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Platelet-Derived Growth Factor Applications in Periodontal and Peri-Implant Bone Regeneration

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Abstract

Introduction—Achieving successful tissue regeneration following traditional therapeutic protocols, combining bone grafts and barrier membranes, may be challenging in certain clinical scenarios. A deeper understanding of periodontal and peri-implant wound healing and recent advances in the field of tissue engineering have enabled clinicians with novel means to obtain predictable clinical outcomes. The use of growth factors such as recombinant human platelet-derived growth factor-BB (rhPDGF) with biocompatible matrices to promote tissue regeneration represents a promising approach in the disciplines of periodontology and implantology.

Areas covered—This review covers the basic principles of bone and periodontal regeneration, and provides overview of the biology of PDGF and its potential to predictably and reproducibly promote bone regeneration in regular clinical practice. The results of preclinical and clinical human studies evaluating the effectiveness of growth factor-enhanced matrices are analyzed and discussed.

Expert opinion—Current available evidence supports the use of rhPDGF-enhanced matrices to promote periodontal and peri-implant bone regeneration.

Keywords

Regenerative medicine; platelet-derived growth factor; periodontal regeneration/periodontal diseases; dental implants

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Declaration of interest

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A. INTRODUCTION

Clinicians are frequently faced with the challenge of treating patients with significant alveolar bone loss due to periodontal disease, congenital abnormalities, tumors, traumatic injury, or resorption secondary to tooth loss. Conventional treatment procedures may be ineffective in achieving bone regeneration, leaving both the clinician and the patient dissatisfied with the outcome. Growth factors (GFs) have long been believed to have the potential to accelerate the healing process and, therefore, enhance tissue regeneration in challenging clinical scenarios.

GFs are natural biological mediators that regulate key cellular events that are part of the process of tissue repair and regeneration. After binding of GFs to specific cell membrane receptors of target cells, intracellular signaling pathways are induced, which typically results in the activation of genes that may ultimately change cellular activity and phenotype. However, the effect of each GF is regulated through a complex system of feedback loops, which involve other GFs, enzymes, and binding proteins. Recent advances in the areas of cellular and molecular biology allowed better understanding of the functions of GFs and their participation in the different phases of wound healing. *In vitro* and *in vivo* studies have confirmed that GFs can enhance the capacity of tissues to regenerate by regulating cell chemoattraction, differentiation and proliferation.[1, 2]

One of the most extensively studied GFs is platelet-derived growth factor (PDGF). This growth factor has been well characterized and has broad wound healing activities in both hard (bone) and soft (skin, gingival) tissue. Recently, a combination of purified recombinant human PDGF (rhPDGF) with synthetic ceramic matrices (beta-tricalcium phosphate [β-TCP]) has been proposed as a periodontal regenerative agent. The efficacy of growth factor-enhanced matrices in periodontal therapies has been rigorously examined in a variety of preclinical animal models and long-term human clinical studies. The results of these studies will be discussed in this review, along with the potential for PDGF-enhanced matrices to predictably and reproducibly promote bone regeneration in clinical practice.

B. OSSEOUS REGENERATION

B.1. Bone Grafting

A variety of biologic and synthetic materials to augment existing bone and enhance bone regeneration are available to clinical practitioners. Autogenous bone grafting has been traditionally considered the gold standard for treating bone defects or deficiencies. The clinical benefits derived from the use of autogenous bone grafts are primarily due to 1) the presence of osteoblasts and osteoprogenitor cells within the graft; 2) release of naturally occurring GFs and other biochemical mediators; and 3) the osteoconductive nature of the substrate itself. Autogenous grafts may be obtained from intraoral sites such as the mandibular symphysis or the ascending ramus, or may be harvested from extraoral sites such as the iliac crest or the proximal tibia.[3] However, the use of autogenous bone grafts may also involve a series of disadvantages, such as limited availability and increased morbidity associated with a second surgical site.

When autogenous bone is not readily available, alternative bone sources can be utilized. Tissue matrices, including allogenic, xenogenic and synthetic graft materials are available for use. These bone substitutes function primarily by passively guiding or “conducting” cell migration through the matrix, eventually leading to repair of the defect. These materials may be used alone, in combination with autogenous grafts or in combination with titanium meshes, barrier membranes, or other passive materials designed to act as a physical guide or cell-occlusive element.[4] While these options are useful for maintaining space and a

framework for tissue deposition during the process of bone regeneration, results obtained with passive therapeutic matrices have been variable, depending upon their inherent physical and chemical properties as well as the patient's individual healing response.[5, 6]

B.2. Tissue Engineering Approaches for Bone Regeneration

Novel tissue engineering techniques have been recently developed to regenerate bone in challenging defect sites, where spontaneous repair is not achievable.[7] On a fundamental level, bone tissue engineering involves supplying four basic elements required for bone formation to the defect site: adequate blood supply, bone forming cells, scaffolds or matrices, and signaling molecules, such as GFs (Figure 1). Osteoblasts or bone precursor cells may be provided by direct scaffold seeding (*in vitro* tissue engineering) or they may be induced by biochemical mediators to migrate into the scaffold from the marginal host bone (*in vivo* tissue engineering). Scaffolds provide a foundation to support cell attachment and proliferation in the defect site, and facilitate blood clot stabilization, which additionally prevents tissue collapse, all essential events in the initial stages of healing regenerative processes.[8] Some scaffold materials used in bone regeneration are collagen, autogenous or allograft bone, resorbable polymers and porous calcium phosphate ceramics. GFs serve to stimulate native cell migration into the defect site and increase proliferation of these cells to populate the scaffold through specific chemotactic and mitogenic signals. Different scaffold materials (naturally-derived and synthetic) are available which are biocompatible with GFs and through their use, enable the delivery of GFs to different sites. With newer bioengineered materials, GFs can be incorporated directly into the scaffold and their release from these materials controlled over a predetermined period of time.[9] This mechanism of action contrasts with bone morphogenetic proteins (BMPs), which primarily exert their effect through osteoinduction (stimulating differentiation of mesenchymal cells into bone forming cells).[10, 11]

C. PDGF FOR BONE REGENERATION IN PERIODONTAL AND PERI-IMPLANT SITES

GFs and BMPs have been the focus of considerable attention in recent years by dental and orthopedic researchers.[12, 13] These biological molecules offer the possibility of using biomaterials that are readily available for the clinician to attempt bone regeneration in a controlled, predictable manner. While a considerable number of bone GFs and morphogens have been identified, one of the most extensively characterized growth factors for clinical applications is PDGF.

