

Effect of Platelet-Rich Plasma on Bone Growth and Osseointegration in Human Maxillary Sinus Grafts: Three Bilateral Case Reports



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Platelet-rich plasma is an autologous product that is derived from whole blood through the process of gradient density centrifugation. The proposed value of this product in dental implantology and in bone augmentation procedures lies in the ability to incorporate high concentrations of the growth factors PDGF, TGF- β_1 , TGF- β_2 , and IGF, as well as fibrin, into the graft mixture. Research has shown an increased bone maturation rate and improved bone density when this product, or its recombinant growth factors, is added to small bony defects or to larger defects that use autogenous bone as the grafting material. This study tested the efficacy of platelet-rich plasma in three bilateral sinus graft cases with grafts of anorganic bovine bone that contained minimal or no autogenous bone. Histomorphometric analysis indicated that the addition of platelet-rich plasma to the grafts did not make a significant difference either in vital bone production or in interfacial bone contact on the test implants. (Int J Periodontics Restorative Dent 2002;22:45-53.)

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The subantral augmentation (sinus elevation) procedure has been shown to be a predictable method for increasing maxillary posterior bone volume for the successful placement of load-bearing root-form implants.¹ Initial sinus elevation techniques relied on grafts that consisted of 100% autogenous bone harvested from either oral (ramus, chin) or extraoral (iliac crest) donor sites.²⁻⁷ It has subsequently been found that the autogenous bone graft can be replaced, in whole or in part, by a variety of allografts, xenografts, alloplasts, and bone morphogenetic proteins with a highly predictable graft and implant survival rate.⁸⁻²⁰ In fact, the addition of autogenous bone to a composite graft may result in a higher vital bone percentage at an earlier time, allowing for earlier implant placement and subsequent loading.^{20,21}

The sequence of treatment for delayed implant placement with a composite or nonautogenous graft begins with a graft maturation period of 6 to 12 months. This interval is determined by the clinician and is based on such factors as

height of remaining crestal bone, quality of the remaining crestal bone, percentage of autogenous bone in the composite graft, and surface texture of the implant(s) being placed. As early loading protocols generally do not apply to grafted bone, an osseointegration period of approximately 6 months is allowed prior to second-stage surgery (if applicable) and loading. Consequently, with staged implant placement, the patient must wait between 12 and 18 months to receive the implant restoration. Grafts of 100% autogenous bone may require only 4 to 6 months for maturation, reducing the waiting period to 10 to 12 months.

The incorporation of platelet-rich plasma (PRP) activated with bovine thrombin (autologous platelet gel) in a sinus graft has been proposed as a method of creating dense, vital bone in a shorter interval. If effective, this could reduce the interval from composite grafting to implant loading to one resembling that applicable to 100% autogenous bone grafting (10 to 12 months).

PRP is derived from whole blood by sequestering and concentrating the platelets via gradient density centrifugation. Improved technology has allowed the blood draw required for production of the final product to be reduced from 450 mL to a much more manageable 50 mL. This negates the need for autotransfusion of the unused fraction to maintain patient fluid volume. As the growth factor source is autologous, there is no

risk of disease transmission associated with use of this technology. The proposed value of PRP in bone grafting lies in the ability to incorporate high concentrations of the growth factors PDGF, TGF- β_1 , TGF- β_2 , and IGF, as well as fibrin, into the graft mixture.

Marx et al²² used this technology in treating large mandibular continuity defects. The increased bone maturation rate and bone density in these defects warranted a controlled clinical, histologic, and histomorphometric study to evaluate the healing response in sinus augmentation surgery using autologous platelet gel (thrombin-activated PRP) with composite grafts containing minimal or no autogenous bone.

