

Subperiosteal Minimally Invasive Aesthetic Ridge Augmentation Technique (SMART): A New Standard for Bone Reconstruction of the Jaws



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Traditional guided bone regeneration techniques include flap mobilization and placement of a bone graft, often with the use of space-maintaining devices and cell-occlusive membranes. This approach is associated with frequent complications that negatively affect the outcome of the augmentation and the peri-implant soft tissue esthetics. Although current tunneling techniques have focused on periodontal soft tissue applications, earlier publications described their use for horizontal augmentation of mandibular posterior edentulous ridges in full-denture patients. More recently, the use of recombinant human platelet-derived growth factor (rhPDGF-BB) was tested with different bone matrices to treat maxillary anterior edentulous spans. The present case series reports the use of a subperiosteal minimally invasive aesthetic ridge augmentation technique (SMART) to treat 60 single and multiple edentulous, dentate, and implant sites on 21 patients with a follow-up period ranging from 4 to 30 months. The technique includes the use of a laparoscopic approach to deliver a growth factor/xenograft combination into a subperiosteal pouch. No flap elevation, cell-occlusive membranes, space-maintaining devices, or decortication procedures were used. The results from this case series demonstrated predictable and consistent bone regeneration. Horizontal ridge augmentation averaged 6.47 mm, which compares favorably with previously published reports. Morbidity and complication rates were consistently reduced as well. Human histology results show xenograft particles surrounded by newly formed bone. The role of the periosteum as a source of pluripotent cells in growth factor-mediated bone regeneration is discussed. Int J Periodontics Restorative Dent 2017;37:165–173. doi: 10.11607/prd.3171

Alveolar ridge deficits traditionally have been treated with surgical techniques that involve reflection of a mucoperiosteal flap. Once the area is accessed, particulate or block bone grafts are placed, with or without the use of space-maintaining devices and cell-occlusive membranes.

Because these techniques involve the reflection and advancement of a mucoperiosteal flap, there is a risk of complications that include incomplete wound closure and soft tissue dehiscences, leading to exposure of the membrane or graft material.¹ Aside from decreasing the predictability of the bone augmentation, patients may experience increased morbidity including pain, infection, swelling, and delayed healing.

The effect of these procedures on the morphology of the peri-implant soft tissues is an important consideration. The fact that esthetic outcomes in implant therapy are highly dependent on the architecture of the peri-implant soft tissues has been well established.² Furthermore, there is growing evidence that bone augmentation procedures, guided bone regeneration (GBR), and techniques that involve papillae splitting may be esthetically deleterious to the peri-implant soft tissues, frequently resulting in sequelae ranging from scar formation to disfiguring gingival defects.^{3–5}

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Minimally invasive procedures offer the potential to decrease postoperative discomfort, swelling, complications, and morbidity while preserving or enhancing soft tissue profiles. Tunneling techniques are currently advocated mainly for the treatment of mucogingival defects.⁶⁻⁸ In the past, tunneling approaches were reported for horizontal bone augmentation of mandibular posterior edentulous ridges.^{9,10} Dibart et al reported on the use of tunneling in combination with bone grafting and piezosurgical corticotomies as an adjunct to orthodontic therapy.¹¹

Nevins et al compared the use of recombinant human platelet-derived growth factor BB (rhPDGF-BB) in combination with three different particulate bone matrices in the treatment of maxillary anterior edentulous spans.¹² The purpose of this article is to present the results of a case series where flapless ridge augmentation was performed using a minimally invasive subperiosteal aesthetic ridge augmentation technique (SMART) to treat single and multiple edentulous, dentate, and implant sites.

Materials and Methods

This article reports the results of a private practice-based, prospective case series that included 60 treated sites in 21 subjects, with a postoperative observation period ranging from 4 to 30 months. Gender distribution consisted of 16 female and 5 male subjects with an age range of 17 to 65 years. Although the

SMART protocol was primarily used for bone augmentation as it relates to implant therapy, grafting was extended to adjacent areas exhibiting thin labial plates or bone dehiscences. All patients were treated by the author exclusively using the SMART method.

Subjects were examined in vivo, and their eligibility for the procedure was determined through a review of their dental history, medical history, intraoral condition, periapical radiographs, and preoperative cone beam computerized tomographs (CBCTs). Details of the surgical procedure, including risks and benefits, were explained, and signed informed consent was obtained.

