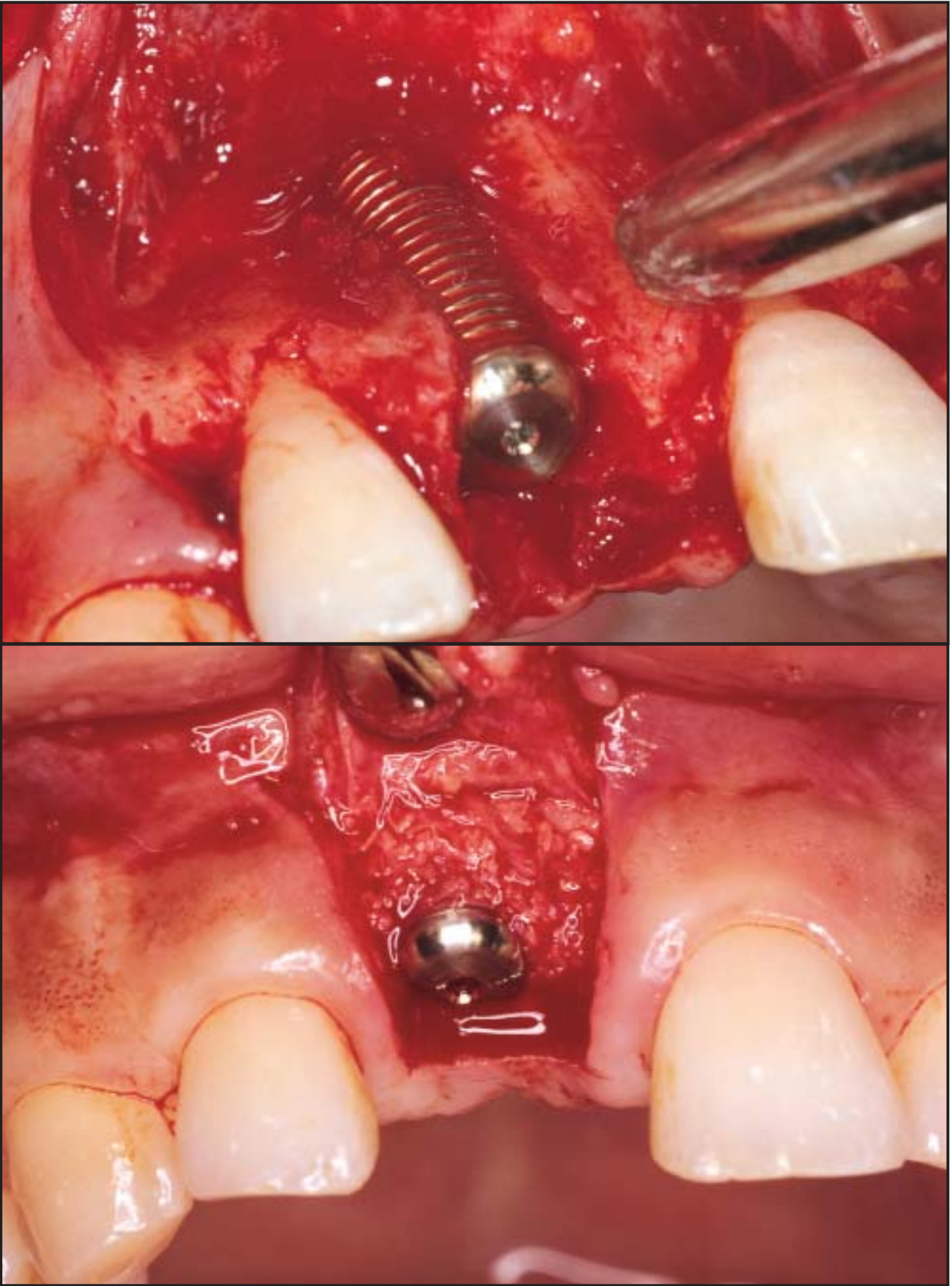


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"Sandwich" Bone Augmentation Technique: Rationale and Report of Pilot Cases



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The aim of this article is to present a new technique for augmentation of deficient alveolar ridges and/or correction of osseous defects around dental implants. Current knowledge regarding bone augmentation for treatment of osseous defects prior to and in combination with dental implant placement is critically appraised. The "sandwich" bone augmentation technique is demonstrated step by step. Five pilot cases with implant dehiscence defects averaging 10.5 mm were treated with the technique. At 6 months, the sites were uncovered, and complete defect fill was noted in all cases. Results from this pilot case study indicated that the sandwich bone augmentation technique appears to enhance the outcomes of bone augmentation by using the positive properties of each applied material (autograft, DFDBA, hydroxyapatite, and collagen membrane). Future clinical trials for comparison of this approach with other bone augmentation techniques and histologic evaluation of the outcomes are needed to validate these findings. (Int J Periodontics Restorative Dent 2004;24:232-245.)

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When a tooth is lost and replacement by means of a dental implant is indicated, several factors need to be considered during treatment planning for optimal function and esthetics of the implant-supported prosthesis. One key factor is the amount of available alveolar bone. Inadequate alveolar height, width, and quality may compromise ideal implant placement and, as a consequence, jeopardize the final clinical outcome. In addition, soft tissue profile is largely influenced by the remaining bone height and width. Correction of osseous deficiencies will not only allow ideal implant placement in terms of angulation and size, but also enable correction of soft tissue deficiencies to improve overall esthetics.