Method and materials

Three patients were selected from those who presented for maxillary posterior implant therapy at the New York University Department of Implant Dentistry. All were diagnosed as requiring bilateral sinus augmentation procedures prior to the placement of the implants. All patients were advised of alternative treatment plans and selected the plan requiring maxillary sinus elevation. All patients with absolute contraindications for this procedure, such as uncontrolled diabetes, long-term steroid usage, and blood disorders, were excluded. All patients were informed of the requirements for participation in the study, and all had the option of withdrawing from the study at any time. The nature of

the study was explained to each patient, and each signed an informed consent form that was approved by both the University Committee on Activities Involving Human Subjects and the New York State Department of Health Blood Resources Program.

On the day of surgery, a flip of a coin determined the experimental side (PRP) and the control side (non-PRP). All six sinuses in this pilot study were grafted with anorganic bovine bone (0.25 to 1 mm cancellous BioOss, Osteohealth). All sinus grafts were performed with a lateral window approach, modified from the technique presented by Wood and Moore.⁴ The step-by-step surgical technique and histomorphometric evaluation protocols have been described in a previous article.²⁰ PRP was obtained from a blood draw of 350 to 450 mL processed with a Sequestra 1000 gradient density cell separator (Medtronic). This yielded approximately 30 mL of PRP for clinical use. The remaining blood fraction was autotransfused through the closed system to minimize blood volume loss. The BioOss graft material was hydrated with the PRP (experimental side only) in a dappen dish. Bovine thrombin was added just prior to placement of the graft, resulting in the formation of an autologous platelet gel containing the particulate graft material. Membranes were placed over all six lateral windows, as this has been shown to result in improved vital bone counts.²³

In case 3, miniature test implants of 2.0 mm in diameter and 10 mm in

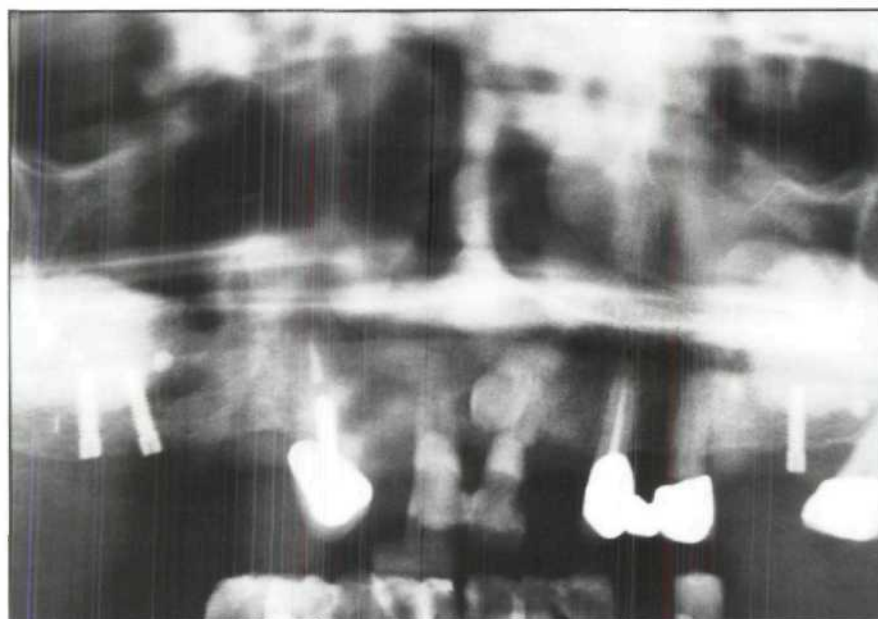
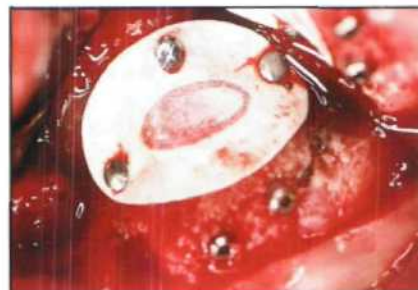


Fig 1 (left) Panoramic view of test implants in place in grafted sinuses in case 3. Test sinus is on right, control is on left.

