥1 year.2-4,6,7,10,11,14 Since ABBM has been shown to have a relatively slow rate of resorption, the percentage of residual ABBM particles integrated with newly formed bone is generally reported as high.

In contrast to the relatively wide body of literature examining ABBM-mediated bone regeneration and implant survival following sinus augmentation, a far narrower body of literature exists examining similar parameters for mineralized allogenic sinus grafts, the majority of which focuses on percent vital bone regeneration at various postgrafting time points.6,8,26-28 As in ABBM studies, mineralized allograft investigations tend to be small case series with a range of percent vital bone formation varying from approximately 18% at 6 to 8 months28 to 42% at 36 months.8 Compared to ABBM, particulate mineralized allograft resorption rates are relatively rapid, yielding less residual graft material at comparable time points.5,8,26 Data for implant survival in mineralized allografted sinuses are less available than for ABBM-grafted sinuses and are derived primarily from small clinical case series. However, a number of studies with data up to 36 months suggest survival rates ranging from 93% to 97% in 100% allogenic-grafted sinuses.29-31

Advances in tissue engineering and recombinant growth factor technology may provide opportunities for improved regenerative outcomes in sinus augmentation procedures. rhPDGF-BB, in its integral role in promoting neovascularization, as well as its mitogenic and chemotactic effects on osteoblast-lineage cells, may serve an important role in promoting improved regenerative outcomes in sinus augmentation procedures.32-34 In vitro and in vivo studies confirm effective attachment and release of rhPDGF-BB when combined with ABBM, human bone allograft, and other matrices.35,36 A recent proof-of-principle study examining the potential role of rhPDGF-BB when combined with ABBM particulate grafts in human sinus augmentation surgeries noted increased osteogenic activity at 6 to 8 months when compared to ABBM-grafted sites alone. In addition, more efficient replacement resorption of ABBM particles was apparent in a number of sites when ABBM was saturated with rhPDGF-BB.18 Additional studies examining grafts of either ABBM or mineralized allograft combined with rhPDGF-BB, but for procedures other than sinus augmentation, appear to verify the potential for improved bone regenerative outcomes over ABBM or allograft matrices alone.37-46

In the following two case reports, composite grafts of ABBM, mineralized bone allograft, and rhPDGF-BB were

| FIGURE 1a | At baseline, patient #1 with ≤3 mm of right sinus alveolar bone. | FIGURE 1b | Enhanced cross-sectional view at baseline, patient #1. |

†Bio-Oss, Osteohealth, Shirley, NY.
used in sinus augmentation surgeries to treat significant posterior maxillary alveolar bone deficiencies. In both cases, early implant placement and loading following sinus grafting, as well as long-term clinical follow-up, document potential benefits of growth-factor mediated bone regenerative sinus augmentation procedures. Histologic and histomorphometric examinations at the time of implant placement provide additional insight into the potential role growth factors may play in the management of the atrophied posterior edentulous maxilla.

Clinical Presentation and Case Management

Two mature adult males were referred for correction of severe posterior maxillary alveolar bone deficiency prior to prosthetic rehabilitation with implant-supported restorations. At the initial visit, in addition to a comprehensive dental examination, full-mouth periapical radiographs, clinical photographs, and maxillary computerized tomographic scans were obtained. Any necessary periodontal or restorative care was conducted prior to surgery. In each case subsinus bone height was negligible, varying from a maximum of 3 mm in patient #1 (Figs. 1a and 1b) to <1 mm in patient #2 (Figs. 2a and 2b). Except for a mucous retention cyst in patient #2, both maxillary sinuses were healthy and disease free.

At surgery, following elevation of a full-thickness mucoperiosteal flap, a traditional maxillary lateral wall osteotomy approach to the sinus was used in each case. Prior to grafting, a 50:50 particulate composite graft of ABBM and mineralized allograft‡ was hydrated with US Food and Drug Administration (FDA) off-label dose of 1 mL of 0.3 mg/mL rhPDGF-BB for a minimum of 10 minutes to allow for adequate growth factor attachment to the graft matrix. Following careful sinus membrane elevation and removal of the mucous retention cyst from patient #2, incremental quantities (approximately 3 to 4 g per sinus) of the graft material were placed into the newly created subantral space. A resorbable collagen membrane was placed over each lateral wall window. Full-thickness mucoperiosteal flaps closed primarily via multiple expanded polytetrafluoroethylene sutures.

FIGURE 2a Patient #2 at baseline, with <1 mm of subsinus bone height and a mucous retention cyst in the left sinus. 2b Enhanced cross-sectional view at baseline from the #14 position. (Please note large mucous retention cyst).