Regeneration of bone in a defect is an elaborate process.^{1,2} New bone develops from the periosteum and marrow-derived cells that possess osteogenic potential. In addition, three fundamental elements are necessary for this regeneration: the presence of a blood clot, preserved osteoblasts, and contact with living tissue.^{3,4} The

main limiting factor in regeneration of osseous/bony defects seems to be related to the quick population of osseous wounds by soft tissue cells, since these cells migrate and proliferate at faster rates than bone-forming cells.^{5,6} As a consequence, ingrowth of soft tissue disturbs or prevents osteogenesis in osseous defects. Various methods have been described for bone regeneration or augmentation: osteoinduction (bone-inducing substances), osteoconduction (graft as a scaffold for new bone growth), distraction osteogenesis (surgical fracture stimulated), onlay grafts (blocks of living bone transplanted to recipient sites), and guided bone regeneration (GBR; space maintenance by barriers to be filled with bone).^{7,8}

The concept of GBR was developed for implant dentistry based on promising results achieved using guided tissue regeneration (GTR) for periodontal defects. GBR is defined as "procedures attempting to regenerate or augment bone for proper dental implant placement."⁹ Initial experiments showed that barrier-protected osseous defects have more bone regeneration compared to unprotected defects.^{10,11} These experiments demonstrated that the roles of barrier membranes in osseous wounds are protection of the blood clot from invasion by nonosteogenic cells, facilitation of wound stabilization, and creation/maintenance of the necessary space for new bone growth.^{11,12} The space created by the barrier membranes is filled with young, actively growing bone by 90 days, whereas no new

bone formation is observed in unprotected sites.^{13,14} Nyman et al¹⁵ reported the first clinical cases of GBR for implant dentistry; since then, GBR has become part of implant therapy. Research has shown that particulate bone grafts associated with barrier membranes provide better results than particulate bone grafts alone, and that GBR provides an effective means of bone regeneration.¹⁵⁻²¹ However, results seem to vary considerably, possibly because of use of different types of grafting materials.

The aim of the present article is to introduce a new technique for augmentation/correction of ridge deficiency in implant dentistry. The "sandwich" bone augmentation technique (SBA) is illustrated step by step, and results from five pilot cases are reported.

Sandwich Bone Augmentation Technique

Rationale

Autogenous bone graft is considered to be the ideal bone graft material, since it is quickly incorporated and/or replaced by host bone and possesses osteogenic, osteoinductive, and osteoconductive properties. The drawback of autograft use is related to availability. Intraoral sources for harvesting are limited and usually require an additional surgical intervention, which increases the risk of morbidity. Commercially available graft materials (ie, demineralized freeze-dried bone

allograft [DFDBA], hydroxyapatite [HA]) are commonly used to overcome this deficiency. However, these materials do not harbor osteogenic properties and mainly act as scaffolds for new bone formation (osteoconduction).

The main component of the SBA technique is autogenous bone, which constitutes the first layer, applied immediately against the implant surface. During preparation of implant osteotomies, a considerable amount of bone (osseous coagulum) can be collected by simply cleaning the drills after use. If the autograft is not sufficient to cover the defect to the level of adjacent bone, additional bone grafts are needed. DFDBA is the first choice, since it is mainly constituted of collagen, the most important organic component of bone tissues. DFDBA may also release bone morphogenetic proteins (BMP), which are known to induce bone formation, into the wound. The close proximity among the surface of the implant, autograft, DFDBA, and surrounding host bone creates an ideal environment for migration and proliferation of osteogenic cells and subsequent replacement of the graft materials by newly formed bone.

To ensure that the space needed for augmentation is created/maintained, bovine HA is layered on top of the graft materials. Generally, this layer of graft is covered up to 2 to 3 mm (buccolingual direction) beyond the adjacent bone level to ensure adequate space maintenance. In addition, to avoid the invasion of soft tissue cells into layers of graft mate-

rials, a barrier membrane is often recommended. Absorbable collagen membranes are preferable because of their high biocompatibility with oral tissues, hemostatic properties, chemotactic effects on fibroblasts ensuring adequate wound closure, and lack of need for retrieval.

To ensure the success of this approach, two additional factors should be addressed. Primary implant stability must be achieved before any attempt at bone augmentation, since a mobile implant is unlikely to achieve osseointegration. Mobile implants (eg, micromovements of more than 100 μm) often heal with fibrous encapsulation,²²⁻²⁷ similar to the pseudoarthrosis observed in unstabilized fracture sites. Another important factor to consider is primary wound coverage with passive tension. A sealed (primary wound coverage) environment eliminates the negative influence of the oral microflora and promotes undisturbed healing.

Indications

Indications for the SBA technique are horizontal alveolar ridge defects and alveolar ridge dehiscence/fenestration defects.²⁸ Other potential indications are alveolar ridge augmentation/preservation and immediate implant placement.

Contraindications

Any medical problem that would prohibit a patient from undergoing

routine periodontal or implant surgery is also a contraindication for the SBA procedure. In addition, no active infection can be present at the site to be treated. Active infections must be treated before any bone regeneration is attempted.

Surgical principles

The SBA technique employs three layers of bone graft materials and an absorbable collagen membrane to exclude undesirable soft tissue cells from the wound. The following surgical principles must be followed for successful bone augmentation following SBA procedures.

The most common complications of bone augmentation procedures are flap recession or sloughing.^{8,29} For this reason, initial surgical incisions should be made in keratinized tissue, since this tissue is more resistant to laceration than nonkeratinized oral mucosa. Adequate initial incisions and flap management will dictate the capacity to achieve adequate wound closure without tension.

Full-thickness flap elevation is mandatory. If periosteal fibers remain attached to the bone surface after flap elevation, the area must be completely debrided before any grafting procedure is attempted. Partial-thickness reflection can be performed apical to the treatment site to allow adequate release of the mucoperiosteal flap, ensuring proper wound closure without tension.

Intramarrow penetrations, also called regional acceleratory phe-

nomena,³⁰ may aid faster vascularization of the graft by allowing blood vessels originating from the marrow spaces to more easily migrate into the treatment site. This procedure may result in faster population of osteogenic cells in the grafted site and facilitate bone regeneration/augmentation.

The inner bone graft layer is composed of autogenous bone. Autograft collected during osteotomy preparation (osseous coagulum) is applied directly against the surface of the implant, providing viable osteogenic cells and enhancing migration of cells from the host bone into the surface of the implant.