Fig 2 (below) Clinical view of test (PRP) sinus graft completed and test implants in place in case 3.



length (3i/Implant Innovations) were placed through the crestal bone into the sinus grafts. Figures 1 and 2 show the test implants in place in case 3. Placement of the permanent implants was performed at 7 months, 7.5 months, and 11 months, respectively, for cases 1, 2, and 3. At the time of implant placement, trephine cores of 3 mm in diameter and 10 mm in length were harvested through the site of the former lateral window. The three test implants were removed with a special guide and trephine at the same time. The cores were fixed and sent to the Hard Tissue Research Laboratory at the University of Oklahoma College of Dentistry for blinded histologic and histomorphometric evaluation. The test implants were evaluated for total volume of calcified material, percentage of vital bone,

percentage connective tissue, percentage residual graft material, and percentage of bone at the implant-bone interface.

Case 1

The patient was a 43-year-old non-smoking woman with an unremarkable medical history. Bilateral sinus grafts were placed using 100% BioOss. PRP activated with bovine thrombin was used to hydrate the graft on the experimental side prior to graft placement. A bioabsorbable BioGide membrane (Osteohealth) was placed over both lateral windows and stabilized in position with titanium tacks. Cores were taken at the time of implant placement, which occurred 7 months after sinus grafting.

Case 2

The patient was a 35-year-old woman who was a light smoker (three to five cigarettes per day) with an unremarkable medical history. Bilateral sinus grafts were placed using 95%+ BioOss and < 5% autogenous bone harvested from the tuberosity. PRP activated with bovine thrombin was added to the graft material for the left sinus prior to graft placement. BioGide membranes were placed over both lateral windows and stabilized in position with titanium tacks. Cores were taken at the time of implant placement, which occurred 7.5 months after sinus grafting.

Case 3

The patient was a 69-year-old non-smoking man with a history of hypertension. Bilateral sinus grafts were placed using 100% BioOss. PRP activated with bovine thrombin was added to the graft material for the right sinus prior to graft placement. Nonabsorbable expanded polytetrafluoroethylene (e-PTFE) membranes (Gore-Tex Augmentation Material oval-9, 3i/WL Gore) were trimmed and placed over both lateral windows and stabilized with titanium tacks. Two test implants were placed in the right (test) and one in the left (control) sinus at the time of sinus grafting. The sites chosen for these implants were determined to be future final implant positions by use of computed tomographic scanning and SimPlant (Columbia Scientific) analysis with radiographic and surgical templates. Cores were taken from the lateral window area and the test implants were removed with surrounding bone cores at the time of implant placement, which occurred 11 months after sinus grafting.

Results

Table 1 presents the vital bone content of the three bilateral sinus grafts. The two test implants placed in the PRP sinus had slightly higher percentages of implant-bone contact (37.6% and 38.8%) than the test implants placed in the contralateral non-PRP sinus (33.8%). Figures 3 and 4 show representative histologic samples of bone cores from case 3.

Figures 5 and 6 depict representative histologic samples of the implant-bone interface of the test implants.

Discussion

There has been some confusion in the literature regarding the nomenclature of the blood product described in this article. It has been referred to as PRP, platelet concentrate, and autologous platelet gel. The definition of these blood products or fractions can be found in the technical manual of the American Association of Blood Banks.²⁴ These definitions may not be applicable to the technique that we are clinically describing, as the plasma volume in which the sequestered platelets are ultimately suspended is left to the discretion of the clinician. The authors have opted for the use of the term PRP in this article, as it is the nomenclature most often encountered in the literature. In the literature review, however, we have left the original authors' nomenclature unchanged.

Numerous references in the periodontal literature relate to the effectiveness and mode of action of PDGF, TGF- β , IGF, and fibrin in periodontal regeneration. These are readily available and are beyond the scope of this article. Ross et al²⁵ and Westermarck²⁶ have published comprehensive reviews of the biology of PDGF. A limited number of references, however, are found in the dental literature relating to the use of PRP, platelet concentrate, autologous platelet gel, or its recombinant

components as an adjunct to intra-oral bone grafting, implant placement, and/or grafting of the maxillary sinus.