FIGURE 3a Removal of mucous retention cyst. 3b ABBM + mineralized allograft + rhPDGF-BB composite graft placed within the newly created subantral space. 3c Resorbable collagen membrane placed over the lateral wall window. 3d Full-thickness mucoperiosteal flaps closed primarily via multiple expanded polytetrafluoroethylene sutures.

‡LifeNet, Virginia Beach, VA.
§Bio-Gide, Osteohealth.
CV, Gore-Tex, W.L. Gore & Associates, Flagstaff, AZ.
1 tablet twice a day starting 2 days prior to surgery and continuing for 8 days following surgery. Ibuprofen 800 mg was prescribed for pain and inflammation, and the patients were prescribed 0.12% chlorhexidine rinses and instructed not to brush or floss at the surgical sites until after suture removal.

Postoperatively, each patient was seen at 1 week and then monthly until implant placement. For patient #1 and patient #2, implants were placed and core biopsies obtained 4.5 months and 3.5 months, respectively, following sinus grafting. At insertion, each implant achieved 25 Newton cm (Ncm) of torque. In addition to the implant core biopsies, a lateral wall osteotomy biopsy was obtained for patient #2 (Figs. 4a through 4d and Figs. 5a through 5d).

Clinical Outcomes

Patient #1
Given the accelerated implant insertion time following sinus grafting, each patient received careful long-term follow-up. For patient #1, 3 months after implant placement both maxillary right implants successfully tolerated a 25 Ncm torque test. One month later a definitive cement retained restoration in full occlusion was inserted. For patient #1, 8.5 months elapsed between sinus augmentation surgery and final placement of the definitive, implant-supported restoration. A radiograph taken 3 years following implant placement demonstrates well-integrated implants with no evidence of radiolucency at the implant-to-bone interface (Fig. 6).

Patient #2
As in patient #1, 3 months following implant insertion, all three implants for patient #2 successfully tolerated the manufacturer’s recommended 25 Ncm torque test. At this same visit, cement retained restorative abutments were placed and an interim restoration inserted (Figs. 7a through 7c). One month later the maxillary left posterior quadrant was definitively restored with single unit implant-supported crowns (Figs. 8a and 8b). For patient #2, approximately 7.5 months elapsed between sinus augmentation surgery and placement of definitive, implant-supported restorations. Clinical and radiographic examination 2.4 years following implant placement demonstrates well-integrated implants with no evidence of radiolucency at the implant-to-bone interface (Fig. 9).

Histologic Outcomes

Patient #1: 4.5 Months Following Sinus Grafting
Figure 10 represents a relatively intact core specimen at 2.5× magnification. The left portion of the slide demonstrates dense lamellar bone representative of native, alveolar crestal bone. The right or apical portion of the slide reveals a number of residual ABBM particles integrated with relatively dense vital regenerated bone. Newly formed bone bridging adjacent ABBM particles is seen throughout the specimen. Both residual particles and regenerated bone are surrounded by fatty marrow. Complete resorption of the mineralized allograft occurred, with no evidence of allograft particles present.

At 5× and 10× magnification, newly regenerated bone is seen intimately integrating with residual ABBM graft particles. Abundant amounts of osteoid are evident, indicative of ongoing active osteogenesis (Figs. 11a and 11b). At 20× magnification, osteoblasts are seen rimming the advancing front of newly formed osteoid, indicating

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increased metabolic activity and bone regeneration (Fig. 12).

Finally, at moderate magnification (10×), blood vessels can be observed within some of the residual ABBM-grafted particles (Fig. 13). As in the previous views, newly formed bone is seen bridging gaps between ABBM particles.
Osteoid, with adjacent osteoblasts, can again be seen, indicative of active, continuing osteogenesis.

Patient #2: 3.5 Months Following Sinus Grafting

Lateral Window Bone Core

At 3.5 months post-sinus grafting, an intact lateral window osteotomy core reveals significant amounts of newly regenerated bone throughout the specimen (Fig. 14). Importantly, since the core was obtained from the lateral window area, all bone present represents newly formed hard tissue. As in patient #1, residual ABBM particles remain, but allograft particulate appears completely absent at 3.5 months. At increased magnification, considerable amounts of osteoid are evident, indicative of ongoing bone formation (Fig. 15). At
FIGURE 12 Patient #1. Residual ABBM particles are in intimate contact with dense regenerated bone. Osteoblasts are seen at the advancing front of newly formed osteoid. (20x) Sanderson’s rapid bone stain + van Gieson picro fuchsin. BV = blood vessel; NB = new bone; O = osteoid; OB = osteoblasts.