If the collected autograft is not sufficient to achieve the first layer of bone coverage (to the level of adjacent bone height in a buccolingual dimension), an additional layer of graft would be added. The middle bone graft layer is composed of DFDBA or human demineralized allograft (Puros, Centerpulse). Active human allograft or DFDBA may release BMPs into the surrounding wound to induce bone formation. The close proximity among the surface of the implant, autograft, allograft, and surrounding host bone creates an ideal environment for migration and proliferation of osteogenic cells and subsequent replacement of the graft materials by newly formed bone.

The outer bone graft layer is composed of dense particles of HA, which acts as a scaffold/space occupier because of its osteoconductive properties. It facilitates new bone formation by preserving and/or

Table 1 Results after application of sinus bone augmentation technique for correction of implant dehiscence defects*

Patient	Age (y)	Gender	Baseline implant thread exposure (mm)	6 mo implant thread exposure (mm)
1	36	F	13.0	0.0
2	41	F	7.0	0.0
			9.0	0.0
3	46	M	6.0	0.0
4	39	M	13.0	0.0
5	28	F	15.0	0.0
Mean	38		10.5	0.0

*100% defect fill occurred at all implants.

maintaining the space essential for bone augmentation procedures.

After application of these layers of bone graft, a collagen membrane is applied to cover the recipient site. Application of a barrier membrane provides stabilization for the treatment site and exclusion of unwanted cells. Collagen membranes are preferable because of their physiologic absorption process and high biocompatibility with oral tissues. In addition, collagen is a hemostatic agent and possesses the ability to stimulate platelet aggregation and enhance fibrin linkage, which may lead to initial clot formation, stability, and maturation.³¹ Furthermore, collagen is chemotactic for fibroblasts in vitro.³² This property could enhance cell migration and promote the primary wound coverage that is key for bone augmentation.

The mucoperiosteal flap is then coronally repositioned for complete wound coverage without tension. Techniques for flap release include apical partial-thickness elevation and/or dissection of the periosteum,

which are normally associated with vertical releasing incisions. Flaps united with tension are likely to undergo secondary or even tertiary healing during wound contraction.³³ To ensure maintenance of wound closure during the healing process, use of long-lasting suture materials (eg, Vicryl, Ethicon/Johnson & Johnson; Gore-Tex, WL Gore) is recommended.

Postoperative care includes rinsing twice daily with warm salt water for the first 2 weeks before switching to twice-daily rinsing with a solution of 0.12% chlorhexidine gluconate for the next 2 weeks. Systemic antibiotic prophylaxis is also recommended (amoxicillin 500 mg 3 times a day for 10 days; if allergic, azithromycin 500 mg/day for 3 days is prescribed).

Sutures are generally removed 10 to 14 days after surgery. The patient should be seen every 4 to 6 weeks for evaluation of the wound healing progress. If initial membrane exposure is avoided, healing normally proceeds uneventfully.³⁴

Implant placement or second-stage implant surgery should not be performed before a 5- to 6-month healing period.

Method and materials

Five systemically healthy patients with buccal dehiscence alveolar defects around dental implants were treated at the Graduate Periodontics Clinic, School of Dentistry, University of Michigan. Defects measured 6 to 15 mm (mean 10.5 mm) immediately after implant placement.

Clinical data were collected at the time of implant surgery and 6 months later, during implant uncovering. The amount of exposed implant threads was measured using a standard North Carolina probe to the nearest millimeter. Radiographs as well as 1:1 magnification color photographs were also taken. All surgical procedures were performed following the principles of the SBA technique, discussed previously. All implants were placed in a two-staged approach.

Results

During the course of treatment, no adverse events occurred. Bone augmentation using the SBA principles achieved a mean of 10.5 mm of bone formation, or 100% defect fill (Table 1). The tissue surrounding the implants was resistant to probing and hard in consistency, clinically resembling natural bone (Figs 1 to 4).



Fig 1a Sandwich bone augmentation technique in patient 1: Flap reflection shows inadequate buccolingual bone width.



Fig 1b Implant preparation indicates fenestration of buccal plate.



Fig 1c Pure titanium implant (3.75 mm × 13 mm; Brånemark, Nobel Biocare) was placed with primary stability.



Fig 1d Autograft collected during osteotomy is applied as inner layer, and middle layer consists of DFDBA.



Fig 1e Outer layer is bovine HA (Bio-Oss).



Fig 1f Collagen membrane (BioMend Regular, Zimmer Dental) is trimmed and adapted.



Fig 1g (left) Flap is coronally advanced and secured with No. 5-0 Vicryl sutures.

Fig 1h (right) Implant stage-two surgery (6 months postsurgical) shows complete defect fill.



Fig 2a (left) Sandwich bone augmentation technique in patient 2: Flap reflection shows implant thread exposure (7 and 9 mm).

Fig 2b (right) Stage-two surgery (6 months postsurgical) shows complete defect fill.





Fig 3a (left) Sandwich bone augmentation technique in patient 3: Flap reflection shows implant thread exposure (13 mm).



Fig 3b (right) Stage-two surgery (6 months postsurgical) shows complete defect fill.



Fig 4a (left) Sandwich bone augmentation technique in patient 5: Flap reflection shows implant thread exposure (15 mm).



Fig 4b (right) Stage-two surgery (6 months postsurgical) shows complete bone fill.

Discussion

Implants should be placed with ideal location and angulation.³⁵⁻³⁹ This approach may result in exposure of implant threads because of insufficient alveolar ridge width and/or height, which may lead to higher implant failure rates.^{16,28} To avoid these complications, bone augmentation is generally required. GBR has been proposed to reconstruct alveolar ridge defects not only before, but also at the time of, implant placement.⁴⁰ Buser et al²⁹ applied the principles of GBR in humans and found 1.5 to 5.5 mm of horizontal bone formation, concluding that GBR is a highly predictable approach for ridge augmentation. However, further reports have shown varying results,

possibly because of different techniques and materials used.^{15,41-57}

Autograft has been regarded as the gold standard bone graft material for GBR because of its osteogenic, osteoinductive, and osteoconductive properties. Nevertheless, intraoral sources of autogenous bone are limited, and the risk of morbidity at the donor site exists. Commercially available graft materials (ie, DFDBA, HA) are commonly used to overcome this deficiency. However, these materials have limitations, eg, DFDBA's low mechanical rigidity and relatively quick absorption rate compared to freeze-dried bone allograft and HA, and the slow absorption rate associated with HA. The sandwich GBR technique was developed using the positive properties of each graft

material and the barrier function of a collagen membrane. The barrier membrane would exclude unwanted soft tissue cells, prevent graft exfoliation, and enhance wound stability to promote uneventful healing.^{2,58-64}