Lynch et al²⁷ reported on the effects of combined recombinant PDGF-IGF on bone formation around roughened titanium implants in the dog model. Direct application to the implants stimulated the regeneration of bone in periimplant sites in the early phase of healing. Both the implant-bone contact and fill of the periimplant spaces were improved. An immediate extraction-implant placement dog study²⁸ observed a twofold increase in implant-bone contact and in areas of bone adjacent to the implant surface when using a recombinant PDGF and IGF-I gel beneath an e-PTFE membrane. Tayapongsak et al²⁹ showed a 50% decrease in time for remodeling and graft incorporation with the addition of autologous fibrin adhesive to particulate cancellous bone and marrow grafts in major mandibular reconstruction surgery.

Marx et al²² reported on a group of 88 cancellous cellular marrow bone graft reconstructions of 5 cm or greater mandibular continuity defects; 44 received grafts with PRP added, with 44 additional cases serving as a control. The grafts with PRP added showed a radiographic maturation rate that was 1.62 to 2.16 times that of the grafts without PRP. Histomorphometry demonstrated a greater bone density in the PRP-added sites (74.0% \pm 11%) than in the sites where PRP was not added (55.1% \pm 8%). Additionally,

Table 1 Histomorphometric analysis of vital bone in grafted sinuses

Case	Time (mo)	Graft	% vital bone PRP (test)	% vital bone non-PRP (control)
1	7	100% BioOss	15	13
2	7.5	95%+ BioOss < 5% autogenous bone	21	19
3	11	100% BioOss	34	32
Mean			23.3	21.3

Fig 3 (left) Non-demineralized section from test (PRP) bone core (Stevenel's blue–van Gieson's picric fuchsin stain; original magnification $\times 25$).

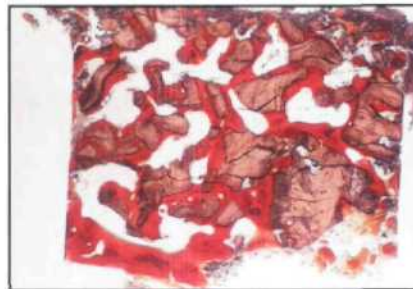


Fig 4 (right) Non-demineralized section from control (non-PRP) bone core (Stevenel's blue–van Gieson's picric fuchsin stain; original magnification $\times 25$).

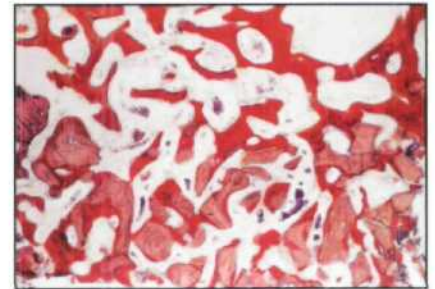


Fig 5 (left) Test implant from control (non-PRP) sinus from case 3. The superior portion of the implant is in crestal bone. The apical portion is in the sinus graft (Stevenel's blue–van Gieson's picric fuchsin stain; original magnification $\times 2$).

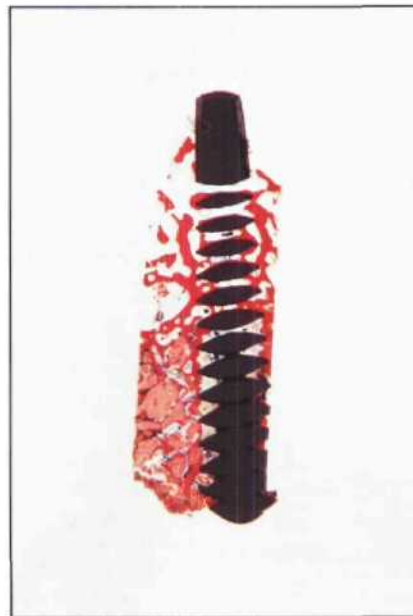


Fig 6 (right) Test implant from the test (PRP) sinus from case 3, which demonstrated an overall 38.8% bone contact at the interface (Stevenel's blue–van Gieson's picric fuchsin stain; original magnification $\times 10$).