In the late 1980's, Lynch and co-workers first discovered in an animal study that PDGF promotes regeneration of periodontal tissues including bone, cementum and periodontal ligament.[14] Since then, numerous studies have been published providing a deeper understanding of the mechanism of action and therapeutic potential of this molecular mediator. PDGF is a naturally occurring protein that is found abundantly in the bone matrix in at least three different forms: PDGF-AA, PDGF-AB and PDGF-BB.[15] This GF is locally released by blood platelets during clotting following soft or hard tissue injury.[16] Once it is released from the platelets, PDGF binds to specific cell surface receptors promoting rapid cell migration (chemotaxis), and proliferation (mitogenesis), in the area of injury.[17] *In vitro and in vivo* studies have demonstrated that PDGF is a potent chemotactic and mitogenic factor for gingival and periodontal ligament fibroblasts, cementoblasts and osteoblasts.[14, 18–20]

While growth factor proteins have been shown to be potent stimulators of wound repair, the ability to utilize concentrated forms of these proteins contained within blood platelets for

routine oral surgical treatment was not introduced until 1998, when Marx and co-workers proposed the use of autologous platelet concentrates.[21] The preparation of platelet concentrates consists of isolating the platelets naturally present in whole autologous blood by a selective process of centrifugation, and subsequently activating them to release their growth factor content, including super-physiologic concentrations of PDGF, TGF-β and IGF-I, among others.[22] These factors are directly applied to the treatment site in order to promote tissue regeneration or repair. Thrombin/calcium preparations initiate clotting, including the conversion of fibrinogen to fibrin, resulting in a clinically useful platelet rich plasma (PRP) gel that can additionally improve the handling and efficacy of particulate autografts and bone substitutes. A variety of protocols to produce platelet concentrates have been described to date. However, studies evaluating the effect of platelet gel concentrates alone, or in combination with osteoconductive matrices, on graft maturity, bone density, and new bone formation in a number of different clinical applications have demonstrated somewhat variable outcomes ranging from excellent results in some studies to no apparent benefit in others.[23] The differences in outcomes are thought to be a result in variability in platelet concentration as well as individual patient healing responses. In summary, platelet concentrates provide good handling characteristics alone or in combination with a variety of matrices, however with the primary disadvantage of the technique being the need to obtain blood from the patient and lack of a predictable response following treatment according to current evidence.[23]

To overcome some of these limitations other therapeutic approaches have been developed. Advances in recombinant technology have lead to the synthesis of proteins in a controlled manner, which in turn enables production of concentrated and purified molecules in large quantities. This has led to the development and commercialization of recombinant growth factor/matrix combination products. Combination products represent an emerging new trend in regenerative therapeutics and have gained increasing attention as a strategy to optimize tissue regeneration. These products synergize tissue specific matrices with highly concentrated bioactive proteins to actively recruit progenitor cells for the treatment of tissue deficiencies. The ability to combine highly concentrated forms of signaling proteins with scaffolds has enabled clinical researchers to develop improved regenerative products taking advantage of the physical and chemical characteristics required for specific cell attachment, growth and differentiation.

Recombinant human platelet-derived growth factor (rh-PDGF) was the first recombinant protein to be approved by the US Food and Drug Administration for treatment of chronic foot ulcers in diabetic patients (Regranex, Ethicon Inc. Somerville, NJ).[24, 25] Widespread use in this application has established the safety and effectiveness of PDGF for soft tissue regeneration.[26] Additionally, rhPDGF for bone regeneration has been rigorously tested in preclinical studies, which indicate that PDGF has the potential to be used to direct and control bone regeneration in humans. For example, a tibial osteotomy study using PDGF in rabbits demonstrated that this protein substantially increased the rate of fracture repair as compared to untreated control sites.[27] In addition, the biomechanical strength of the repair tissue in rhPDGF treated animals was not significantly different from un-operated normal intact bone. Furthermore, when PDGF was injected subperiosteally in long bones, it induced intramembranous bone formation.[28] In a detailed study in osteoporotic animals involving dual-energy x-ray absorptiometry (DEXA) bone density scans, quantitative computed tomography scans, biomechanical testing and histological analyses, periodic systemic injection of rhPDGF substantially increased bone density in the long bones and in the spine.[29]

C.1. Preclinical Studies Using PDGF for Periodontal and Peri-implant Regeneration

In order to evaluate the potential and safety of this therapy, extensive *in vivo* preclincal studies have been performed using PDGF alone or in combination with other GFs such as insulin-like growth factor (IGF) to treat periodontal and peri-implant defects. In a previously mentioned study, Lynch and co-workers first published evidence of the regenerative potential of PDGF-BB when used to treat naturally occurring periodontal defects in dogs.[14] Most notably, this study showed increased cellular activity after treatment with PDGF-BB, leading to increased bone, cementum and periodontal ligament regeneration. In the related study examining its use around dental implants, direct application of an rhPDGF/IGF mixture into implant sites in dogs produced a two to three times increase in the number of peri-implant spaces filled with bone at early time points.[30] Promising results were also seen in immediate extraction socket implants treated with polytetrafluoroethylene (PTFE) membranes and PDGF/IGF. Bone density and bone-to-implant contact were increased twofold for the growth factor treated sites, as compared to the membrane alone or membranes combined with bone grafts.[31] These early studies were instrumental in establishing preclinical evidence for the potential of PDGF treatment in not only periodontal, but also peri-implant sites.