The inner-layer autograft was used to provide viable osteogenic cells to the defect. The close proximity between the host bone and autograft allowed the creation of an ideal scaffold for migration and proliferation of osteogenic cells and subsequent replacement of the graft material by newly formed bone. This scaffold could be enhanced if needed by adding another layer of human allograft. Human mineralized allograft or DFDBA has been widely used as a bone-replacement graft based on

its reported osteoconductive and believed osteoinductive capabilities.⁶⁵⁻⁷⁰ DFDBA permits rapid vascular and hard tissue ingrowth and may help stimulate osseous regeneration without the need of harvesting autologous bone from a second site.^{71,72} Osteoinductive activity is believed to occur because of exposure of BMPs during the allograft demineralization process.^{67-69,73} DFDBA is produced by acid extraction of the mineral components of bone. This process results in a graft material containing collagen, noncollagenous bone matrix proteins, and growth factors, but little residual bone mineral.^{73,74} Hence, demineralization exposes the bone-inductive proteins located in the bone matrix and may activate them.^{22,75-79} However, recent studies raise concern that the amount of BMPs present in the graft particles may not be sufficient to promote osteoinduction.⁸⁰⁻⁸⁵

Other mineralized forms of bone graft may be used for this purpose. A recently introduced mineralized allograft (Puros) could be an alternative. It constitutes a mineralized bone allograft material processed through a unique solvent-preserved process for tissue preservation and viral inactivation, which differs from the standard cryo-preserved process. The bone structure that undergoes this process appears to remain intact compared to other forms of bone treatment, providing excellent bone matrix and load-bearing capabilities.⁸⁶ Studies have also shown that hydrogen peroxide application during processing is

capable of inactivating relevant pathogens (eg, HIV and hepatitis), ensuring the material's safety for clinical use.⁸⁷ In addition, histologic studies confirm that the biotolerance of solvent-dehydrated grafts is comparable with cryo-preserved bone grafting materials.⁸⁸ Although its bone-formation mechanism is still unclear, preliminary studies demonstrate that this grafting material does not elicit a foreign-body reaction and is highly effective in inducing bone formation.^{89,90}

The outer bone graft layer, composed of dense HA, ensured that the space created was maintained during the healing process. Bovine HA (Bio-Oss, Osteohealth) has been widely used for treatment of periodontal and peri-implant defects, and its osteoconductive properties have been confirmed by various studies.⁹¹⁻⁹⁴

Grafted areas were covered with absorbable collagen barrier membranes for exclusion of soft tissue cells from the wound. Use of barrier membranes in bone augmentation procedures enhances the amount of bone formation.⁹⁵⁻⁹⁹ Lang et al¹⁰⁰ measured the amount of alveolar bone that could be regenerated with nonabsorbable membranes following different healing periods and found that membranes removed between 3 and 5 months result in regeneration of 0% and 60%, whereas membranes left for 6 to 8 months regenerate between 90% and 100% of the possible volume.¹⁰⁰ For this reason, absorbable membranes are preferable, since they do not require an additional surgical

intervention for removal, helping to maintain undisturbed wound healing until bone maturation is completed. Collagen membranes are preferable because of their high biocompatibility with oral tissues, hemostatic properties, and chemotactic effects on fibroblasts promoting primary wound closure.¹⁰¹ In addition, collagen is an important constitutive element of the human body and therefore is absorbable. With absorbable collagen membranes for ridge augmentation, appreciable results are obtained even when the membranes become exposed during the healing process.¹⁰² Membrane exposure was observed 2 weeks postoperative in the present study, but complete defect fill was nevertheless observed (Fig 1h).

Stability of bone formed during GBR has to be evaluated after implant placement and loading. Several reports have shown that the bone regenerated with GBR remains stable after implant loading, and the success rate of these implants is comparable to those placed in native bone.¹⁰³⁻¹⁰⁹ Similar findings have been reported for bone regeneration into dehiscence defects.¹¹⁰⁻¹¹⁴

Bone regeneration is possible in selected peri-implant bony defects when appropriate surgical techniques are used, implant surface preparation is achieved, and the cause of the defect is eradicated.¹¹⁵ Other possible applications of the SBA technique may include treatment of the failing implant (bone loss with pocketing but static at maintenance checks)

and the failing implant (bone loss with pocketing, bleeding on probing, purulence, and evidence of continuing bone loss irrespective of therapy), as well as ridge (socket) preservation. GBR around peri-implantitis is enhanced when bone grafts are added to absorbable membranes.¹¹⁶⁻¹¹⁸ Future studies in these areas are needed to further validate application of the SBA technique in these types of defects.

Conclusion

Advances in bone reconstructive techniques, including the potential of barrier membrane use for osteogenesis, have increased the indications for implant placement. Experimental and clinical findings have shown that the type of adjunctive grafting material and barrier membrane used, healing time, type and size of the bony defect, and membrane exposure all influence the end result. The SBA technique seems to maximize the outcomes of GBR by using the positive properties of different bone graft materials. Promising results have been achieved by our group, encouraging the development of future clinical trials for comparison of this approach with other bone augmentation techniques. Further histologic evaluation is needed to validate the results obtained via this approach.