the harvested cancellous marrow was shown to have receptor sites for PDGF and TGF- β . These were predominantly centered around blood vessels (endosteal osteoblasts) but were also found in lesser numbers in the marrow (marrow stem cells and osteoprogenitor cells).

Anitua³⁰ used PRP in the preparation of future implant sites. Extraction sockets in 20 patients were either treated with PRP or left untreated as controls. The sockets with PRP added exhibited greater buccolingual/palatal bone width, greater bone density, and faster soft tissue coverage than the controls.

Kassolis et al³¹ recently published the results from 14 sinus grafts and three maxillary ridge augmentations using PRP with freeze-dried bone allografts (LifeNet). The grafts were mixed at a ratio of 0.5 g:2 mL PRP prior to insertion into the sinus. The grafts were then covered with a PRP "membrane." Histologic sections revealed numerous areas of osteoid and bone formation around the freeze-dried bone allograft particles, with no evidence of inflammatory cell infiltrate. Histomorphometry was not performed, and there were no controls; therefore, quantitative measurements could not be made.

While the reports using autogenous bone with PRP are promising, other reports indicate that PRP may not be effective when used with bone substitutes. Wironen et al³² have shown that PRP is not osteoinductive when added to demineralized bone matrix placed in pouches created in the recti

abdomini muscles of athymic nude rats. More specifically related to the present article, Terheyden³³ compared rhOP-1 and PRP in bilateral sinus grafts that used 100% anorganic bovine bone as a grafting material. The PRP was not effective in producing bone regeneration, whereas in the contralateral sinus the rhOP-1 was effective.

The literature appears to indicate that PRP may be effective in the relatively small periodontal defect and in larger bone defects when they are grafted with autologous bone. When autologous bone is not present in the graft, and the graft is of large volume, PRP may not produce the desired stimulatory response because vital bone cells are needed for this stimulation to occur.

Several authors^{22,34-35} (and Russo and Garg, unpublished data) have explained the mode of action of platelet growth factors. In review, platelet degranulation and release of growth factors occurs within 3 to 5 days, and the growth factor activity may end in as soon as 7 to 10 days. The PDGF that is released during degranulation is chemotactic for macrophages, which then make their own contribution to the wound-healing cascade. The combined roles of PDGF, TGF- β , and IGF are chemotaxis and mitogenesis of stem cells and osteoblasts, angiogenesis for capillary ingrowth, bone matrix formation, and collagen synthesis. Fibrin maintains the regenerative space and provides a matrix for cell migration and proliferation.

The sinus model may be considered to be a relatively large-volume graft. Uchida et al³⁶ showed that a sinus graft for multiple 15-mm implants is likely to require 5.5 mL of graft material. When using a bone graft substitute that contains neither vital cells nor bone morphogenetic proteins, bone formation must originate from the bony walls (endosteal osteoblasts and circulating stem cells). This healing pattern was proposed by Boyne and James² and later demonstrated in monkeys³⁷ and humans.⁸

The most effective way to evaluate the effects of PRP on the formation of bone in a sinus graft is to study the effect in bilateral sinus grafts, with the addition of PRP being the only controlled variable. This is the first study to be performed in this manner. We chose to use a nonvital bone substitute as a graft material for two reasons. First, reports using autogenous bone in the nonsinus model have shown PRP to have a positive effect on bone formation. Second, we felt it important to determine if PRP would have a similar positive effect on a noninductive, nonvital graft material.

