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REVIEW ARTICLE

Twenty-five years of recombinant human growth factors rhPDGF-BB and rhBMP-2 in oral hard and soft tissue regeneration

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1 | INTRODUCTION

Recombinant human growth factor-mediated regenerative approaches have progressively raised a great deal of interest within the scientific community.[1] The perspective of receiving advanced and minimally invasive regenerative treatment for severe hard and soft tissue deficiencies has also been promising for patients.[2,3] The goal of growth factor-mediated approaches is to enhance wound healing events in order to have superior clinical outcomes, together with an accelerated healing and recovery.[1,3,4] Indeed, the past few decades have witnessed increased attention to patient perspective, quality of life, and satisfaction related to the treatment. Healing outcomes perceived by patients and patient-reported outcome measures have become as important as clinical outcomes.[5–12]

Growth factors are a collective group of highly active signaling molecules able to promote cell chemotaxis, proliferation, differentiation, and morphogenesis.[2,13,14] These biological mediators regulate key wound healing events by binding to specific cell receptors. Growth factors have the potential to induce intracellular signaling pathways, activating genes that change the activity and the phenotype of the targeted cell.[14,15] Advancements in cellular and molecular biology have allowed for a better understanding of the role of the different growth factors and cytokines on the wound healing dynamics, which is the basis of tissue engineering approaches utilizing recombinant human growth factors or biologic agents for application for bone repair around teeth and implants.[14,16,17]

Four different and partially overlapping wound healing phases have been identified: hemostasis, inflammatory, granulation, and maturation.[18,19] Following blood clot formation, degranulating platelets release platelet-derived growth factor (PDGF) that is responsible for stimulating chemotaxis and mitogenicity of neutrophils, monocytes, macrophages, and fibroblasts, which play a key role on the initiation of the inflammatory response.[14,16] At this stage, platelets also release transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF) to promote cell chemotaxis and autocrine expression of additional cytokines and increase vascular permeability, respectively.[14,16,18] Macrophages are the main actors of the following wound healing phases, contributing to the wound debridement and secreting growth factors, such as PDGF, TGF-β, epidermal growth factor (EGF), fibroblast growth factor-2 (FGF-2), and VEGF.[14,16,18] Among other functions, PDGF, FGF-2 and TGF-β stimulate the proliferation of fibroblasts that play a key role

on the extracellular matrix synthesis.[20,21] Proliferation of endothelial and epithelial cells is promoted by EGF, FGF-2, KGF, PDGF, TGF-β and VEGF, that are released by macrophages, keratinocytes, fibroblasts, and endothelial cells.[14,16,18] The phase of matrix synthesis and maturation involves several cell populations, based on the injured tissue. Bone morphogenetic proteins (BMPs) are a group of growth factors released by osteoblasts that stimulate mesenchymal progenitor cell migration and osteoblast differentiation (BMPs 2–4 and BMP-7).[14,22,23] Insulin-like growth factor-2 (IGF-2) is released by macrophages and fibroblasts and also contributes to osteoblast proliferation and bone matrix synthesis.[14,16] At this later stage, PDGF stimulates mesenchymal progenitor cell migration and, together with TGF-β, promotes fibroblasts differentiation into myofibroblasts, which is a crucial step for wound healing contraction and closure. The apoptosis of endothelial cells and fibroblasts is orchestrated by TGF-β, while VEGF promotes angiogenesis and antiapoptotic effects on bone-forming cells.[14,16]

The aim of growth factor therapy is to regenerate damaged tissue by mimicking the processes occurring during embryonic and postnatal development.[14,24] Although several signaling molecules play a role during wound healing, it may be assumed that using a single recombinant growth factor can induce molecular and biochemical cascades that will eventually promote tissue regeneration.[14,17,25] The most investigated recombinant human (rh) growth factors for oral regeneration have been rhBMPs and rhPDGF-BB.[3]

The aim of the present manuscript is to review the applications, clinical, and patient-reported outcomes of rhBMPs and rhPDGF-BB for oral tissue regeneration over the last 25 years.