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References

1. Gotfredsen K, Warrer K, Hjørting H, Karring T. Effect of membranes and porous hydroxyapatite on healing in bone defects around titanium dental implants. An experimental study in monkeys. *Clin Oral Implants Res* 1991;2:172-178.
2. Grunder U, Hürzeler MB, Schupbach P, Strub JR. Treatment of ligature-induced peri-implantitis using guided tissue regeneration: A clinical and histologic study in the beagle dog. *Int J Oral Maxillofac Implants* 1993;8:282-293.
3. Murray C, Holden R, Roachlan W. Experimental and clinical study of the new growth of bone in a cavity. *Am J Surg* 1957;95:385-387.
4. Hurley A. The role of soft tissues in osteogenesis. *J Bone Joint Surg Am* 1959;41:1243-1249.
5. Engler WO, Ramfjord SP, Hiniker JJ. Healing following simple gingivectomy. A tritiated thymidine radioautographic study. I. Epithelialization. *J Periodontol* 1966;37:298-308.
6. Ramfjord SP, Engler WO, Hiniker JJ. A radioautographic study of healing following simple gingivectomy. II. The connective tissue. *J Periodontol* 1966;37:179-189.
7. Buser DA, Tonetti M. Clinical trials on implants in regenerated bone. *Ann Periodontol* 1997;2:329-342.
8. Buser D, Dahlin C, Schenk R. *Guided Bone Regeneration in Implant Dentistry*. Chicago: Quintessence, 1994.
9. American Academy of Periodontology. *Glossary of Periodontal Terms*, ed 4. Chicago: AAP, 2001:1.
10. Linghorne W. The sequence of events in osteogenesis as studied in polyethylene tubes. *Ann N Y Acad Sci* 1960;xy:445.
11. Melcher A, Dreyer CJ. Protection of the blood clot in healing circumscribed bone defects. *J Bone Joint Surg Br* 1962;44:424-435.
12. Dahlin C, Sennerby L, Lekholm U, Lindé A, Nyman S. Generation of new bone around titanium implants using a membrane technique: An experimental study in rabbits. *Int J Oral Maxillofac Implants* 1989;4:19-25.
13. Seibert J, Nyman S. Localized ridge augmentation in dogs: A pilot study using membranes and hydroxyapatite. *J Periodontol* 1990;61:157-165.
14. Kostopoulos L, Karring T. Guided bone regeneration in mandibular defects in rats using a bioresorbable polymer. *Clin Oral Implants Res* 1994;5:66-74.
15. Nyman S, Lang NP, Buser D, Brägger U. Bone regeneration adjacent to titanium dental implants using guided tissue regeneration: A report of two cases. *Int J Oral Maxillofac Implants* 1990;5:9-14.
16. Wilson TG Jr, Buser D. Advances in the use of guided tissue regeneration for localized ridge augmentation in combination with dental implants. *Tex Dent J* 1994;111:5, 7-10.
17. von Arx T. 5 years of guided bone regeneration (GBR) in implant dentistry. A report on the membrane symposium of 10 and 11 December 1993 at Basel [in German]. *Schweiz Monatsschr Zahnmed* 1994;104:494-496, 515-517.
18. Shanaman RH. A retrospective study of 237 sites treated consecutively with guided tissue regeneration. *Int J Periodontics Restorative Dent* 1994;14:292-301.
19. Saadoun AP, Le Gall M. Keys to success in implant osseointegration [in French]. *Int J Dent Symp* 1994;2:6-11.
20. Rominger JW, Triplett RG. The use of guided tissue regeneration to improve implant osseointegration. *J Oral Maxillofac Surg* 1994;52:106-112.