Exclusion criteria included American Society of Anesthesiologists physical status III or IV, substance abuse, smoking habit within the last year, uncontrolled diabetes, radiation therapy of the jaws, bisphosphonate therapy, pregnancy, untreated periodontal disease, presence of periapical cysts or abscesses, acute infections, intraoral lesions, and gingival/mucosal tissue thickness of less than 2 mm.

In situations where gingival thickness was inadequate, patients were only included in the case series after soft tissue grafting was performed and allowed to heal for a minimum of 4 weeks. Postoperative CBCTs were taken in periods ranging from 3 months to 18 months.

Surgical Procedure

Subjects were prescribed amoxicillin 500 mg three times a day for 10

days, with instructions to start taking the medication 2 days prior to the surgical procedure. Clindamycin 300 mg three times a day was prescribed when a penicillin allergy was reported. All sites were subjected to a presurgical dental prophylaxis where calculus, biofilm, and food residue were removed.

The surgical sites were examined to verify soft tissue health and absence of inflammation on the day of the procedure. Local anesthesia was achieved using articaine hydrochloride 4% with epinephrine 1:200,000. Additionally, lidocaine 2% with epinephrine 1:50,000 was injected sparingly to enhance vasoconstriction.

One or more full-thickness vertical incisions were made in areas remotely located from the sites requiring bone grafting. These incisions were kept away from the gingival margin and sulcus. The number and location of the incisions varied depending on the extent of the area where bone augmentation was planned. A Bard-Parker #15 blade was used to cut through the gingiva, oral mucosa, and periosteum until contact with bone was made. Specially designed instruments were subsequently used to carefully elevate the full thickness of the mucosa with an intact periosteum attached to the intaglio surface. Mucoperiosteal elevation proceeded in a tunnel-like fashion until the target site for bone augmentation was accessed (Fig 1).

A subperiosteal pouch was then created that could accommodate an adequate extension and volume of the bone graft material. Every effort

was made to preserve the integrity of the periosteum throughout the procedure. Decortication or intramarrow penetration were not performed.

Anorganic bovine bone particles were mixed with rhPDGF-BB. The mixture was delivered and manipulated through the tunnel access until the bone graft material reached the defect areas. Once an adequate volume of the particulate material was in place, specially designed instruments were used to compact and shape the xenograft particles. No tenting screws, other space-making devices, or cell-occlusive membranes were used. Primary closure of the vertical incisions was achieved with single interrupted Vicryl 5-0 sutures. All patients tolerated the procedure well. An analgesic nonsteroidal anti-inflammatory (ibuprofen 800 mg every 6 hours for 2 days, and as needed for pain thereafter) and an antibacterial rinse (chlorhexidine gluconate 2% twice a day) were prescribed. An opiate analgesic (oxycodone/acetaminophen 5/325 mg) was prescribed only if necessary for pain.

The sutures were removed at periods ranging from 12 to 14 days, and the patients were seen for subsequent postoperative follow-ups 4, 6, and 10 weeks from the date of the surgical procedure.

Results

Patient-related outcomes were evaluated through a survey administered by a surgical assistant. Patients were asked to rate their

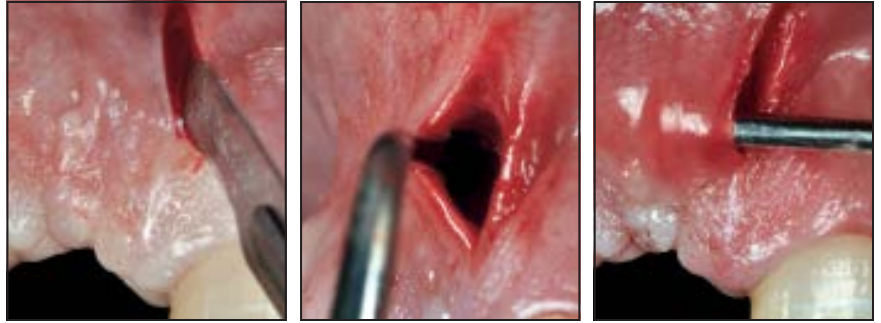


Fig 1 SMART protocol involves a remote full-thickness incision. A laparoscopic tunnel access and subperiosteal pouch must be surgically developed while preserving the integrity of the periosteum.