2 | RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEINS (RHBMPS)

2.1 | Historical background and biological properties

The application of growth factors possessing osteoinductive features in combination with biomaterials is currently a tissue engineering strategy to treat and regenerate severe oral bone defects. In fact, several bone regenerative procedures involving vertical and horizontal bone grafting techniques still cannot ensure a successful and complete bone regeneration in major bone defects, mainly due to graft exposure, necrosis, insufficient graft vascularization, and postoperative infection.[26,27] Furthermore, surgical approaches involving autogenous bone block grafts are technical sensitive, have limited availability, and may need a secondary surgical donor site. Mesenchymal stem cells and their differentiation over remodeling processes possess significant roles in bone regeneration. Consequently, molecular signaling pathways involved in regenerative processes are crucial for bone regeneration.[27] As follows, complex cases in oral and periodontal surgery have introduced the use of bone morphogenetic proteins (BMPs) to enhance the osteogenic and osteoinductive potential for the regeneration of large grafted areas. BMPs are defined as a group of pleiotropic morphogens capable of recruiting, proliferating, and differentiating mesenchymal cells into osteoblast lineage. BMPs were discovered by Marshall Urist in 1960s, where he identified that BMPs could induce preosteoprogenitor cells to differentiate into osteoblasts and stimulate bone formation in ectopic extraskeletal sites.[28] BMPs are classified as natural multifunctional growth factors that correspond to the transforming growth factor ß (TGF- ß) family. BMPs are involved in various pathways such as Smad, Hegehog, and TGF-ß pathways and cytokine-cytokine receptor interactions that stimulate osteoblastogenesis and bone repair.[29]

Several in vitro, preclinical, and human studies evidenced that BMP-2, 4, 6, 7, 9, and 14 isoforms can promote osteoinduction.[26] Based on these findings, clinical trials have also incorporated BMP-2 into periodontal and peri-implant grafting applications since this growth factor can be a biological mediator and an effective promoter for bone regeneration that can shorten healing periods when compared to other grafting strategies.[30–34] Bowers et al.[31] demonstrated that the growth factor was able to regenerate cementum, connective tissue, and bone at periodontal sites; yet this strategy is not commonly employed owing to a risk of ankylosis. Moreover, Sigurdsson et al.[35] showed that BMP-2 was capable to regenerate bone at peri-implant defects and induce osseointegration. Furthermore, bioengineering technological advances have developed and cloned many BMP isoforms. One of them is recombinant human BMP-2 (rhBMP-2), which was FDA approved in 2004 for orthopedic and oral surgery applications. RhBMP-2 in combination with a bovine collagen sponge has been tested in several animal and human studies showing comparable results in bone regeneration when compared to autogenous grafts and also promoting a high rate of de novo bone growth.[27,29] Presently, the American Academy of Periodontology best evidence consensus statement exposed the importance of the use of biologics such as BMPs in periodontal and oral surgery applications.[26] Numerous studies have applied rhBMP-2 to perform lateral and horizontal ridge augmentation, alveolar ridge preservation, sinus floor elevation and peri-implant bone augmentation. RhBMP-2 has been recognized as a potent growth factor to induce bone regeneration (Figure 1).[30,35–39] As follows, the succeeding paragraphs describe the main clinical applications and related outcomes in bone augmentative oral procedures.

2.2 | Clinical applications of rhBMPs in bone regeneration

2.2.1 | Horizontal and vertical ridge augmentation

Major alveolar horizontal and vertical ridge deficiencies require invasive surgical procedures typically involving autogenous block grafts. Thus, the mentioned invasive surgical technique requires a second site to harvest bone, longer surgical times, and has higher patient morbidity. As follows, the application of growth factors such as BMP-2 in combination with diverse carriers have shown several advantages such as decreased surgical time, lower morbidity, easier