The above-outlined wound-healing mechanisms, coupled with the relatively large graft size, could explain the minimal difference in vital bone between test and control sinuses in our study. With the exception of case 2, which had minimal autogenous bone in the graft, there were no cells (endosteal osteoblasts or stem cells) present in the body of the graft. Endothelial migration (revascularization) and migration of

cells from the bony sinus walls is unlikely to happen in an interval that would render the released growth factors effective (7 to 10 days). Therefore, the stimulating effect of these growth factors may only occur close to the bony walls. Each of the three cases in this pilot study showed only a 2% increase in vital bone on the test (PRP) side, which is not clinically or statistically significant. It would appear that the differences in vital bone formation between the three cases relate to maturation time of the graft and not to any effect of the PRP. The effect of time on the formation of vital bone in sinus grafts was demonstrated in prior articles from the authors' sinus graft study.^{20,38}

Our findings of similar vital bone formation in the test (PRP) and control (non-PRP) sinuses are paralleled by the results seen in the cores containing the test implants that were placed bilaterally in case 3. The two test implants placed in the PRP sinus had slightly higher percentages of implant-bone contact (37.6% and 38.8%) than the test implant placed in the contralateral non-PRP sinus (33.8%). Considering that the native crestal bone above both sinuses was approximately 5 mm, the above values represent an accurate reflection of the healing response of the graft materials. As all three test implants were well-integrated, it seems that the difference in implant-bone contact was not significant to implant success. Of course, these values should be viewed in light of the 11-month implant and graft healing period.

Aside from any effect that PRP might have on wound healing, the handling properties of the particulate graft material were dramatically improved by the addition of the thrombin-activated PRP. The resultant fibrin formation consolidated the graft, allowing it to be cut into conveniently sized blocks that could be easily carried to and inserted into the lateral window. These soft blocks could then be moved to any desired location, such as the narrow and often hard-to-reach anterior region, where they could be molded into position. Additionally, graft placement can be accomplished without the inadvertent spillage of graft material into the buccal flap area. Tayapongsak et al²⁹ reported similar handling qualities when adding autologous fibrin adhesive activated with bovine thrombin to cancellous bone and marrow grafts.

Marx et al²² showed a mean increase in platelet concentration of 338% using an Electro Medics 500 (Medtronic) gradient density cell separator with a 400- to 450-mL whole blood sample. Other centrifuge units, which require a whole blood sample approximating 50 mL, are the Platelet Concentrate Collection System (3i/Implant Innovations) and the SmartPReP (Harvest Technologies). Both of the above small-draw units report higher platelet concentrations than the large-draw Medtronic unit.

It is of interest to note that the manufacturers of platelet sequestration and concentration systems give varying values for the final platelet concentration achieved. This may

vary from three to eight times the platelet concentration in the patient's blood. Additionally, the operator may alter the final concentration by increasing or decreasing the volume into which the platelet button is suspended. It then becomes obvious that the final platelet concentration will depend upon three factors: (1) the total number of platelets in the original sample; (2) the recovery rate of the system used; and (3) the final volume of plasma into which the platelets are suspended. For purposes of factoring in the actual platelet concentration used in our future cases, we propose to obtain platelet counts from the initial blood sample and also from the harvested PRP. A standardized technique should be devised that includes dilution of the concentrated platelets, resuspension, and multiple sampling to ensure an accurate platelet count.

Conclusions

The following conclusions may be drawn from these three case reports:

1. Platelet-rich-plasma did not make a significant difference in the production of vital bone in sinuses grafted with BioOss.
2. Platelet-rich plasma did not make a significant difference in bone contact at the implant-bone interface.
3. The use of platelet-rich plasma with grafts consisting of 100% BioOss should be considered only in respect to the improved handling quality (containment) of the particulate graft material that can be achieved through the activation of the platelet-rich plasma with thrombin.