Table 1 Results from a Survey of Patient-Related Outcomes

| Patient-related outcomes | None (0) | Mild (1–3) | Moderate (4–6) | Severe (7–10) |
|---------------------------------|----------|------------|----------------|---------------|
| Discomfort during the procedure | 19 | 2 | 0 | 0 |
| Postoperative pain | 14 | 6 | 1 | 0 |
| Swelling | 15 | 4 | 2 | 0 |
| Total | 48 | 12 | 3 | 0 |

Subjects were asked to rate their experience using a visual analog scale ranging from 0 to 10.

degree of discomfort during the procedure, postoperative pain, and swelling using a visual analog scale ranging from none (0) to severe (10). The procedure appeared to reduce pain, swelling, and discomfort, with all patients reporting better-than-expected postoperative symptoms. Results from the survey are shown in Table 1.

Clinical outcomes were evaluated by intraoral examination and comparison of preoperative and postoperative CBCTs (Fig 2). The grafted sites healed uneventfully, and the corresponding soft tissue profiles were visibly enhanced. Minimal or no swelling was observed at the suture removal appointment. The releasing incisions healed with no complications or obvious scar formation.

A postoperative complication was observed in one patient, where particulate granules were exfoliated through a residual communication in the labial mucosa, secondary to a previous fistulous tract of endodontic origin.

Although the main treatment objectives in this case series were related to implant therapy, bone grafting was extended to include adjacent areas in situations where prominent roots with thin labial plates or bone dehiscences were present (Fig 3). A distribution analysis of the SMART-treated sites revealed that the largest percentage of procedures (70%) was performed in the anterior region. Following healing of the bone grafts, the majority of dental implants (64%) were also placed in anterior sites.

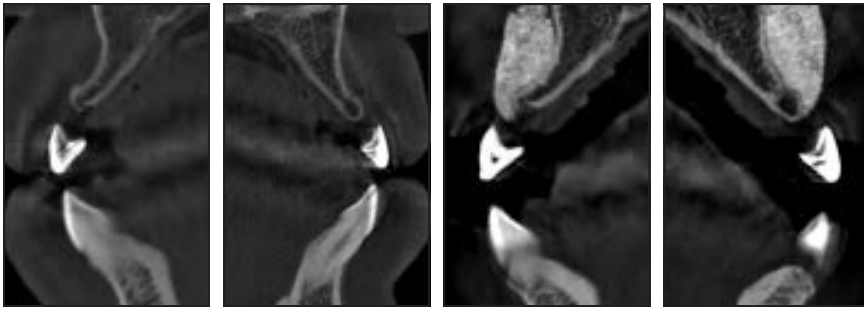


Fig 2 Patient with congenitally missing lateral incisors. SMART bone grafting was performed prior to implant placement.

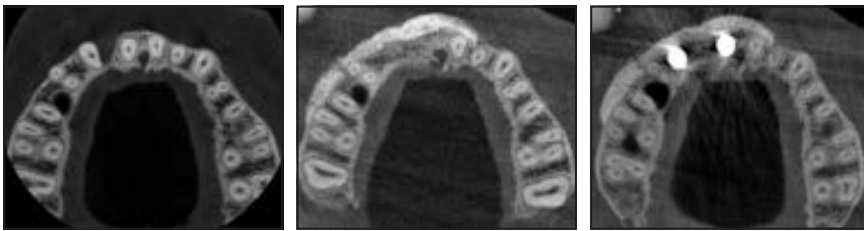


Fig 3 Treatment of an iatrogenic defect on the maxillary right incisors and canine. SMART procedure was extended to include thin/dehisced buccal plates of adjacent teeth. Implants were placed 6 months following minimally invasive bone grafting.

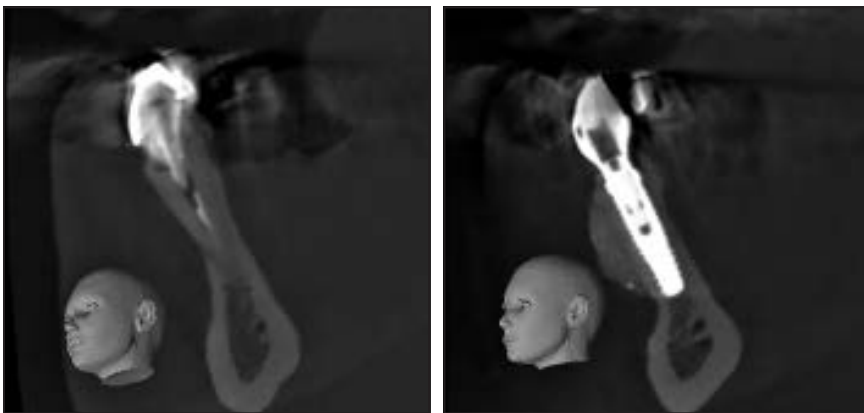


Fig 4 A mandibular right canine exhibited compromised tooth structure and thin/dehisced buccal plate. SMART bone grafting was performed simultaneously with immediate implant placement and provisionalization.