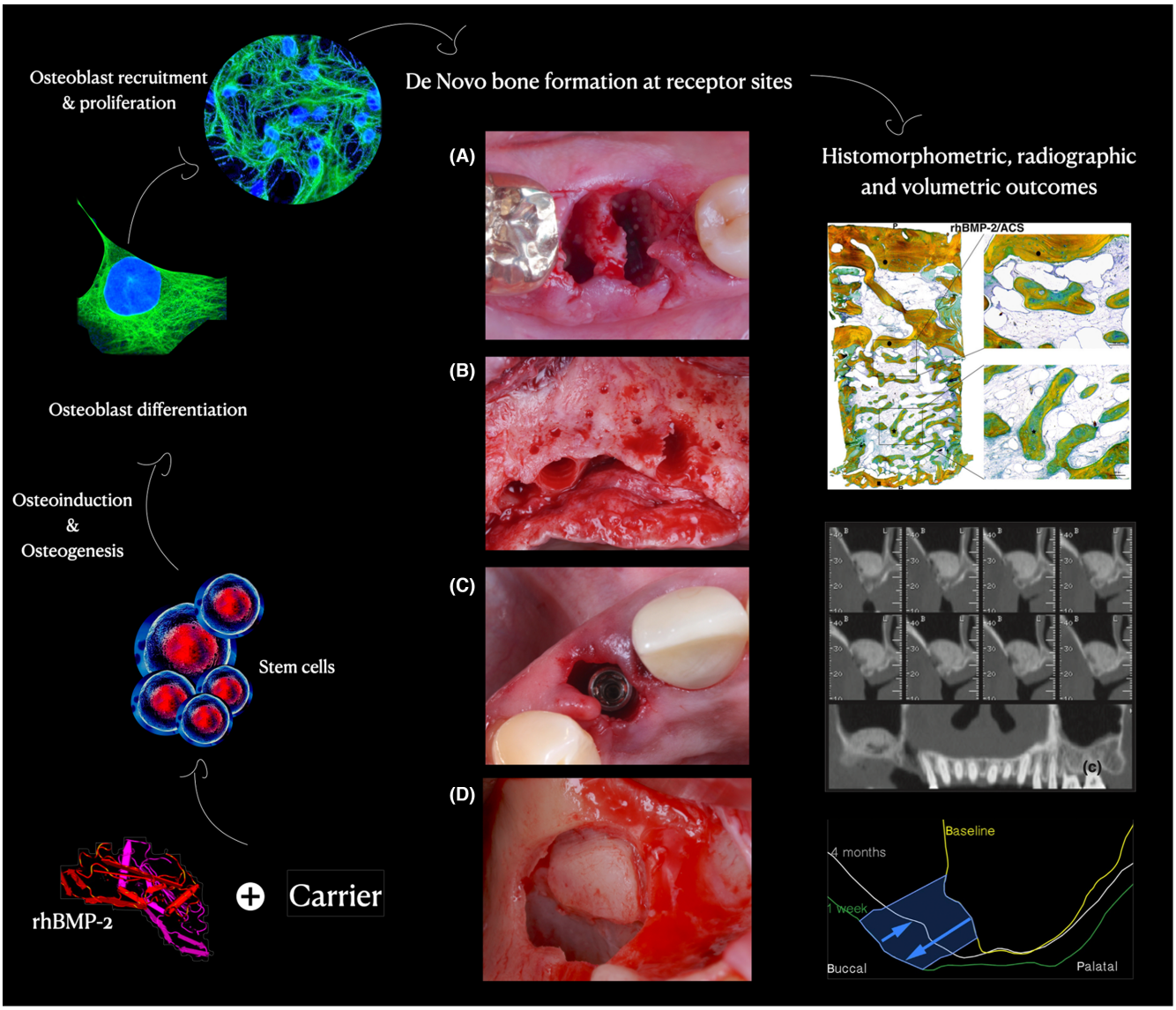

FIGURE 1 Schematic diagram depicting the osteoinductive role of rhBMP-2 when combined with a carrier for bone augmentation procedures. Stem cells are induced by rhBMP-2 to differentiate into osteoblasts at the receptor surgical site, consequently osteoblast recruitment and proliferation is promoted. As follows, de Novo bone formation can be stimulated by BMP-2 at (A) alveolar ridge sites following tooth extraction, (B) horizontal and vertical major bone defects, (C) peri-implant sites, and (D) sinus floor elevation, which has been assessed through histomorphometric (adapted from de Freitas et al.),[43] radiological (adapted from Kim et al.)[52] and volumetric analyses (adapted from Thoma et al.).[30]