FIGURE 13 Patient #1. Well-formed bone bridges the gaps between ABBM graft particles. Osteoid and osteoblasts are seen, as well as blood vessels forming within some of the residual ABBM particles. (10x) Sanderson’s rapid bone stain + van Gieson picro fuchsin. BV = blood vessel; NB = new bone; O = osteoid; OB = osteoblasts.

FIGURE 14 Patient #2. At 3.5 months following sinus grafting, an intact lateral window core reveals significant amounts of well-formed regenerated bone in close apposition with residual ABBM particles. (2.5x) Sanderson’s rapid bone stain + van Gieson picro fuchsin. NB = new bone.

FIGURE 15 Patient #2. At increased magnification, osteoid is seen adjacent to newly regenerated bone, indicative of ongoing bone formation. (5x) Sanderson’s rapid bone stain + van Gieson picro fuchsin. NB = new bone; O = osteoid.

FIGURE 16 Patient #2. Osteoblastic rimming along the advancing front of osteoid demonstrates continued osteogenesis at the lateral window ostectomy site. Sanderson’s rapid bone stain + van Gieson picro fuchsin (10x). O = osteoid; OB = osteoblasts.

FIGURE 17 Patient #2. At 3.5 months post-sinus grafting, significant amounts of newly regenerated bone are seen throughout the intact implant core. Residual particles of ABBM remain. (2.5x) Sanderson’s rapid bone stain + van Gieson picro fuchsin. NB = new bone.
yet higher magnification, osteoblastic rimming along the outer edges of osteoid becomes apparent, emphasizing intense osteogenesis at the lateral window sinus osteotomy site (Fig. 16).

**Implant Core**

As in the lateral window bone core, considerable quantities of newly regenerated bone are seen throughout an intact implant core at 3.5 months following grafting. Since the initial height of native crestal alveolar bone was no more than 1 mm, all bone present in this core specimen is newly formed following grafting (Fig. 17). Once again, ABBM particles are evident but mineralized allograft appears completely resorbed. At higher magnification, considerable amounts of osteoid line well-formed trabeculae of newly regenerated woven bone, indicating ongoing osteogenic activity (Fig. 18).

**Histomorphometric Outcomes**

**Patient #1: Implant Core – Table 1**

As noted in Table 1, at 4.5 months following grafting with ABBM, mineralized human allograft, and rhPDGF-BB, 43% of the implant core consisted of bone. Since no allograft remained, 100% of the bone present was vital. Although ABBM particles remained, only 7% of the examined core represented ABBM particulate by 4.5 months.

**Patient #2**

**Lateral Window Bone Core – Table 2**

At 3.5 months postgrafting, 33% of the core removed from the lateral window osteotomy site consisted of newly regenerated bone. No allograft particles remained. Twenty-six percent (26%) of the intact core at this 3.5-month time point represented residual ABBM particulate graft.

**Implant Core – Table 2**

At 3.5 months, 15% of the subantral grafted implant site consisted of newly regenerated bone. Again, since no allograft particulate remained, 100% of the examined bone was vital. ABBM occupied 41% of the volume of the implant-related bone core.

**Discussion**

Regeneration of vital, well-vascularized bone is central to long-term positive clinical outcomes following maxillary sinus augmentation procedures.2-18 With the introduction of such bioactive molecules as BMP-2 and rhPDGF-BB into clinical practice, opportunities may now exist to improve long-term clinical outcomes in sinus augmentation procedures by including tissue-engineered proteins into our grafting regimens.18 Inclusion of tissue-engineered proteins may also allow procedural modifications to current sinus augmentation protocols, i.e., variations in graft matrices, loading times, and potential elimination of barrier membranes placed over the lateral osteotomy site.
In the current cases, rhPDGF-BB was added to sinus augmentation composite grafts of ABBM and mineralized allograft. Strongly mitogenic and chemotactic for osteoblasts and osteoblastic precursor cells, as well as integral in promoting neovascularization, the addition of rhPDGF-BB may have played important roles in allowing accelerated treatment times as well as supporting stable long-term clinical outcomes.32–34 In both cases, native subsinus alveolar bone height at initial examination was minimal: <3 mm in one patient and <1 mm in the other. With such minimal alveolar bone height, initial implant stabilization in both cases was completely dependent upon the quality and quantity of newly regenerated bone.