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References

1. Academy of Osseointegration. Sinus Graft Consensus Conference, Wellesley, Mass, 16–17 November 1996. *Int J Oral Maxillofac Implants* 1998;13(suppl).
2. Boyne PJ, James RA. Grafting of the maxillary sinus floor with autogenous marrow and bone. *J Oral Surg* 1980;38:613–616.
3. Tatum OH. Maxillary and sinus implant reconstruction. *Dent Clin North Am* 1986;30:207–229.
4. Wood R, Moore D. Grafting of the maxillary sinus with intraorally harvested autogenous bone prior to implant placement. *Int J Oral Maxillofac Implants* 1988;3:209–214.
5. Kent JN, Block MS. Simultaneous maxillary sinus floor bone grafting and placement of hydroxyapatite-coated implants. *J Oral Maxillofac Surg* 1989;47:238–242.
6. Raghoobar GM, Brouwer TJ, Reintsema H, Van Oort RP. Augmentation of the maxillary sinus floor with autogenous bone for the placement of endosseous implants: A preliminary report. *J Oral Maxillofac Surg* 1993;51:1198–1203.
7. Chanavez M. Sinus grafting relating to implantology. Statistical analysis of 15 years of surgical experience (1979–1994). *J Oral Implantol* 1996;22:199–230.
8. Smiler DG, Holmes RE. Sinus lift procedure using porous hydroxyapatite: A preliminary report. *J Oral Implantol* 1987;13:239–253.
9. Wagner JR. A 3 1/2-year clinical evaluation of resorbable hydroxyapatite OsteoGen (HA Resorb) used for sinus lift augmentations in conjunction with the insertion of endosseous implants. *J Oral Implantol* 1991;17:152–164.
10. Smiler DG, Johnson PW, Lozada JL, et al. Sinus lift grafts and endosseous implants. Treatment of the atrophic posterior maxilla. *Dent Clin North Am* 1992;36:151–186.
11. Misch CE, Dietsch F. Bone grafting materials in implant dentistry. *Implant Dent* 1993;2:158–162.
12. Small SA, Zinner ID, Panno FV. Augmenting the maxillary sinus floor for implants. *Int J Oral Maxillofac Implants* 1993;8:523–528.
13. Hürzeler MB, Kirsch A, Ackermann KL, Quiñones CR. Reconstruction of the severely resorbed maxilla with dental implants in the augmented maxillary sinus. *Int J Oral Maxillofac Implants* 1996;11:466–475.
14. Wheeler SL, Holmes RE, Calhoun CJ. Six-year clinical and histologic study of sinus lift grafts. *Int J Oral Maxillofac Implants* 1996;11:26–34.
15. Valentini P, Abensur D. Maxillary sinus floor elevation for implant placement with demineralized freeze-dried bone and bovine bone (Bio-Oss): A clinical study of 20 patients. *Int J Periodontics Restorative Dent* 1997;17:233–242.
16. Langer B, Langer L. Maxillary sinus augmentation with demineralized freeze-dried bone allograft: A 5–6 year clinical evaluation. Presented at the Annual Meeting of the American Academy of Periodontology, Orlando, Fla, April 1997.
17. Wheeler SL. Sinus augmentation for dental implants. The use of alloplastic materials. *J Oral Maxillofac Surg* 1997;155:1287–1293.
18. Fugazzotto PA, Vlassis J. Long-term success of sinus augmentation using various surgical approaches and grafting materials. *Int J Oral Maxillofac Implants* 1998;113:52–58.
19. Boyne PJ, Marx RE, Nevins M, et al. A feasibility study evaluating rhBMP-2/absorbable collagen sponge for maxillary sinus floor augmentation. *Int J Periodontics Restorative Dent* 1997;17:11–25.