surgical techniques, no second site for bone harvest, and faster healing periods.[30] However, BMPs osteogenic properties might be more effective in combination with specific bone graft biomaterials and in particular with specific space maintenance scaffolds to ensure an adequate bone regeneration in the targeted site. Jung et al. showed in a randomized clinical trial that a xenogeneic bone substitute mineral combined with rhBMP-2 can promote bone maturation, enhance bone regeneration, and increase the contact between graft and bone at lateral bone augmentation sites.[40–42] Moreover, the implant survival rate at the mentioned grafted sites was of 100% after 3 and 5 years of follow-up. Particularly, de Freitas et al.[43] evidenced in a human histological and genetic analysis that the application of rhBMP-2 coupling with an absorbable collagen sponge presented bone formative processes after implantation for horizontal augmentation in the maxilla. The mentioned core biopsies mainly exhibited cell and blood vessel rich marrow and newly woven and lamellar bone. In contrast, the aforementioned study evidenced that autogenous bone grafted sites presented mainly remodeling and resorptive processes, where core biopsies mainly presented vital lamellar bone, areas of nonvital bone, and fatty marrow.[43] Moreover, Marx et al.[44] presented in a clinical study that large maxillary vertical defects grafted with rhBMP-2 + PRP (platelet-rich plasma) and allogeneic bone were efficiently regenerated presenting new bone formation and less morbidity when compared to autogenous grafted sites. The current evidence from clinical studies assessing rhBMP-2 for horizontal and vertical bone augmentation supports the safety of the

growth factor for these procedures. Nevertheless, it should be mentioned that erythema and swelling are common findings after bone augmentation with rhBMP-2.[8,9,44,45] Clinical studies reporting the long-term outcomes of rhBMP-2-based bone augmentation procedures are advocated. Clinical trials showing the application, clinical, and histomorphometric outcomes of rhBMP-2 for lateral and vertical ridge augmentation is summarized in Table 1.

2.2.2 | Alveolar ridge preservation

Several clinical studies evidenced that the alveolar process undergoes significant volumetric changes following tooth extraction.[46–48] In fact, a traumatic tooth extraction, the presence of a thin bone buccal wall (<1 mm), or large periapical infections may increase the bone resorption process in height and width, which might consequently limit an adequate bone ridge dimension for a future appropriate implant positioning.[47,49] Thus, various studies have developed diverse bone grafting techniques for alveolar ridge preservation and counteraction of bone loss.[49] Some cases presenting acute infections and baseline severe bone loss may need osteoinductive agents and biomaterials to reduce bone resorption and attenuate postextraction ridge atrophy following tooth extraction.[45] RhBMP-2 has been studied in combination with different carriers for alveolar ridge preservation, its efficacy has been proven towards de novo bone formation at grafted sites, thus, the delivery system or carrier for BMPs might be crucial for an appropriate osteoinductive effect. Several clinical trials have shown that the use of rhBMP-2 can be beneficial to induce bone formation at socket sites.[36,45] Fiorellini et al.[50] compared in a randomized clinical trial, two concentrations of rhBMP-2 (i.e., 1.5 and 0.75 mg/mL) with a bioabsorbable collagen sponge as a carrier versus a bioabsorbable collagen sponge alone. This study substantiated that those patients treated with 1.5 mg/mL rhBMP-2 presented a significantly higher bone formation when compared with the other groups. Hence, the growth factor concentration might be crucial for an effective de novo osseous formation.[50] Moreover, Jo et al.[51] evaluated in a randomized controlled clinical trial two different rhBMP-2 delivery systems (i.e., absorbable collagen sponge vs. beta-tricalcium phosphate and hydroxyapatite particles) in alveolar ridge preservation. The aforementioned study evaluated radiographic and histological changes for both grafted groups ($N = 32$ patients each) and revealed that none of the groups presented severe adverse events over the healing period, both delivery systems evidenced a similar efficacy for alveolar ridge preservation after 12 weeks of surgery; however, the difference in bone height and width between both groups was not statistically significant. Histological analysis evidenced new bone formation at both groups, thus, Beta-tricalcium phosphate and hydroxyapatite particles were still observed in the control group after 12 weeks of healing. This study showed that for alveolar ridge perseveration, rhBMP-2 with a collagen sponge is sufficient to maintain the ridge dimensions, since the synthetic graft in combination with rhBMP-2 did not show any additional benefit toward bone formation.[51] However, Kim et al.[52] compared the safety and efficacy of demineralized bone matrix alone versus rhBMP-2 in combination with demineralized bone matrix for alveolar ridge preservation and showed that sockets with <50% bone loss in the buccal wall were effectively preserved with both treatment modalities, thus, no statistically difference could be observed among the groups. Still, diversity of results among the current studies might depend on the rhBMP-2 dose, carrier, graft composition, volume maintenance, and type of defect to achieve a substantial clinical benefit.