21. Nevins M, Mellonig JT. The advantages of localized ridge augmentation prior to implant placement: A staged event. *Int J Periodontics Restorative Dent* 1994;14:96–111.
22. Aspenberg P, Goodman S, Toksvig-Larsen S, Ryd L, Albrektsson T. Intermittent micromotion inhibits bone ingrowth. Titanium implants in rabbits. *Acta Orthop Scand* 1992;63:141–145.
23. Szmukler-Moncler S, Salama H, Reingewirtz Y, Dubruille JH. Timing of loading and effect of micromotion on bone-dental implant interface: Review of experimental literature. *J Biomed Mater Res* 1998;43:192–203.
24. Brunski JB, Moccia AF Jr, Pollack SR, Korostoff E, Trachtenberg DI. The influence of functional use of endosseous dental implants on the tissue-implant interface. II. Clinical aspects. *J Dent Res* 1979;58:1970–1980.
25. Brunski JB, Moccia AF Jr, Pollack SR, Korostoff E, Trachtenberg DI. The influence of functional use of endosseous dental implants on the tissue-implant interface. I. Histological aspects. *J Dent Res* 1979;58:1953–1969.
26. Roberts WE, Smith RK, Zilberman Y, Mozsary PG, Smith RS. Osseous adaptation to continuous loading of rigid endosseous implants. *Am J Orthod* 1984;86:95–111.
27. Brunski JB. Avoid pitfalls of overloading and micromotion of intraosseous implants. *Dent Implantol Update* 1993;4(10):77–81.
28. Wang HL, Al-Shammari K. HVC ridge deficiency classification: A therapeutically oriented classification. *Int J Periodontics Restorative Dent* 2002;22:335–343.
29. Buser D, Brägger U, Lang NP, Nyman S. Regeneration and enlargement of jaw bone using guided tissue regeneration. *Clin Oral Implants Res* 1990;1:22–32.
30. Frost HM. The biology of fracture healing. An overview for clinicians. Part II. *Clin Orthop* 1989;248:294–309.
31. Sableman E. Biology, Biotechnology, and Biocompatibility of Collagen. *Biocompatibility of Tissue Analogs*. Boca Raton, FL: CRC, 1985:27.
32. Postlethwaite AE, Seyer JM, Kang AH. Chemotactic attraction of human fibroblasts to type I, II, and III collagens and collagen-derived peptides. *Proc Natl Acad Sci U S A* 1978;75:871–875.
33. Zanetta-Barbosa D, Klinge B, Svensson H. Laser Doppler flowmetry of blood perfusion in mucoperiosteal flaps covering membranes in bone augmentation and implant procedures. A pilot study in dogs. *Clin Oral Implants Res* 1993;4:35–38.
34. Schenk RK, Buser D, Hardwick WR, Dahlin C. Healing pattern of bone regeneration in membrane-protected defects: A histologic study in the canine mandible. *Int J Oral Maxillofac Implants* 1994;9:13–29.
35. Kopp KC, Koslow AH, Abdo OS. Predictable implant placement with a diagnostic/surgical template and advanced radiographic imaging. *J Prosthet Dent* 2003;89:611–615.
36. Cehreli MC, Calis AC, Sahin S. A dual-purpose guide for optimum placement of dental implants. *J Prosthet Dent* 2002;88:640–643.
37. Wat PY, Chow TW, Luk HW, Comfort MB. Precision surgical template for implant placement: A new systematic approach. *Clin Implant Dent Relat Res* 2002;4:88–92.
38. Walton JN, Huizinga SC, Peck CC. Implant angulation: A measurement technique, implant overdenture maintenance, and the influence of surgical experience. *Int J Prosthodont* 2001;14:523–530.
39. Cehreli MC, Iplikcioglu H, Bilir OG. The influence of the location of load transfer on strains around implants supporting four unit cement-retained fixed prostheses: In vitro evaluation of axial versus offset loading. *J Oral Rehabil* 2002;29:394–400.
40. Dahlin C, Lindé A, Gottlow J, Nyman S. Healing of bone defects by guided tissue regeneration. *Plast Reconstr Surg* 1988;81:672–676.
41. Kohal RJ, Hürzeler MB. Bioresorbable barrier membranes for guided bone regeneration around dental implants [in German]. *Schweiz Monatsschr Zahnmed* 2002;112:1222–1229.
42. Ou G, Bao C, Liang X, Chao Y, Chen Z. Histological study on the polyhydroxybutyric ester (PHB) membrane used for guided bone regeneration around titanium dental implants [in Chinese]. *Hua Xi Kou Qiang Yi Xue Za Zhi* 2000;18:215–218.
43. Kohal RJ, Wirsching C, Bachle M. Guided bone regeneration around dental implants using a bioabsorbable membrane. A pilot investigation in experimental animals [in German]. *Schweiz Monatsschr Zahnmed* 2001;111:1397–1405.
44. Ito K, Yamada Y, Ishigaki R, Nanba K, Nishida T, Sato S. Effects of guided bone regeneration with non-resorbable and bioabsorbable barrier membranes on osseointegration around hydroxyapatite-coated and uncoated threaded titanium dental implants placed into a surgically-created dehiscence type defect in rabbit tibia: A pilot study. *J Oral Sci* 2001;43:61–67.
45. Schlegel KA, Sindet-Pedersen S, Hoepffner HJ. Clinical and histological findings in guided bone regeneration (GBR) around titanium dental implants with autogeneous bone chips using a new resorbable membrane. *J Biomed Mater Res* 2000;53:392–399.
46. Chong WL, Chu SA, Dam JG, Ong KS. Oral rehabilitation using dental implants and guided bone regeneration. *Ann Acad Med Singapore* 1999;28:697–703.
47. Fiorellini JP, Engebretson SP, Donath K, Weber HP. Guided bone regeneration utilizing expanded polytetrafluoroethylene membranes in combination with submerged and nonsubmerged dental implants in beagle dogs. *J Periodontol* 1998;69:528–535.
48. Hürzeler MB, Quiñones CR, Schupbach P. Guided bone regeneration around dental implants in the atrophic alveolar ridge using a bioresorbable barrier. An experimental study in the monkey. *Clin Oral Implants Res* 1997;8:323–331.