20. Froum SJ, Tarnow DP, Wallace SS, Cho S-C. Sinus floor elevation utilizing anorganic bovine bone matrix (OsteoGraf/N) with and without autogenous bone: A clinical, histologic, radiographic, and histomorphometric analysis: Part 2 of an ongoing prospective study. *Int J Periodontics Restorative Dent* 1998;18:529-543.
21. Tadjoeidin ES, de Lange GL, Holzmann PJ, Kuiper I, Burger EH. Histological observations on biopsies harvested following sinus floor elevation using a bioactive glass material of narrow size range. *Clin Oral Implants Res* 2000;11:334-344.
22. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Goergeff KR. Platelet-rich plasma: Growth factor enhancement for bone grafts. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998;85:638-646.
23. Tarnow DP, Wallace SS, Froum SJ, Rohrer MD, Cho S-C. Histologic and clinical comparison of bilateral sinus floor elevations with and without barrier membrane placement in 12 patients: Part 3 of an ongoing prospective study. *Int J Periodontics Restorative Dent* 2000;20:117-125.
24. American Association of Blood Banks. Technical Manual, ed 13. Bethesda, Md: American Association of Blood Banks, 1999.
25. Ross, R, Raines E, Bowen-Pope D. The biology of platelet-derived growth factor. *Cell* 1986;46:155-169.
26. Westermark B. The molecular and cellular biology of platelet-derived growth factor. *Acta Endocrinol (Copenh)* 1990;123:131-142.
27. Lynch SE, Buser D, Hernandez RA, et al. Effects of the platelet-derived growth factor/insulin-like growth factor-I combination on bone regeneration around titanium dental implants. Results of a pilot study in beagle dogs. *J Periodontol* 1991;62:710-716.
28. Becker W, Lynch SE, Lekholm U, et al. A comparison of e-PTFE membranes alone or in combination with platelet-derived growth factors and insulin-like growth factor-I or demineralized freeze-dried bone in promoting bone formation around immediate-extraction socket implants. *J Periodontol* 1992;63:929-940.
29. Tayapongsak P, O'Brien DA, Monteiro CB, Arceo-Diaz LY. Autologous fibrin adhesive in mandibular reconstruction with particulate cancellous bone and marrow. *J Oral Maxillofac Surg* 1994;52:161-165.
30. Anitua E. Plasma rich in growth factors: Preliminary results of use in the preparation of future sites for implants. *Int J Oral Maxillofac Implants* 1999;14:529-535.
31. Kassolis JD, Rosen PS, Reynolds MA. Alveolar ridge and sinus augmentation utilizing platelet-rich plasma in combination with freeze-dried bone allograft: Case series. *J Periodontol* 2000;17:1654-1661.
32. Wironen JF, Jaw RY, Fox WC. Platelet-rich plasma is not osteoinductive in a nude rat assay. Presented at the International Conference on Bone Substitutes, Davos, Switzerland, 8-10 October 2000.
33. Terheyden H. Experimentelle Sinusbodenaugmentation: Vergleich verschiedener Tragermaterialien mit und ohne rhOP-1 und vergleich der biologischen Faktoren PRP und rhOP-1. Presented at the Sinus-Lift Konferenz, Hamburg, Germany, 9 September 2000.
34. Marx RE, Garg AK. Bone graft physiology with use of platelet-rich plasma and hyperbaric oxygen. In: Jensen OT (ed). *The Sinus Bone Graft*. Chicago: Quintessence, 1999:183-189.
35. Marx RE. Platelet-rich plasma: A source of multiple autologous growth factors for bone grafts. In: Lynch SE, Genco RJ, Marx RE (eds). *Tissue Engineering: Applications in Maxillofacial Surgery and Periodontics*. Chicago: Quintessence, 1999:71-82.
36. Uchida Y, Goto M, Katsuki T, Soejima Y. Measurement of maxillary sinus volume using computerized tomographic images. *Int J Oral Maxillofac Implants* 1998;13:811-818.
37. Misch CE. *Contemporary Implant Dentistry*, ed 1. St Louis: CV Mosby, 1993: 545-574.
38. Wallace SS, Froum SJ, Tarnow DP. Histologic evaluation of the sinus elevation procedure: A clinical report. *Int J Periodontics Restorative Dent* 1996;16: 47-51.