While rhBMP-2 has been shown to be safe for bone regenerative procedures, it should be mentioned that mild erythema and localized swelling are commonly observed at extraction sites augmented with the mentioned growth factor.[3,50,53] Clinical studies reporting the long-term outcomes of augmented sites with rhBMP-2 are needed to further assess the potential benefits of the growth factor for alveolar ridge preservation. Clinical trials utilizing rhBMP-2 with diverse carriers for alveolar ridge preservation are summarized in Table 2 and exemplified in Figures 1 and 2.

2.2.3 | Sinus floor augmentation

The application of rhBMP-2 for sinus floor bone augmentation has been assessed in several clinical trials as shown in Table 3. Studies have compared diverse BMP doses, carriers, biomaterials (i.e., allografts, xenografts, synthetic beta- tricalcium phosphate and hydroxyapatite), and techniques, which affected the clinical, radiographic, and histomorphometric outcomes. Thus, a systematic review and meta-analysis of Lin et al.[38] reported that rhBMP-2 use for sinus floor augmentation had similar clinical and histometric outcomes when compared to conventional sinus lift procedures. Moreover, De Freitas et al.[36] concluded in another systematic review that sinus floor augmentation using autogenous bone graft was significantly higher than using rhBMP-2 with an absorbable collagen sponge. Still, studies have also evidenced that outcomes may vary when rhBMP-2 is combined with different carriers. Particularly, Kao et al.[36] showed that allografts and biphasic calcium phosphate in conjunction with rhBMP-2 presented better results in terms of radiographic and histological bone formation when compared to rhBMP-2 linked to a xenograft for sinus floor augmentation. No significant adverse effects related to rhBMP-2 has been reported for sinus floor augmentation.[3,45,52,54–56] Nevertheless, long-term studies assessing the outcomes of dental implants placed in maxillary sinuses augmented with rhBMP-2 compared to conventional techniques are currently missing.

2.2.4 | Peri-implant bone augmentation

Preclinical studies have demonstrated that the application of rhBMP-2 is overall safe and can be a potential strategy to promote bone formation and re-osseointegration at peri-implant defects.[35,57] Sigurdsson et al.[35] evidenced in a canine model that surgical induced peri-implant defects that were treated with rhBMP-2 with

TABLE 1 Clinical, radiographic, and histomorphometric outcomes of clinical trials utilizing rhBMP-2 with diverse carriers for bone ridge augmentation.