At the time of this report, implants had been placed on 25 of the grafted sites, of which 21 had been restored. The time to implant placement ranged between 4 and 6 months following the SMART procedure, except in those cases where bone augmentation was performed simultaneously with immediate implant placement (Fig 4). No implant failures were observed, and all im-

plants exhibited adequate crestal bone levels.

Five treatment categories were included in this case series as follows (Table 2):

1. Horizontal ridge augmentation of edentulous sites
2. Lateral bone augmentation prior to immediate implant placement
3. Lateral bone augmentation with simultaneous immediate implant placement
4. Bone grafting of pre-existing exposed dental implant surfaces
5. Bone grafting of teeth with thin or dehisced buccal plates

Due to the versatility of the SMART method and its potential application

in a variety of clinical situations, it was deemed more accurate to examine the clinical outcomes separately for each treatment category.

The mean gain in ridge width was calculated by measuring the dimensions at the widest point of the ridge on a sagittal cross section of each site. The presurgical and postsurgical landmarks were identified using only the most recent postoperative CBCTs whenever possible to avoid measuring errors that may result from discrepancies between cross sections on different CBCTs. The results for each treatment category are shown in Table 3. Significantly, the mean horizontal augmentation for edentulous ridges was 6.47 mm (SD 1.4). The average gain in ridge width for all treatment categories was 5.11 mm (SD 0.76).

Histology

After obtaining the appropriate patient's consent, a core was harvested from one of the augmented sites during the implant osteotomy preparation. The biopsy was taken 6 months following the SMART bone grafting procedure. The specimen was placed in 10% neutral buffered formalin and forwarded to the Hard Tissue Research Laboratory at the University of Minnesota for histologic processing.

The specimen was dehydrated, infiltrated, and embedded in resin. It was subsequently prepared following the method of Donath and Breuner and cut to a thickness of 150 μ m on an EXAKT cutting/grinding system.^{13,14} The cores were

Table 2 Distribution of Grafted Sites According to Treatment Category

| Treatment category | Sites (n) |
|--|-----------|
| (i) Horizontal ridge augmentation (edentulous sites) | 19 |
| (ii) Lateral augmentation prior to immediate implant placement | 7 |
| (iii) Lateral augmentation with simultaneous immediate implant placement | 3 |
| (iv) Bone grafting of pre-existing exposed implant surfaces | 5 |
| (v) Bone grafting of teeth with thin or dehiscid buccal plates | 26 |
| Total | 60 |

A total of 60 sites were treated in 21 patients. The SMART protocol was used to treat five different clinical scenarios in this case series.

Table 3 Mean Gain in Ridge Width by Treatment Category

| Treatment category | Mean gain in ridge width (mm) |
|--|-------------------------------|
| (i) Horizontal ridge augmentation (edentulous sites) | 6.47 \pm 1.40 |
| (ii) Lateral augmentation prior to immediate implant placement | 4.86 \pm 0.44 |
| (iii) Lateral augmentation with simultaneous immediate implant placement | 4.69 \pm 1.43 |
| (iv) Bone grafting of pre-existing exposed implant surfaces | 4.87 \pm 0.88 |
| (v) Bone grafting of teeth with thin or dehiscid buccal plates | 4.67 \pm 1.26 |
| Average for all treatment categories | 5.11 \pm 0.76 |

polished to a thickness of 45 to 65 μ m using an EXAKT microgrinding system (EXAKT Technologies). The slides were stained with Stevenel blue and van Gieson picrofuchsin for histologic analysis by means of bright field and polarized microscopic evaluation.

Figures 5, 6, and 7 show xenograft particles surrounded by bone along the buccal aspect of the specimen, which is the area where the SMART procedure was performed. Osteoid tissue is visible along many areas of the specimen.

Histomorphometric analysis was performed and the following parameters were calculated in terms of percentage of the total core area:

bone in the specimen = 50%, bone marrow or fibrous tissue = 47%, total vital bone = 100%, and nonvital residual graft material = 0%.

Discussion

Traditional GBR techniques include flap elevation and placement of a block or particulate graft in conjunction with space-maintaining devices and cell-occlusive membranes. This approach often results in complications that may increase morbidity and negatively affect the outcome of the augmentation procedure as well as the peri-implant soft tissue esthetics.