The adjunctive effect of rhPDGF therapy for implant site development indications has also been investigated in animal models. Simion and co-workers conducted an animal study to investigate the outcomes of vertical bone augmentation following the application of rhPDGF-BB.[32] Bilateral severe bone defects were surgically created in the mandibles foxhound dogs and three months later, each of the defects was treated following one of these three augmentation protocols: 1. Anorganic bovine bone blocks covered with a collagen membrane, 2. Anorganic bovine bone blocks infused with rhPDGF-BB, or 3. Anorganic bovine bone blocks infused with rhPDGF-BB covered with a collagen membrane. In all cases, anorganic bovine bone blocks were secured using two titanium dental implants. At four months the results were more favorable for the group that included the blocks with rhPDGF-BB, illustrating the importance of the periosteal blood supply in the outcomes of GF therapy. This study demonstrated that the rhPDGF-BB infused matrix significantly enhanced bone formation and gingival healing in large, critical size alveolar bone defects. Radiographic and histological analysis indicated that the greatest bone regeneration occurred for the rhPDGF-BB infused graft block without the collagen membrane (Figure 2). Unlike traditional guided bone regeneration procedures, the membrane appeared to block the migration of bone forming cells into the scaffold. Histological analysis indicated that bone formation occurred from both the coronal and apical surfaces of the rhPDGF-BB treated graft, suggesting that osteoblasts and other bone-forming precursor cells were recruited into the graft from both the superior (coronal, periosteal surface) and the inferior (apical, marrow spaces) boundaries. Additionally, bone growth appeared more robust from the periosteal surface when compared to the bone formation observed at the original osseous crest. According to these results, rhPDGF-BB may have exerted a potent chemotactic effect on osteogenic cells present in the periostium, when a barrier membrane was not placed.

In addition to applications of PDGF in vertical ridge augmentation procedures, preclinical studies by Schwarz and coworkers recently evaluated early healing outcomes following horizontal ridge augmentation.[33] Bilateral mandibular surgically created defects were treated with either beta-tricalcium phosphate (β−TCP) covered with a collagen membrane (CM) or a combination of β−TCP and CM plus rhPDGF-BB, following a split-mouth design. The results of this study revealed that the group containing rhPDGF-BB showed better results in terms of mineralized tissue and total augmented area at 3 weeks. Taken together, the promising preclinical evidence of PDGF therapy in periodontal, peri-implant, and bone augmentation indications established the foundation for therapeutic evaluation of PDGF in clinical applications

C.2. Clinical Studies Using PDGF for Periodontal and Peri-implant Regeneration

The use of rhPDGF for dental implant site development (i.e. sinus augmentation)[34], horizontal bone augmentation[35] and ridge preservation[36] has been investigated in human studies, however the primary focus of clinical studies using this agent has been in periodontal and peri-implant regenerative indications.[48]

An early human clinical trial to evaluate the effect of rhPDGF/IGF treatment applied to osseous periodontal defects was reported by Howell and co-workers.[37] The experimental sites received direct application of the GFs contained in a methylcellulose matrix to improve retention. A statistically significant increase in alveolar bone formation was seen in the growth factor treated sites at nine months post-operatively, as compared to untreated control sites. Average bone height for the PDGF/IGF group was 2.08 mm and 43.2 % osseous defect fill was achieved, as compared to 0.75 mm new bone height and 18.5% fill in the control sites.

Based on the principles of tissue engineering, the use of a growth factor enhanced matrix for periodontal regeneration consisting of rhPDGF-BB in combination with an osteoconductive scaffold (i.e., autograft, allograft, xenograft, or a synthetic matrix, such as beta-TCP) was proposed.[38] The rationale underlying this approach is that PDGF stimulates angiogenesis, promotes cell migration into the bone defect from the surrounding tissue margins, and upregulates cell proliferation.[39] The matrix, in addition to its role as a growth factor delivery vehicle, provides mechanical support for migrating cells and contributes to the formation of new bone, cementum and/or periodontal ligament.

Early human clinical studies utilized rhPDGF-BB combined with bone allograft. In one of these studies the effectiveness of rhPDGF-BB treatment for extensive interproximal intrabony defects and Class II furcation lesions associated with advanced periodontitis was evaluated.[40, 41] Surgical procedures involved full-thickness flap reflection, thorough debridement of the defect site, and subsequent filling of the defect with demineralized freeze-dried bone allograft (DFDBA) presoaked in a solution containing rhPDGF-BB at three different concentrations (0.5, 1.0 or 5.0 mg/mL). Control defect sites were filled with commercially available anorganic bovine bone in collagen (Figure 3). Clinical probing depths and attachment levels were assessed at periodic intervals up to nine months post-operatively, at which time the treated teeth were removed en bloc for histological analysis. The study results indicated that substantial improvements in vertical and horizontal probing depths over baseline levels were achieved for all sites treated with rhPDGF-BB. Histological evaluation revealed robust periodontal regeneration in the rhPDGF-BB sites, including new bone, cementum and periodontal ligament formation (Figure 3). Statistical analysis indicated that rhPDGF-BB combined with allograft bone produced robust regeneration and improved gingival attachment in interproximal bone defects and Class II furcation defects, compared to baseline. Comparisons among doses indicated that there were no adverse reactions, even at the highest dose, indicating that rhPDGF-BB was well tolerated in periodontal defect sites. Important to note is that this was the first study reporting clear histological evidence of periodontal regeneration for human Class II furcation defects using this approach.[41] The regenerative effects of rhPDGF in combination with mineralized freeze dried bone allograft have been further documented clinically in a case study reported by Nevins and co-workers.[42] Two patients presenting with extremely severe bone loss (teeth with a poor to hopeless prognosis) and requiring surgical bone grafting were treated with rhPDGF-BB enhanced mineralized allograft. Defect sites were treated with freeze-dried bone allograft saturated with rhPDGF-BB at a concentration of 0.3 (Case 1) or 1.0 mg/mL (Case 2). The growth factor-enhanced matrix was packed into the defect and an absorbable barrier membrane was placed over the defect prior to soft tissue closure. Patients were followed for six months, at which time a surgical re-entry procedure was performed to evaluate the healing response

within these previously severe defects. Both patients in this limited study exhibited excellent soft tissue healing. At six months, probing depths for both patients were 3 mm and gingival recession was 0 mm and 3 mm for Case 1 and Case 2, respectively. The gains in clinical attachment level relative to baseline were 7 mm and 2 mm for Case 1 and Case 2, respectively. No adverse effects associated with either rhPDGF-BB dose were observed. Radiographic findings of excellent bone fill at six months for both patients were confirmed upon surgical reentry of the treated sites. These results demonstrate that rhPDGF-BB combined with freeze-dried bone allograft provides an effective treatment for severe periodontal bone loss.