Both ABBM and mineralized allograft have been associated with positive bone regenerative outcomes in sinus augmentation procedures. Depending upon the duration between sinus grafting and implant placement, percentages of new bone formation vary, with greater amounts of regenerated bone generally seen at longer intervals between grafting and implant insertion.2,4,6–8,10,11,14,26–28 In both of the current cases, the addition of rhPDGF-BB suggested the possibility of abbreviated intervals between sinus grafting and implant placement. In patient #1, 4.5 months elapsed between grafting and implant placement and in patient #2, 3.5 months between augmentation and implant placement. Despite accelerated implant insertion times, percentages of vital bone formation varied from 43% in patient #1 to 33% at the lateral window osteotomy site and 15% at the implant placement site in patient #2. Reported vital bone percentages for ABBM and mineralized allograft without growth factors are generally lower at similar time points.2,5–8,10–12,17,26–28 Moreover, the abundance of osteoid seen histologically for both patients suggests further ongoing bone regeneration and increased amounts of new vital bone over time within both grafted sites.

Although the attachment and release kinetics for rhPDGF-BB when combined with ABBM and mineralized allograft are similar, normal resorption times of each matrix tend to differ, more rapidly for mineralized allograft and rather prolonged for ABBM.6,8,10,11,26–28 Understanding that both matrices appear to have equivalent attachment and release kinetics for rhPDGF-BB, more rapid allograft resorption might allow for additional space for bone regeneration to occur, while the much slower resorption rate of ABBM might help maintain graft height by preventing slumping consolidation. Notably, at both early implant insertion time points, only ABBM particulate remained, with mineralized allograft completely resorbed at early time points. In each case, graft height was maintained without evidence of slumping. Interestingly, however, in patient #1 only 7% of the ABBM graft remained at 4.5 months, suggesting growth factor may have accelerated resorption of ABBM matrices as seen in other studies.18,37,40 This is particularly interesting given the prolonged resorption times of ABBM normally reported in the literature. The positive regenerative findings seen for each patient are equally matched by positive long-term clinical outcomes. Despite early implant placement into a grafted sinus, at 3 months following implant insertion all implants successfully tolerated a 2.5 Ncm torque test. In each case, insertion of definitive final implant-supported restorations was accelerated relative to normal clinical practice following sinus augmentation grafting. Eight and one-half (8.5) months and 7.5 months elapsed between augmentation surgery and placement of definitive final restorations in full functional occlusion for patient #1 and patient #2, respectively. Long-term clinical and radiographic follow-up at 3 years (patient #1) and 2.4 years (patient #2) following implant placement demonstrated well-integrated implants, no evidence of breakdown at the bone-to-implant interface, and well functioning implant-supported restorations. While both cases suggest significant benefits with the addition of tissue-engineered proteins to sinus augmentation protocols, final confirmation of efficacy can come only from adequately powered, randomized, controlled clinical trials. Nevertheless, tissue engineering technologies hold great promise to shorten healing times and increase treatment predictability.
### Summary

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<th>Why is this case new information?</th>
<th>Tissue engineering &amp; recombinant growth factor technology may lead to the following improved sinus augmentation outcomes:</th>
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<td>■ Accelerated bone regeneration</td>
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<td>■ Abbreviated interval between sinus grafting and implant placement</td>
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<td>■ Abbreviated interval between implant placement and definitive implant-supported prosthetic restoration</td>
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<td>■ Improved long-term implant survival</td>
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<th>What are the keys to successful management of these cases?</th>
<th>Proper management includes the following key items:</th>
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<td>■ Choosing carrier matrices with proper attachment &amp; release kinetics when combined with rhPDGF-BB</td>
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<td>■ Allowing sufficient time for attachment of rhPDGF-BB to carrier matrices</td>
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<td>■ Choosing carrier matrices with different resorption rates</td>
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<td>■ Carefully elevating the sinus membrane to avoid perforation</td>
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<td>■ Thoroughly grafting the entire subsinus space</td>
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<th>What are the key limitations to success in these cases?</th>
<th>Key limitations include the following:</th>
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<td>■ Little available data from prospective clinical trials documenting the short and long-term efficacy of growth factor-mediated procedures in sinus augmentations with rhPDGF-BB + ABBM + mineralized allograft</td>
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<td>■ Study is off-label, without current FDA approval for present study graft composition in sinus augmentation procedures</td>
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 References


41. Simion M, Rocchiutta I, Monforte M, Maschera E. Three-dimensional alveolar bone reconstruction with a combination of recombinant