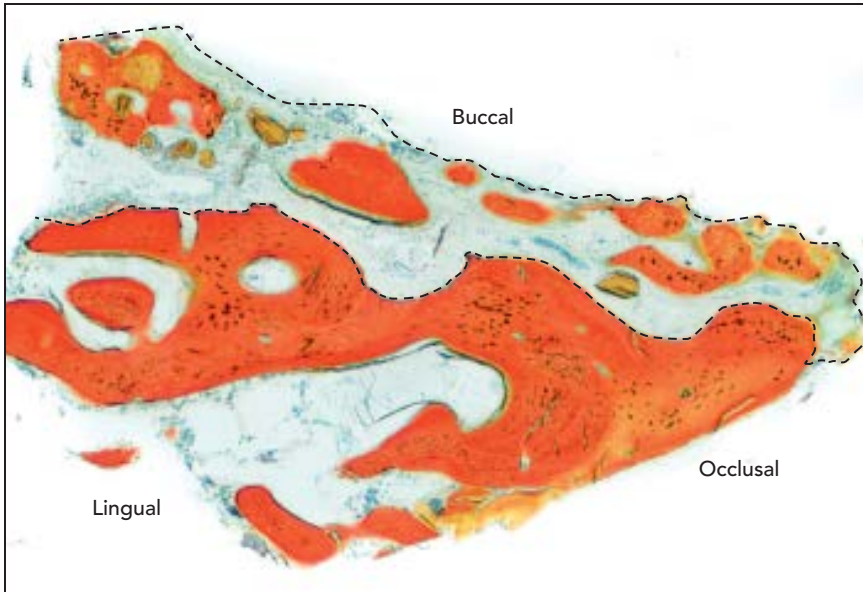


Fig 5 Histologic section encompassing the entire dimension of the human biopsy core sample. Surfaces are identified for proper orientation. SMART graft was placed on the buccal aspect, as highlighted by the dotted line.

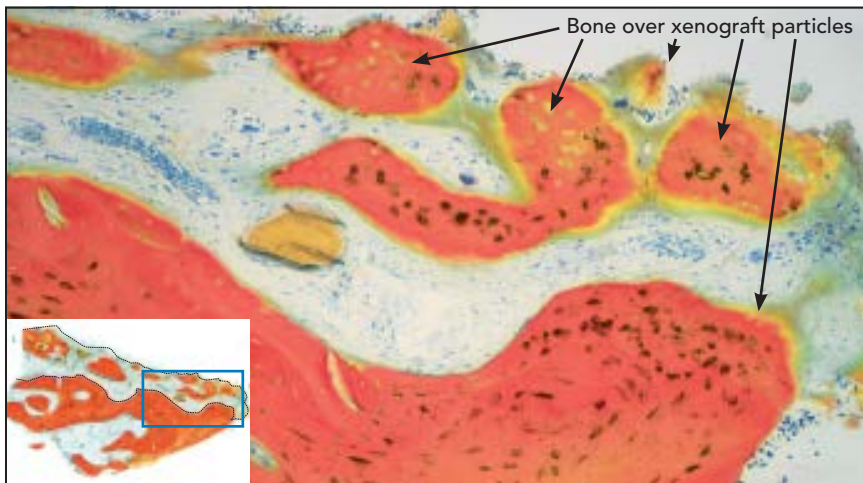


Fig 6 Photograph at higher magnification shows layer of human bone overlapping bovine-derived xenograft particles.