An alternative to an allograft is the use of a completely synthetic growth factor enhanced matrix system. rhPDGF-BB has been combined with β−tricalcium phosphate (β-TCP), a well-established resorbable ceramic biomaterial commonly used in oral reconstructive surgery. The results of a large, multicenter clinical trial evaluating the effectiveness of rhPDGF-BB combined with a porous β-TCP matrix have been recently reported.[43] This study included 180 participants with one interproximal periodontal defect 4 mm or deeper after debridement. Other noteworthy inclusion criteria included a baseline probing depth of 7 mm or greater, sufficient keratinized gingiva to allow complete coverage of the defect, radiographic defect base at least 3 mm coronal to the apex of the tooth, and no evidence of localized aggressive periodontitis. Grade I and Grade II furcation defects were acceptable for inclusion in the study. Smokers who consumed up to one pack per day were also included in the study. Three treatment groups were evaluated: 1) β-TCP plus 0.3 mg/ml rhPDGF-BB (Group I), 2) β-TCP plus 1.0 mg/ml rhPDGF-BB (Group II), and 3) β-TCP plus buffer alone (Group III). Defects were classified as 1-wall, 2-wall or 3-wall / circumferential, indicating the extent of involvement and severity. At the time of surgery, β-TCP granules were saturated with rhPDGF-BB before the graft was placed in the defect site. Patients were followed for a period of six months and outcome measures included evaluation of soft tissue changes and assessment of bone growth. Safety was monitored throughout the trial by assessing the frequency and severity of clinical and/or radiographic adverse events.

Excellent healing was observed for all defects treated with rhPDGF-BB. The study results demonstrated that there was a significantly greater clinical attachment level gain at three months for the 0.3 mg/ml rhPDGF-BB (Group I), as compared to the β-TCP controls (Group III), indicating an early benefit of rhPDGF-BB treatment. At six months, the clinical attachment level gain for the lower rhPDGF-BB concentration group continued to be greater than the control group, although statistical significance was not achieved. Additionally, rhPDGF-BB treatment resulted in significantly less gingival recession at three months, as compared to the untreated control group. This difference was no longer apparent at six months, however, as the control group exhibited a slight gain in gingival height over time. Increasing the rhPDGF-BB concentration appeared to reduce the effectiveness of the growth factor-enhanced matrix. No statistically significant differences were observed in clinical attachment level or gingival recession for the higher rhPDGF-BB concentration (Group II), as compared to the β-TCP controls. Radiographic assessment revealed that bone fill was significantly increased at six months for the lower rhPDGF-BB concentration, as compared to both the higher rhPDGF-BB concentration and the control group (Figure 4). A subgroup analysis further indicated that rhPDGF-BB treatment improved bone fill in smokers and for all defect types (1, 2, 3 wall and circumferential) (Figure 5). Similarly, linear bone growth was also significantly greater for Group I, as compared to Groups II and III. No significant differences were observed in the number or severity of adverse events among the three groups, indicating that both rhPDGF-BB and the β-TCP matrix were safe and adequately tolerated in the defect site. The results of this study demonstrate that the use of rhPDGF-BB

in combination with a synthetic β-TCP matrix accelerates the rate of bone regeneration and improves bone fill and clinical attachment level in surgically treated periodontal defects.

These positive outcomes were maintained over time as reported in a patient case series.[44] Four patients, selected from centers participating in the original pivotal clinical trial, exhibited significantly enhanced results for sites treated with 0.3 mg/ml rhPDGF and β-TCP in a long-term (24 month) evaluation. These results remained significantly improved over results observed for the β-TCP control group (Figure 6).

Placing these clinical results in perspective, the use of 0.3 mg/ml rhPDGF and β-TCP for the treatment of periodontal defects compares very favorably to existing FDA approved treatments in terms of clinical attachment level gain and bone fill. This therapeutic approach significantly improved both clinical soft tissue and radiographic measures, as compared to the control group. The superior results for the lower dose suggest that there may be an optimum level of rhPDGF required to effectively stimulate a cellular response that leads to regeneration in periodontal defects. This observation emphasizes the need for rigorous clinical studies of new growth factor therapies, including systematic examination of dose effects.

Though delivery of rhPDGF has shown clinical efficacy in the treatment of intrabony defects, it has also been examined for the treatment of soft tissue recession defects. In a case series study conducted by McGuire and colleagues,[45] seven subjects presenting contralateral > 3 mm-deep recession defects (Miller Class I and II) receive two different types of treatment in a split-mouth design. Test therapy consisted of a combination of rhPDGF/β-TCP and a collagen membrane. The control treatment applied was the gold standard for root coverage: the subepithelial connective tissue graft (CTG). Healing was evaluated at 8, 16, and 24 weeks following the interventions. Primary outcome measure was recession depth. Results indicated a favorable tissue response to the test therapy, with comparable clinical outcomes to CTG in terms of root coverage and keratinized tissue width.

In a later publication, McGuire and co-workers reported histologic and microtomographic findings following analysis of human *en-block* samples of teeth that received either CTG or a combination of rhPDGF/β-TCP and a wound healing dressing.[46] Two patients requiring the extraction of a total of six premolars as part of orthodontic therapy were included in the study. Gingival recession defects were surgically created in the buccal aspect of these teeth and when necessary, alveolar bone was resected to position the crest at 2–3 mm from the newly created gingival margin. In all teeth reference notches were created at the level of the new gingival margin and at the bone crest. Defects were left untouched for two months prior to the performance root coverage procedures and a total of two CTG and four rhPDGF/β-TCP procedures were performed. After a nine-month healing period biopsies were obtained and defects were grafted. Clinically, 100% root coverage was achieved in all surgical sites. However, histologic and microtomographic results were distinct for both treatment groups. While, none of the CTG-treated sites showed signs of periodontal regeneration (healing was characterized by a long juctional epithelium and parallel connective tissue fibers, with minimal new cementum formation), all four rhPDGF/β-TCP-treated sites exhibited periodontal regeneration. This was evidenced by the presence of periodontal ligament interposed between newly formed cementum and alveolar bone, situated above the reference apical notch.