49. Schlegel AK, Donath K, Weida S. Histological findings in guided bone regeneration (GBR) around titanium dental implants with autogenous bone chips using a new resorbable membrane. *J Long Term Eff Med Implants* 1998;8: 211-224.
50. Stentz WC, Mealey BL, Gunsolley JC, Waldrop TC. Effects of guided bone regeneration around commercially pure titanium and hydroxyapatite-coated dental implants. II. Histologic analysis. *J Periodontol* 1997;68:933-949.
51. Stentz WC, Mealey BL, Nummikowski PV, Gunsolley JC, Waldrop TC. Effects of guided bone regeneration around commercially pure titanium and hydroxyapatite-coated dental implants. I. Radiographic analysis. *J Periodontol* 1997;68: 199-208.
52. Hermann JS, Buser D. Guided bone regeneration for dental implants. *Curr Opin Periodontol* 1996;3:168-177.
53. Mattout P, Nowzari H, Mattout C. Clinical evaluation of guided bone regeneration at exposed parts of Brånemark dental implants with and without bone allograft. *Clin Oral Implants Res* 1995;6:189-195.
54. Danesh-Meyer MJ. Dental implants. Part II: Guided bone regeneration, immediate implant placement, peri-implantitis, failing implants. *J N Z Soc Periodontol* 1994; 78:18-28.
55. Gher ME, Quintero G, Assad D, Monaco E, Richardson AC. Bone grafting and guided bone regeneration for immediate dental implants in humans. *J Periodontol* 1994;65:881-891.
56. Sinclair G. A comparison of two techniques of bone regeneration: Bone grafting alone, and bone grafting with guided tissue regeneration in the successful replacement of two fractured teeth by dental implants. *J N Z Soc Periodontol* 1991;71:6-11.
57. Hempton TJ, Fugazzotto PA. Ridge augmentation utilizing guided tissue regeneration, titanium screws, freeze-dried bone, and tricalcium phosphate: Clinical report. *Implant Dent* 1994;3:35-37.
58. Meffert RM. How to treat ailing and failing implants. *Implant Dent* 1992;1:25-33.
59. Wachtel HC, Langford A, Bernimoulin JP, Reichart P. Guided bone regeneration next to osseointegrated implants in humans. *Int J Oral Maxillofac Implants* 1991;6:127-135.
60. Artzi Z, Tal H, Chweidan H. Bone regeneration for reintegration in peri-implant destruction. *Compend Contin Educ Dent* 1998;19:17-20, 22-23, 26-28.
61. Hürzeler MB, Quiñones CR, Morrison EC, Caffesse RG. Treatment of peri-implantitis using guided bone regeneration and bone grafts, alone or in combination, in beagle dogs. Part 1: Clinical findings and histologic observations. *Int J Oral Maxillofac Implants* 1995;10:474-484.
62. Hürzeler MB, Quiñones CR, Schupbach P, Morrison EC, Caffesse RG. Treatment of peri-implantitis using guided bone regeneration and bone grafts, alone or in combination, in beagle dogs. Part 2: Histologic findings. *Int J Oral Maxillofac Implants* 1997;12:168-175.
63. Persson LG, Ericsson I, Berglundh T, Lindhe J. Guided bone regeneration in the treatment of periimplantitis. *Clin Oral Implants Res* 1996;7:366-372.
64. von Arx T, Kurt B, Hardt N. Treatment of severe peri-implant bone loss using autogenous bone and a resorbable membrane. Case report and literature review. *Clin Oral Implants Res* 1997;8:517-526.
65. Urist MR. Bone: Formation by autoinduction. *Science* 1965;150(698):893-899.
66. Urist MR, Silverman BF, Buring K, Dubuc FL, Rosenberg JM. The bone induction principle. *Clin Orthop* 1967;53:243-283.
67. Urist MR, Dowell TA, Hay PH, Strates BS. Inductive substrates for bone formation. *Clin Orthop* 1968;59:59-96.
68. Urist MR, Iwata H. Preservation and biodegradation of the morphogenetic property of bone matrix. *J Theor Biol* 1973;38:155-167.
69. Urist MR, Iwata H, Ceccotti PL, et al. Bone morphogenesis in implants of insoluble bone gelatin. *Proc Natl Acad Sci U S A* 1973;70:3511-3515.
70. Becker W, Becker BE, Caffesse R. A comparison of demineralized freeze-dried bone and autologous bone to induce bone formation in human extraction sockets. *J Periodontol* 1994;65:1128-1133.
71. Sassard WR, Eidman DK, Gray PMJ. Analysis of spine fusion utilizing demineralized bone matrix. Presented at Western Orthopedic Association Meeting, August 1994, Philadelphia.
72. An HS, Simpson JM, Glover JM, Stephany J. Comparison between allograft plus demineralized bone matrix versus autograft in anterior cervical fusion. A prospective multicenter study. *Spine* 1995;20:2211-2216.
73. Mellonig JT. Decalcified freeze-dried bone allograft as an implant material in human periodontal defects. *Int J Periodontics Restorative Dent* 1984;4(6): 40-55.
74. Gazdag AR, Lane JM, Glaser D, Forster RA. Alternatives to autogenous bone graft: Efficacy and indications. *J Am Acad Orthop Surg* 1995;3:1-8.
75. Schwartz Z, Mellonig JT, Carnes DL Jr, et al. Ability of commercial demineralized freeze-dried bone allograft to induce new bone formation. *J Periodontol* 1996;67: 918-926.
76. Mellonig JT, Triplett RG. Guided tissue regeneration and endosseous dental implants. *Int J Periodontics Restorative Dent* 1993;13:108-119.
77. Nevins M, Mellonig JT. Enhancement of the damaged edentulous ridge to receive dental implants: A combination of allograft and the Gore-Tex membrane. *Int J Periodontics Restorative Dent* 1992;12: 96-111.
78. Werbitz MJ, Goldberg PV. The immediate implant: Bone preservation and bone regeneration. *Int J Periodontics Restorative Dent* 1992;12:206-217.
79. Shanaman RH. The use of guided tissue regeneration to facilitate ideal prosthetic placement of implants. *Int J Periodontics Restorative Dent* 1992;12:256-265.

80. Tsai CH, Chou MY, Jonas M, Tien YT, Chi EY. A composite graft material containing bone particles and collagen in osteoinduction in mouse. *J Biomed Mater Res* 2002;63:65–70.
81. Paul BF, Horning GM, Hellstein JW, Schafer DR. The osteoinductive potential of demineralized freeze-dried bone allograft in human non-orthotopic sites: A pilot study. *J Periodontol* 2001;72:1064–1068.
82. Schwartz Z, Weesner T, van Dijk S, et al. Ability of deproteinized cancellous bovine bone to induce new bone formation. *J Periodontol* 2000;71:1258–1269.
83. Boyan BD, Lohmann CH, Somers A, et al. Potential of porous poly-D,L-lactide-co-glycolide particles as a carrier for recombinant human bone morphogenetic protein-2 during osteoinduction in vivo. *J Biomed Mater Res* 1999;46:51–59.
84. Becker W, Urist M, Becker BE, et al. Clinical and histologic observations of sites implanted with intraoral autologous bone grafts or allografts. 15 human case reports. *J Periodontol* 1996;67:1025–1033.
85. Piattelli A, Scarano A, Corigliano M, Piattelli M. Comparison of bone regeneration with the use of mineralized and demineralized freeze-dried bone allografts: A histological and histochemical study in man. *Biomaterials* 1996;17:1127–1131.
86. Scharf H-P. Humane Tibialis-Anterior-Sehnen als Lösungsmittelkonserviertes Transplantat für den Kreuzbandersatz [thesis]. Ulm, Germany: Ulm University, 1990.
87. Diring H, Braig HR. Infectivity of unconventional viruses in dura mater. *Lancet* 1989;1(8635):439–440.
88. Günther KP, Scharf H-P, Pesch H-J, Puhl W. Osteointegration of solvent-preserved bone transplants in an animal model. *Osteologie* 1996;5:4–12.
89. Dalkyz M, Ozcan A, Yapar M, Gokay N, Yuncu M. Evaluation of the effects of different biomaterials on bone defects. *Implant Dent* 2000;9:226–235.
90. Gapski R, Neiva R, Oh T, Wang H. Histologic analyses of human hydroxyapatite grafting material in sinus elevation procedures: A case series. *Int J Periodontics Restorative Dent* (forthcoming).
91. Camelo M, Nevins ML, Lynch SE, Schenk RK, Simion M, Nevins M. Periodontal regeneration with an autogenous bone–Bio-Oss composite graft and a Bio-Gide membrane. *Int J Periodontics Restorative Dent* 2001;21:109–119.
92. Fugazzotto PA. GBR using bovine bone matrix and resorbable and nonresorbable membranes. Part 1: Histologic results. *Int J Periodontics Restorative Dent* 2003;23:361–369.
93. Nevins ML, Camelo M, Lynch SE, Schenk RK, Nevins M. Evaluation of periodontal regeneration following grafting intrabony defects with Bio-Oss Collagen: A human histologic report. *Int J Periodontics Restorative Dent* 2003;23:9–17.
94. Camelo M, Nevins ML, Schenk RK, et al. Clinical, radiographic, and histologic evaluation of human periodontal defects treated with Bio-Oss and Bio-Gide. *Int J Periodontics Restorative Dent* 1998;18:321–331.
95. Dogan N, Okcu KM, Ortakoglu K, Dalkiz M, Gunaydin Y. Barrier membrane and bone graft treatments of dehiscence-type defects at existing implant: A case report. *Implant Dent* 2003;12:145–150.
96. Sottosanti J, Anson D. Using calcium sulfate as a graft enhancer and membrane barrier [interview]. *Dent Implantol Update* 2003;14:1–8.
97. Peled M, Machtei EE, Rachmiel A. Osseous reconstruction using a membrane barrier following marginal mandibulectomy: An animal pilot study. *J Periodontol* 2002;73:1451–1456.
98. Yamada S, Shima N, Kitamura H, Sugito H. Effect of porous xenographic bone graft with collagen barrier membrane on periodontal regeneration. *Int J Periodontics Restorative Dent* 2002;22:389–397.
99. Buser D, Dula K, Hirt HP, Schenk RK. Lateral ridge augmentation using autografts and barrier membranes: A clinical study with 40 partially edentulous patients. *J Oral Maxillofac Surg* 1996;54:420–432.