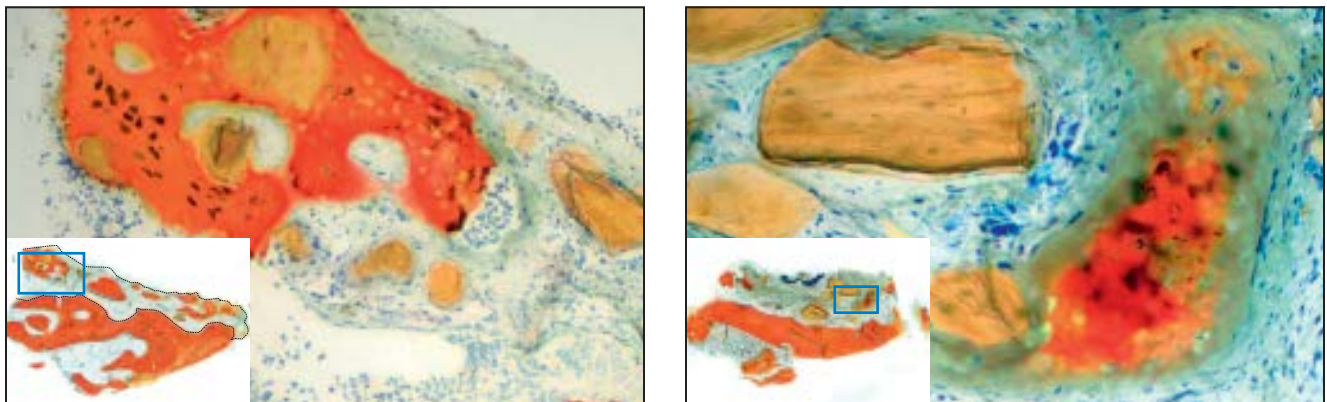


Fig 7 High-power microphotographs of different histologic sections demonstrate xenograft particles contained within newly formed bone.

Current tunneling techniques have focused primarily on the treatment of mucogingival defects.⁶⁻⁹ Early publications reported the use of tunneling approaches for horizontal augmentation of mandibular posterior edentulous ridges.^{10,11} More recently, Nevins et al used rhPDGF-BB with three different particulate bone matrices to treat maxillary anterior edentulous spans.¹²

This article reports the use of the SMART technique to treat single and multiple edentulous, dentate, and implant sites grouped into five treatment categories (Table 2). The results from this case series demonstrated predictable and consistent bone augmentation, with a reduction in morbidity and complications.

The mean horizontal augmentation of edentulous ridges using the SMART method was 6.47 mm (SD 1.40). This compares favorably with outcomes reported by Urban et al in 2013, where the average lateral ridge augmentation was 5.68 mm in a group of 25 patients treated with a collagen membrane in combination with particulate autogenous and anorganic bovine bone-derived mineral.¹⁵ Previously, Proussaefs and Lozada in 2006¹⁶ and Pieri et al in 2008¹⁷ reported mean horizontal augmentation of 4.47 mm and 4.16 mm respectively, using a titanium mesh with a combination of autogenous and anorganic bovine bone particles. In 2008, Hammerle et al published the results of 12 cases treated with bioresorbable membranes and deproteinized bovine bone blocks and particles. The mean increase in crestal bone width reported was 3.7 mm.¹⁸

Clearly, a greater increase in horizontal ridge width is to be expected following the augmentation of deficient edentulous ridges than in situations where bone grafting is performed lateral to an existing tooth or implant. Nevertheless, the average horizontal augmentation achieved with the SMART method was 5.11 mm (SD 0.76) for all treatment categories.

Tenting screws or other space-maintaining devices were not used in the present case series. The degree of horizontal augmentation achieved was a function of the ability to establish the confines of the subperiosteal pouch, so that the bulk of the particulate graft material is contained within, causing the mucosa to distend labially as the graft particles are delivered and condensed into place. A concern was that excessive tension on the mucosa may lead to a dehiscence and exposure of the graft. For this reason, only sites with a minimum gingival/mucosal tissue thickness of 2 mm were included. Sites that did not meet this criteria were treated with a soft tissue graft prior to the bone augmentation procedure.

Another departure from the traditional GBR technique involved the exclusion of cell-occlusive membranes. This was a result of a pilot study conducted by the present author that demonstrated technical difficulties in containing the particulate material within the confines of the membrane. The excess graft material, however, proceeded to mineralize even though it was not covered by the cell-occlusive membrane. The observations from the

pilot study resulted in a decision not to use barrier membranes in the SMART case series.

The results from 60 treated sites clearly demonstrate consistent bone regeneration without the use of membranes. Consequently, the role of the periosteum as a potential source of osteoprogenitor cells in growth factor-mediated bone-regenerative procedures must be considered.

Simion et al reported superior regenerative results using a PDGF-infused xenograft block without membrane placement.^{19,20} Similar findings have also been reported in studies where bone morphogenetic protein-2 was used without barrier membranes.²¹⁻²³

Current knowledge suggests that the periosteum contains a population of progenitor cells that mediate the repair of bone defects.²⁴ The osteoinductive potential of the periosteum as a source of undifferentiated mesenchymal cells in bone repair also has been reported.²⁵⁻²⁸

An experiment designed to investigate cell-related differences in bone formation on autologous fibrin and BMP-2 stimulation demonstrated 26.9% newly formed bone when using bone marrow mesenchymal stem cells, 41.1% when using alveolar bone cells, and 58.2% when using periosteal cells. These results suggest that periosteal cells may be the best choice for enhancing bone formation in tissue engineering bone regeneration applications.²⁹