Preliminary evidence provided by these studies suggests the need for further investigation consisting of the conduction of controlled clinical trials of greater magnitude, designed to evaluate the application of GF-based therapy as a more favorable option than CTG for

patients requiring gingival recession coverage, since the need for a second surgical site could be eliminated.

EXPERT OPINION

A combination of rhPDGF with a tissue specific scaffold, such as those comprised of allograft materials or synthetic bioresorbable ceramics, has the potential to fulfill the clinical need for a biomaterial that predictably leads to periodontal or peri-implant regeneration. The results of a large, multi-center clinical trial aimed at evaluating the clinical safety and effectiveness of rhPDGF-BB incorporated in a β-TCP matrix demonstrate that this product is safe for long-term use. This treatment approach is supported by extensive and rigorous *in vitro*, preclinical and clinical studies, which provide strong evidence for the mechanism of action of PDGF in periodontal and peri-implant healing and regeneration. Growth factor-enhanced matrices provide clinicians with a new, highly effective treatment option for challenging periodontal lesions, which are difficult to treat using conventional methods. Promising clinical results for rhPDGF in combination with osteoconductive matrices in a diverse array of periodontal and periimplant sites suggest that growth factor-enhanced matrices incorporating rhPDGF have the potential to become routine, a standard of care treatment modality.

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References

1. Zhao M, Jin Q, Berry JE, Nociti FH Jr, Giannobile WV, Somerman MJ. Cementoblast delivery for periodontal tissue engineering. J Periodontol 2004 Jan;75(1):154–61. [PubMed: 15025227]
2. Ripamonti U, Herbst NN, Ramoshebi LN. Bone morphogenetic proteins in craniofacial and periodontal tissue engineering: experimental studies in the non-human primate Papio ursinus. Cytokine Growth Factor Rev 2005 Jun;16(3):357–68. [PubMed: 15951219]
3. McAllister BS, Haghighat K. Bone augmentation techniques. J Periodontol 2007 Mar;78(3):377–96. [PubMed: 17335361]
4. Retzepi M, Donos N. Guided Bone Regeneration: biological principle and therapeutic applications. Clin Oral Implants Res 2010 Jun;21(6):567–76. [PubMed: 20666785]
5. Chiapasco M, Casentini P, Zaniboni M. Bone augmentation procedures in implant dentistry. Int J Oral Maxillofac Implants 2009;24(Suppl):237–59. [PubMed: 19885448]
6. Sculean A, Nikolidakis D, Schwarz F. Regeneration of periodontal tissues: combinations of barrier membranes and grafting materials - biological foundation and preclinical evidence: a systematic review. J Clin Periodontol 2008 Sep;35(8 Suppl):106–16. [PubMed: 18724845]
7. Lynch, SE. Bone regeneration techniques in the orofacial region. In: Lieberman, JR.; Friedlaender, GE., editors. Bone Regeneration and Repair: Biology and Clinical Applications. Totowa: Humana; 2005. p. 359-90.
8. Mooney DJ, Silva EA. Tissue engineering: a glue for biomaterials. Nat Mater 2007 May;6(5):327–8. [PubMed: 17471269]
9. Mooney DJ, Organ G, Vacanti JP, Langer R. Design and fabrication of biodegradable polymer devices to engineer tubular tissues. Cell Transplant 1994 Mar-Apr;3(2):203–10. [PubMed: 7516806]
10. Fiorellini JP, Chen PK, Nevins M, Nevins ML. A retrospective study of dental implants in diabetic patients. Int J Periodontics Restorative Dent 2000 Aug;20(4):366–73. [PubMed: 11203576]
11. Triplett RG, Nevins M, Marx RE, Spagnoli DB, Oates TW, Moy PK, et al. Pivotal, randomized, parallel evaluation of recombinant human bone morphogenetic protein-2/absorbable collagen sponge and autogenous bone graft for maxillary sinus floor augmentation. J Oral Maxillofac Surg 2009 Sep;67(9):1947–60. [PubMed: 19686934]