100. Lang NP, Hämmeler CH, Brägger U, Lehmann B, Nyman SR. Guided tissue regeneration in jawbone defects prior to implant placement. *Clin Oral Implants Res* 1994;5:92–97.
101. Parodi R, Santarelli G, Carusi G. Application of slow-resorbing collagen membrane to periodontal and peri-implant guided tissue regeneration. *Int J Periodontics Restorative Dent* 1996; 16:174–185.
102. Parodi R, Carusi G, Santarelli G, Nanni F. Implant placement in large edentulous ridges expanded by GBR using a bioresorbable collagen membrane. *Int J Periodontics Restorative Dent* 1998; 18:266–275.
103. Buser D, Ruskin J, Higginbottom F, Hardwick R, Dahlin C, Schenk RK. Osseointegration of titanium implants in bone regenerated in membrane-protected defects: A histologic study in the canine mandible. *Int J Oral Maxillofac Implants* 1995;10:666–681.
104. Fritz ME, Jeffcoat MK, Reddy M, et al. Implants in regenerated bone in a primate model. *J Periodontol* 2001;72: 703–708.
105. Mayfield L, Skoglund A, Nobreus N, Attström R. Clinical and radiographic evaluation, following delivery of fixed reconstructions, at GBR treated titanium fixtures. *Clin Oral Implants Res* 1998;9: 292–302.
106. Fugazzotto PA. Report of 302 consecutive ridge augmentation procedures: Technical considerations and clinical results. *Int J Oral Maxillofac Implants* 1998;13:358–368.
107. Becker W, Dahlin C, Lekholm U, et al. Five-year evaluation of implants placed at extraction and with dehiscences and fenestration defects augmented with ePTFE membranes: Results from a prospective multicenter study. *Clin Implant Dent Relat Res* 1999;1:27–32.
108. Brunel G, Brocard D, Duffort JF, et al. Bioabsorbable materials for guided bone regeneration prior to implant placement and 7-year follow-up: Report of 14 cases. *J Periodontol* 2001;72: 257–264.
109. Zitzmann NU, Schärer P, Marinello CP. Long-term results of implants treated with guided bone regeneration: A 5-year prospective study. *Int J Oral Maxillofac Implants* 2001;16:355–366.
110. Hämmeler CH, Lang NP. Single stage surgery combining transmucosal implant placement with guided bone regeneration and bioresorbable materials. *Clin Oral Implants Res* 2001;12: 9–18.
111. Rosen PS, Reynolds MA. Guided bone regeneration for dehiscence and fenestration defects on implants using an absorbable polymer barrier. *J Periodontol* 2001;72:250–256.
112. Fugazzotto PA, Shanaman R, Manos T, Shectman R. Guided bone regeneration around titanium implants: Report of the treatment of 1,503 sites with clinical reentries. *Int J Periodontics Restorative Dent* 1997;17:292–299.
113. Palmer RM, Smith BJ, Palmer PJ, Floyd PD, Johannson CB, Albrektsson T. Effect of loading on bone regenerated at implant dehiscence sites in humans. *Clin Oral Implants Res* 1998;9:283–291.
114. Lorenzoni M, Pertl C, Polansky R, Wegscheider W. Guided bone regeneration with barrier membranes—A clinical and radiographic follow-up study after 24 months. *Clin Oral Implants Res* 1999;10:16–23.
115. Jovanovic SA. Diagnosis and treatment of peri-implant disease. *Curr Opin Periodontol* 1994;1:194–204.
116. Nociti FH Jr, Caffesse RG, Sallum EA, Machado MA, Stefani CM, Sallum AW. Clinical study of guided bone regeneration and/or bone grafts in the treatment of ligature-induced peri-implantitis defects in dogs. *Braz Dent J* 2001;12:127–131.
117. Nociti FH Jr, Machado MA, Stefani CM, Sallum EA, Sallum AW. Absorbable versus nonabsorbable membranes and bone grafts in the treatment of ligature-induced peri-implantitis defects in dogs. Part I. A clinical investigation. *Clin Oral Implants Res* 2001;12:115–120.
118. Nociti FH Jr, Machado MA, Stefani CM, Sallum EA. Absorbable versus nonabsorbable membranes and bone grafts in the treatment of ligature-induced peri-implantitis defects in dogs: A histometric investigation. *Int J Oral Maxillofac Implants* 2001;16:646–652.