More recently, Ceccarelli et al reported on the capacity of human periosteal cells to exhibit stem cell behavior, demonstrating their ability

to undergo osteoblastic differentiation without osteogenic induction. These results suggest that oral periosteal cells may be more suitable for oral bone regeneration tissue engineering than bone marrow mesenchymal cells.³⁰

Since no decortication or intramarrow penetration were performed in the present case series, the bone regeneration observed may have originated from a growth factor-mediated activation and differentiation of pluripotent cells most likely residing in the cambial layer of the periosteum.

Controlling the dispersion of the graft particles is technique sensitive and may result in irregular augmentation patterns. However, although the particles were visible radiographically they were not associated with any negative biologic or clinical effects. Ongoing development of SMART-specific instrumentation, biomaterials, and alternative growth factors may help resolve current challenges and provide solutions for additional clinical applications.

Conclusions

The SMART method is a disruptive technology with the potential to affect jaw bone grafting procedures by substantially replacing the use of traditional GBR procedures. It offers increased predictability and consistently augmented bone volumes while avoiding the soft tissue disfigurements, complications, and morbidity associated with flap techniques. The SMART method does

not require the use of membranes, tenting screws, or decortication.

The learning curve is faster than in traditional GBR techniques, with the potential for an increased rate of adoption due to its more general appeal and wide variety of applications. Nevertheless, competent training and development of surgical skills, as well as the use of appropriate instrumentation and biomaterials, are essential for successful outcomes.

Further research is required to better understand the role of the periosteum in growth factor-mediated bone regeneration and monitor the long-term stability of clinical outcomes achieved with the SMART method.

Acknowledgments

“Subperiosteal Minimally Invasive Aesthetic Ridge Augmentation Technique” and “SMART” are trademarks of the author, and the methods and devices used in connection with the methods are the subject of one or more pending patent applications. The author reported no conflicts of interest related to this study.

References

1. Jensen AT, Jensen SS, Worsaae N. Complications related to bone augmentation procedures of localized defects in the alveolar ridge. A retrospective clinical study. *Oral Maxillofac Surg* 2016;20:115–122.
2. Fürhauser R, Florescu D, Benesch T, Haas R, Mailath G, Watzek G. Evaluation of soft tissue around single-tooth implant crowns: The pink esthetic score. *Clin Oral Implants Res* 2005;16:639–644.
3. Santing HJ, Raghoebar GM, Vissink A, den Hartog L, Meijer HJ. Performance of the Straumann bone level implant system for anterior single-tooth replacements in augmented and nonaugmented sites: A prospective cohort study with 60 consecutive patients. *Clin Oral Implants Res* 2013;24:941–948.
4. Cosyn J, Eghbali A, Hanselaer L, et al. Four modalities of single implant treatment in the anterior maxilla: A clinical, radiographic, and aesthetic evaluation. *Clin Implant Dent Relat Res* 2013;15:517–530.
5. Cosyn J, Sabzevar MM, De Bruyn H. Predictors of inter-proximal and midfacial recession following single implant treatment in the anterior maxilla: A multivariate analysis. *J Clin Periodontol* 2012;39:895–903.
6. Blanes RJ, Allen EP. The bilateral pedicle flap-tunnel technique: A new approach to cover connective tissue grafts. *Int J Periodontics Restorative Dent* 1999;19:471–479.
7. Zabalegui I, Sicilia A, Cambra J, Gil J, Sanz M. Treatment of multiple adjacent gingival recessions with the tunnel subepithelial connective tissue graft: A clinical report. *Int J Periodontics Restorative Dent* 1999;19:199–206.
8. Zadeh HH. Minimally invasive treatment of maxillary anterior gingival recession defects by vestibular incision subperiosteal tunnel access and platelet-derived growth factor BB. *Int J Periodontics Restorative Dent* 2011;31:653–660.
9. Block MS, Kent JN, Ardoin RC, Davenport W. Mandibular augmentation in dogs with hydroxylapatite combined with demineralized bone. *J Oral Maxillofac Surg* 1987;45:414–420.
10. Hasson O. Augmentation of deficient lateral alveolar ridge using the subperiosteal tunneling dissection approach. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;103:e14–e19.
11. Dibart S, Sebaoun JD, Surmenian J. Piezocision. A minimally invasive, periodontally accelerated orthodontic tooth movement procedure. *Compend Contin Educ Dent* 2009;30:342–350.
12. Nevins ML, Camelo M, Nevins M, et al. Minimally invasive alveolar ridge augmentation procedure (tunneling technique) using rhPDGF-BB in combination with three matrices: A case series. *Int J Periodontics Restorative Dent* 2009;29:371–383.