12. Lee J, Stavropoulos A, Susin C, Wikesjo UM. Periodontal regeneration: focus on growth and differentiation factors. Dent Clin North Am 2010 Jan;54(1):93–111. [PubMed: 20103474]
13. Daniels T, DiGiovanni C, Lau JT, Wing K, Younger A. Prospective clinical pilot trial in a single cohort group of rhPDGF in foot arthrodeses. Foot Ankle Int 2010 Jun;31(6):473–9. [PubMed: 20557811]
14. Lynch SE, Williams RC, Polson AM, Howell TH, Reddy MS, Zappa UE, et al. A combination of platelet-derived and insulin-like growth factors enhances periodontal regeneration. J Clin Periodontol 1989 Sep;16(8):545–8. [PubMed: 2778088]
15. Alvarez RH, Kantarjian HM, Cortes JE. Biology of platelet-derived growth factor and its involvement in disease. Mayo Clin Proc 2006 Sep;81(9):1241–57. [PubMed: 16970222]
16. Pierce GF, Mustoe TA, Altrock BW, Deuel TF, Thomason A. Role of platelet- derived growth factor in wound healing. J Cell Biochem 1991 Apr;45(4):319–26. [PubMed: 2045423]
17. Ronnstrand L, Heldin CH. Mechanisms of platelet-derived growth factor-induced chemotaxis. Int J Cancer 2001 Mar 15;91(6):757–62. [PubMed: 11275976]
18. Lynch SE, Wisner-Lynch L, Nevins M, Nevins ML. A new era in periodontal and periimplant regeneration: use of growth-factor enhanced matrices incorporating rhPDGF. Compend Contin Educ Dent 2006 Dec;27(12):672–8. quiz 9–80. [PubMed: 17191649]
19. Centrella M, McCarthy TL, Kusmik WF, Canalis E. Isoform-specific regulation of platelet-derived growth factor activity and binding in osteoblast-enriched cultures from fetal rat bone. J Clin Invest 1992 Apr;89(4):1076–84. [PubMed: 1313443]
20. Lin Z, Sugai JV, Jin Q, Chandler LA, Giannobile WV. Platelet-derived growth factor-B gene delivery sustains gingival fibroblast signal transduction. J Periodontal Res 2008 Aug;43(4):440–9. [PubMed: 18823454]
21. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998 Jun;85(6):638–46. [PubMed: 9638695]
22. El-Sharkawy H, Kantarci A, Deady J, Hasturk H, Liu H, Alshahat M, et al. Platelet-rich plasma: growth factors and pro- and anti-inflammatory properties. J Periodontol 2007 Apr;78(4):661–9. [PubMed: 17397313]
23. Nikolidakis D, Jansen JA. The biology of platelet-rich plasma and its application in oral surgery: literature review. Tissue Eng Part B Rev 2008 Sep;14(3):249–58. [PubMed: 18601587]
24. Steed DL, Donohoe D, Webster MW, Lindsley L. Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. Diabetic Ulcer Study Group. J Am Coll Surg 1996 Jul; 183(1):61–4. [PubMed: 8673309]
25. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. Diabetes Care 1998 May;21(5):822–7. [PubMed: 9589248]
26. Margolis DJ, Bartus C, Hoffstad O, Malay S, Berlin JA. Effectiveness of recombinant human platelet-derived growth factor for the treatment of diabetic neuropathic foot ulcers. Wound Repair Regen 2005 Nov–Dec;13(6):531–6. [PubMed: 16283867]
27. Nash TJ, Howlett CR, Martin C, Steele J, Johnson KA, Hicklin DJ. Effect of platelet-derived growth factor on tibial osteotomies in rabbits. Bone 1994 Mar–Apr;15(2):203–8. [PubMed: 8086239]
28. Joyce ME, Jingushi S, Scully SP, Bolander ME. Role of growth factors in fracture healing. Prog Clin Biol Res 1991;365:391–416. [PubMed: 1862146]
29. Mitlak BH, Finkelman RD, Hill EL, Li J, Martin B, Smith T, et al. The effect of systemically administered PDGF-BB on the rodent skeleton. J Bone Miner Res 1996 Feb;11(2):238–47. [PubMed: 8822348]
30. Lynch SE, de Castilla GR, Williams RC, Kiritsy CP, Howell TH, Reddy MS, et al. The effects of short-term application of a combination of platelet-derived and insulin-like growth factors on periodontal wound healing. J Periodontol 1991 Jul;62(7):458–67. [PubMed: 1920013]
31. Becker W, Lynch SE, Lekholm U, Becker BE, Caffesse R, Donath K, et al. A comparison of ePTFE 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 Nov;63(11):929–40. [PubMed: 1453308]

32. 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 Oct;26(5):415–23. [PubMed: 17073351]
33. Schwarz F, Sager M, Ferrari D, Mihatovic I, Becker J. Influence of recombinant human platelet-derived growth factor on lateral ridge augmentation using biphasic calcium phosphate and guided bone regeneration: a histomorphometric study in dogs. J Periodontol 2009 Aug;80(8):1315–23. [PubMed: 19656032]
34. Nevins M, Garber D, Hanratty JJ, McAllister BS, Nevins ML, Salama M, et al. Human histologic evaluation of anorganic bovine bone mineral combined with recombinant human platelet-derived growth factor BB in maxillary sinus augmentation: case series study. Int J Periodontics Restorative Dent 2009 Dec;29(6):583–91. [PubMed: 20072735]
35. 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 Apr;27(2):109–15. [PubMed: 17514882]
36. Nevins ML, Camelo M, Schupbach P, Kim DM, Camelo JM, Nevins M. Human histologic evaluation of mineralized collagen bone substitute and recombinant platelet-derived growth factor-BB to create bone for implant placement in extraction socket defects at 4 and 6 months: a case series. Int J Periodontics Restorative Dent 2009 Apr;29(2):129–39. [PubMed: 19408475]
37. Howell TH, Fiorellini JP, Paquette DW, Offenbacher S, Giannobile WV, Lynch SE. A phase I/II clinical trial to evaluate a combination of recombinant human platelet-derived growth factor-BB and recombinant human insulin-like growth factor-I in patients with periodontal disease. J Periodontol 1997 Dec;68(12):1186–93. [PubMed: 9444594]
38. Stephan EB, Renjen R, Lynch SE, Dziak R. Platelet-derived growth factor enhancement of a mineral-collagen bone substitute. J Periodontol 2000 Dec;71(12):1887–92. [PubMed: 11156046]
39. Hollinger JO, Hart CE, Hirsch SN, Lynch S, Friedlaender GE. Recombinant human platelet-derived growth factor: biology and clinical applications. J Bone Joint Surg Am 2008 Feb; 90(Suppl 1):48–54. [PubMed: 18292357]
40. Nevins M, Camelo M, Nevins ML, Schenk RK, Lynch SE. Periodontal regeneration in humans using recombinant human platelet-derived growth factor-BB (rhPDGF-BB) and allogenic bone. J Periodontol 2003 Sep;74(9):1282–92. [PubMed: 14584860]
41. Camelo M, Nevins ML, Schenk RK, Lynch SE, Nevins M. Periodontal regeneration in human Class II furcations using purified recombinant human platelet-derived growth factor-BB (rhPDGF-BB) with bone allograft. Int J Periodontics Restorative Dent 2003 Jun;23(3):213–25. [PubMed: 12854772]
42. Nevins M, Hanratty J, Lynch SE. Clinical results using recombinant human platelet-derived growth factor and mineralized freeze-dried bone allograft in periodontal defects. Int J Periodontics Restorative Dent 2007 Oct;27(5):421–7. [PubMed: 17990438]
43. Nevins M, Giannobile WV, McGuire MK, Kao RT, Mellonig JT, Hinrichs JE, et al. Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: results of a large multicenter randomized controlled trial. J Periodontol 2005 Dec;76(12):2205–15. [PubMed: 16332231]
44. McGuire MK, Kao RT, Nevins M, Lynch SE. rhPDGF-BB promotes healing of periodontal defects: 24-month clinical and radiographic observations. Int J Periodontics Restorative Dent 2006 Jun;26(3):223–31. [PubMed: 16836164]
45. McGuire MK, Scheyer ET. Comparison of recombinant human platelet-derived growth factor-BB plus beta tricalcium phosphate and a collagen membrane to subepithelial connective tissue grafting for the treatment of recession defects: a case series. Int J Periodontics Restorative Dent 2006 Apr; 26(2):127–33. [PubMed: 16642901]
46. McGuire MK, Scheyer T, Nevins M, Schupbach P. Evaluation of human recession defects treated with coronally advanced flaps and either purified recombinant human platelet-derived growth factor-BB with beta tricalcium phosphate or connective tissue: a histologic and microcomputed

tomographic examination. Int J Periodontics Restorative Dent 2009 Feb;29(1):7–21. [PubMed: 19244878]