13. Rohrer MD, Schubert CC. The cutting-grinding technique for histological preparation of undecalcified bone and bone-anchored implants: Improvement in instrumentation and procedures. *Oral Surg Oral Med Oral Pathol* 1992;74:73–78.
14. Donath K, Breuner G. A method for the study of undecalcified bones and teeth with the attached soft tissues: The Säge Schliff (sawing and grinding) technique. *J Oral Pathol* 1982;11:318–326.
15. Urban IA, Nagursky H, Lozada JL, Nagy K. Horizontal ridge augmentation with a collagen membrane and a combination of particulated autogenous bone and anorganic bovine bone-derived mineral: A prospective case series in 25 patients. *Int J Periodontics Restorative Dent* 2013;33:299–307.
16. Proussaefs P, Lozada J. Use of titanium mesh for staged localized alveolar ridge augmentation: Clinical and histologic-histomorphometric evaluation. *J Oral Implantol* 2006;32:237–247.
17. Pieri F, Corinaldesi G, Fini M, Aldini NN, Giardino R, Marchetti C. Alveolar ridge augmentation with titanium mesh and a combination of autogenous bone and anorganic bovine bone: A 2-year prospective study. *J Periodontol* 2008;79:2093–2103.
18. Hämmerle CHF, Jung RE, Yaman D, Lang NP. Ridge augmentation by applying bioresorbable membranes and deproteinized bovine bone mineral: A report of twelve consecutive cases. *Clin Oral Implants Res* 2008;19:19–25.
19. Simion M, Rocchietta I, Kim D, Nevins M, Fiorellini J. Vertical ridge augmentation by means of deproteinized bovine bone block and recombinant human platelet-derived growth factor-BB: A histologic study in a dog model. *Int J Periodontics Restorative Dent* 2006;26:415–423.
20. Simion M, Rocchietta I, Dellavia C. Three-dimensional ridge augmentation with xenograft and recombinant human platelet-derived growth factor-BB in humans: Report of two cases. *Int J Periodontics Restorative Dent* 2007;27:109–115.
21. Miranda DA, Blumenthal NM, Sorensen RG, Wozney JM, Wikesjö UM. Evaluation of recombinant human bone morphogenetic protein-2 on the repair of alveolar ridge defects in baboons. *J Periodontol* 2005;76:210–220.
22. Barboza EP, Duarte ME, Geolas L, Sorensen RG, Riedel GE, Wikesjö UM. Ridge augmentation following implantation of recombinant human bone morphogenetic protein-2 in the dog. *J Periodontol* 2000;71:488–496.
23. Fiorellini JP, Howell TH, Cochran D, et al. Randomized study evaluating recombinant human bone morphogenetic protein-2 for extraction socket augmentation. *J Periodontol* 2005;76:605–613.
24. Hutmacher DW, Sittinger M. Periosteal cells in bone tissue engineering. *Tissue Eng* 2003;9(suppl 1):S45–S64.
25. Allen MR, Hock JM, Burr DB. Periosteum: Biology, regulation, and response to osteoporosis therapies. *Bone* 2004;35:1003–1012.
26. Kanou M, Ueno T, Kagawa T, et al. Osteogenic potential of primed periosteum graft in the rat calvarial model. *Ann Plast Surg* 2005;54:71–78.
27. Malizos KN, Papatheodorou LK. The healing potential of the periosteum molecular aspects. *Injury* 2005;36(suppl 3):s13–s19.
28. Roberts SJ, Geris L, Kerckhofs G, Desmet E, Schrooten J, Luyten FP. The combined bone forming capacity of human periosteal derived cells and calcium phosphates. *Biomaterials* 2011;32:4393–4405.
29. Zhu SJ, Choi BH, Huh JY, Jung JH, Kim BY, Lee SH. A comparative qualitative histological analysis of tissue-engineered bone using bone marrow mesenchymal stem cells, alveolar bone cells, and periosteal cells. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;101:164–169.
30. Ceccarelli G, Graziano A, Benedetti L, et al. Osteogenic potential of human oral-periosteal cells (PCs) isolated from different oral origin: an in vitro study. *J Cell Physiol* 2016;231:607–612.