47. Simion M, Nevins M, Rocchietta I, Fontana F, Maschera E, Schupbach P, et al. Vertical ridge augmentation using an equine block infused with recombinant human platelet-derived growth factor-BB: a histologic study in a canine model. Int J Periodontics Restorative Dent 2009 Jun; 29(3):245–55. [PubMed: 19537464]
48. McAllister, et al. Histologic Evaluation of Extraction Sockets Grafted with Platelet-Derived Growth Factor. International Journal of Periodontics and Restorative Dentistry 2010;30:365–73.

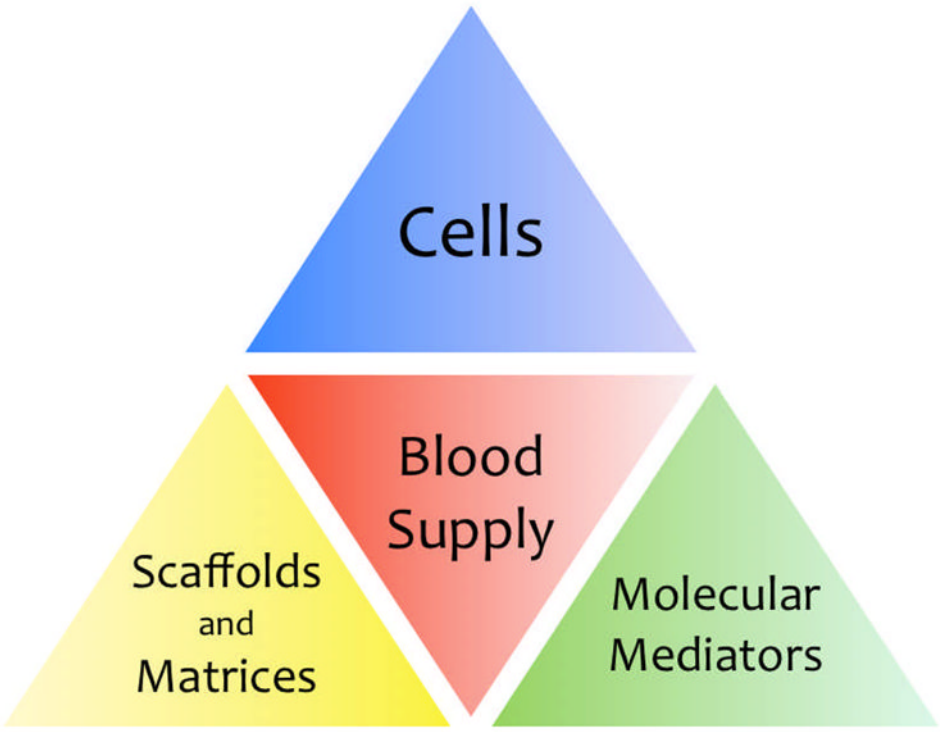

FIGURE 1.

Four basic elements are required for periodontal repair and regeneration: adequate blood supply and wound stability, a source of bone and ligament forming cells, a supporting scaffold or matrix, and growth factors to regulate cell migration, proliferation and synthesis and angiogenesis for revascularization of the site.

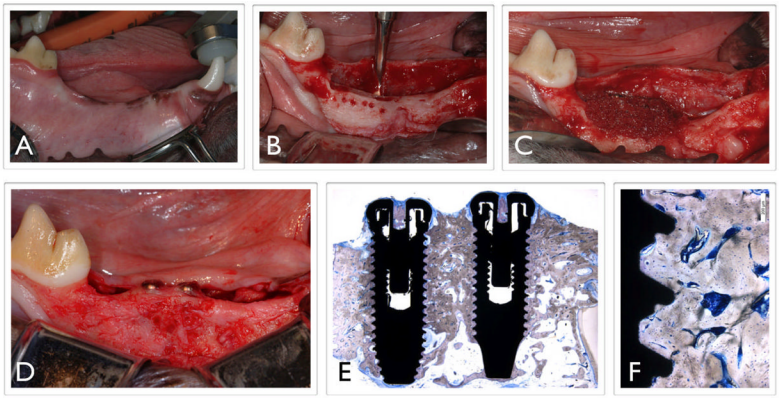

FIGURE 2.

rhPDGF is associated with increased bone formation in a canine alveolar ridge augmentation model. Baseline surgically created defect (A, B), was treated using guided bone regeneration (GBR) with equine bone block infused with rhPDGF-BB (C). Excellent bone formation is seen at four months in the treated site (D). Figures E and F show the histologic outcomes, with special emphasis on the remarkable bone-to-implant contact achieved. Reprinted with permission from Quintessence Publishing Co., Inc.[47]

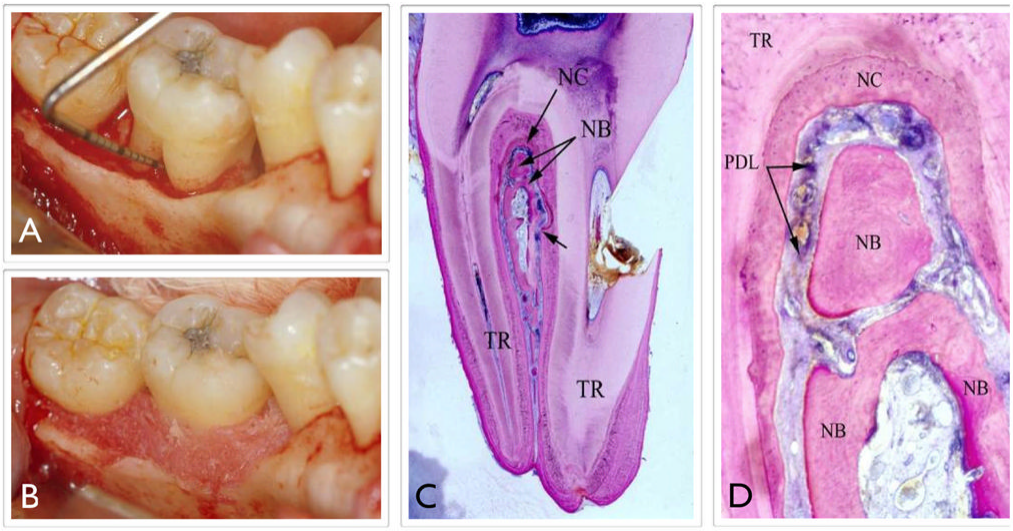

FIGURE 3.

A growth factor-enhanced matrix (GEM) can consist of allograft bone saturated with rhPDGF-BB. The matrix is saturated with pure, recombinant growth factor solution prior to being packed into the defect site. This case illustrates the use of rhPDGF and allograft to treat a class II furcation with a mesial wrap-around defect. A) debrided defect; B) grafted site; C and D) histology showing periodontal regeneration coronal to a reference notch placed at the base of calculus prior to treatment (NC – New cementum; NB – New Bone; PDL – Periodontal ligament; TR – Tooth Roots). Reproduced with permission.[37]

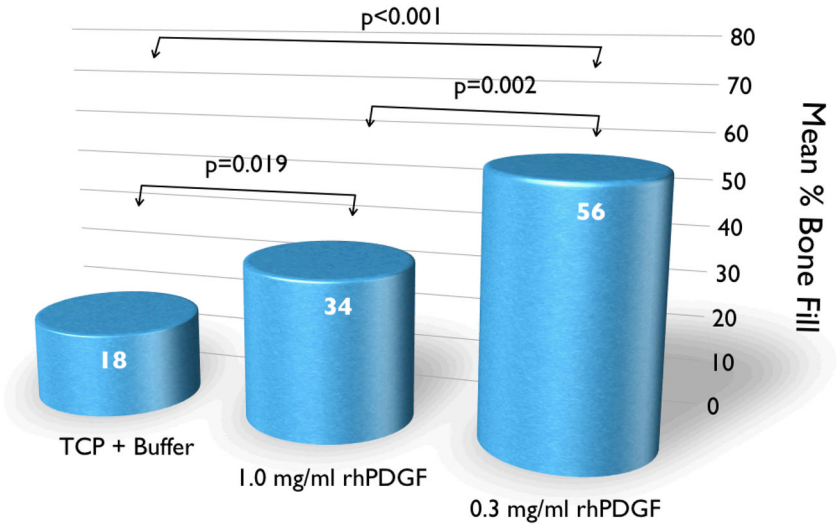

FIGURE 4.
rhPDGF-BB in combination with β-TCP significantly improved %BF of all bone defects compared to β-TCP plus buffer.[43]

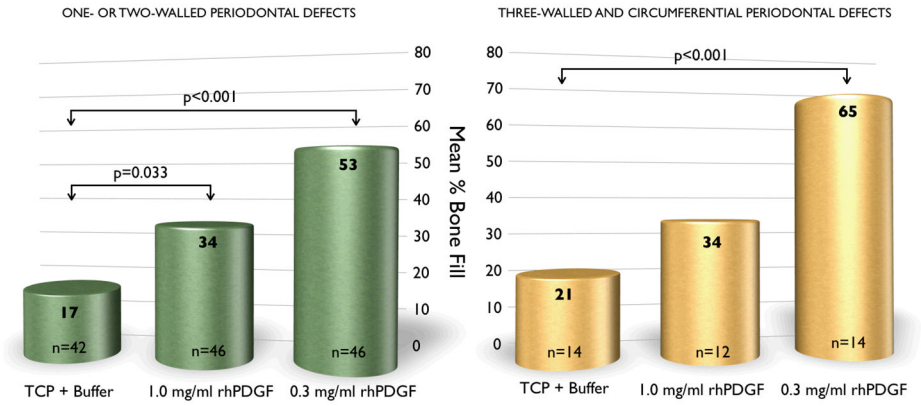

FIGURE 5.

rhPDGF-BB treatment resulted in significantly improved bone fill in 1-, 2-, and 3-wall defects ($p<0.001$); there was no significant difference in bone fill between 1- and 2-wall defects compared to 3-wall and circumferential defects ($p=0.40$ in the 0.3 mg/ml group).[43]

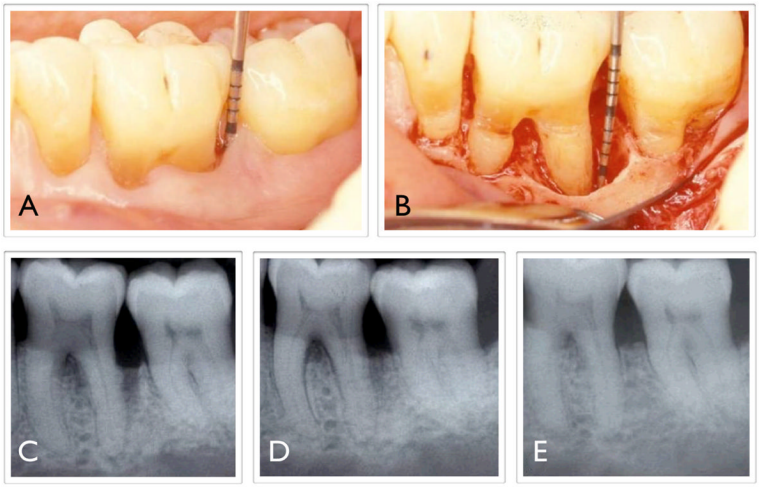

FIGURE 6.

Representative case from pivotal clinical trial treated with 0.3 mg/ml rhPDGF. A, B and C) Baseline; D) 6 months post-surgically; E) 18 months post-surgically. Note progressive increase in radiopacity and trabecular bone pattern in the area of the original defect. Reprinted with permission.[44]