Reference	Ridge defect	Carrier	Comparison	Complications	PROMs	Clinical and histomorphometric outcomes
De Freitas et al. (2013, 2016)[8,43]	Horizontal	Absorbable collagen sponge (+ titanium mesh)	rhBMP-2/ACS (+ titanium mesh) versus Control group: Autogenous bone graft	Higher levels of swelling and erythema in the TEST group (NSSD)	Control group: Temporary discomfort and pain from the donor site	Test group: higher radiographic horizontal bone gain, NSSD in other clinical and radiographic parameters
	Horizontal	Absorbable collagen sponge (+ titanium mesh)	rhBMP-2/ACS (+ titanium mesh) Versus Control group: Autogenous bone graft			Test group: bone marrow rich in capillaries, undifferentiated cells and bone lining cells* Control group: greater presence of non-vital bone particles trapped in lamellar vital bone*
Marx et al. (2013)[44]	Horizontal and vertical	Absorbable collagen sponge + FDBA + PRP (+ titanium mesh)	hBMP-2/ACS + FDBA + PRP Versus Control group: Autogenous bone graft (+ titanium mesh)	Similar in both groups	Test group: low days of analgesics * Higher postop. edema at day 3, 8 and 15* less operative time*	NSSD in terms of regenerated bone for implant placement and bone-to-implant contact % (osseointegration) Test group: higher vascular density at grafted areas NSSD for other outcomes
Thoma et al. (2018)[9]	Horizontal	Xenogeneic bone block (+ CM)	rhBMP-2 + Xenogeneic bone block Versus Control Group: Autogenous bone block	1 case presented exposure of autogenous block (NSSD)	Test group: less pain during the surgery*. NSSD for the other PROMs	NSSD Similar CBCT and 3D volumetric changes (NSSD)
Thoma et al. (2019)[30]	Horizontal	Xenogeneic bone block (+ CM)	rhBMP-2 + Xenogeneic bone block Versus Control Group: Autogenous bone block	1 case presented exposure of autogenous block (NSSD)	Test group: less pain during the surgery*. NSSD for the other PROMs	Test group: lower mineralized tissue compared to the control group*

* Statistical significant difference ($p < 0.05$).

Abbreviations: CM, bioabsorbable collagen membrane; DBBM, demineralized bovine bone mineral; EBM, equine bone matrix; FBS, fetal bovine serum; FDBA, freeze-dried bone allograft; HAP, hydroxyapatite; IMDM, Iscove's modified Dulbecco's medium; NR, not reported; NSSD, Not statistically significant difference ($p > 0.05$); rhBMP, recombinant human bone morphogenetic protein; rhPDGF, recombinant human platelet-derived growth factor; xBG, xenogeneic bone graft; β-TCP, beta-tricalcium phosphate.

TABLE 2 Clinical, radiographic, and histomorphometric outcomes of clinical trials utilizing rhBMP-2 with diverse carriers for alveolar ridge preservation.

Reference	Alveolar defect type	Carrier	Comparison	Flap design/complete closure	Complications	PROMs	Clinical, radiographic, and histomorphometric outcomes
Fiorellini et al. (2005)[50]	BBD ≥ 50%	CS	0.75 or 1.5 mg/mL rhBMP-2 + CS versus Control groups CS versus Spontaneous healing	Flaps raised, primary closure No membrane	Higher edema and erythema cases in the test group	Pain NSSD	Test group: greater bone augmentation than control groups* Test group: less sites requiring additional augmentation than control* No inflammation or residual collagen matrix from the absorbable CS
Huh et al. (2011)[165]	Teeth to be extracted with <50% alveolar vertical bone loss	HAP/β-TCP	rhBMP-2 + HAP/β-TCP versus Control group HAP/β-TCP	NR, NR No membrane	NR	NR	Test group: less bone remodeling (height and width) than control*
Kim et al. (2014)[166]	Residual socket with <50% bone loss	DBM	rhBMP-2 + DBM + CM versus Control group DBM	Flaps raised, no primary closure Collagen membrane	NSSD	NR	NSSD in radiographic outcomes
Coomes et al. (2014)[53]	BBD ≥50%	CS	rhBMP-2 + CS versus Control group CS	Flapless, no primary closure No membrane	Minor erythema and swelling in Test group	NR	Test group: higher buccal plate regeneration, clinical ridge width and radiographic ridge width* Test group: less buccal bone dehiscence* and less implants needed additional bone augmentation*
Shim et al. (2018)[167]	NR	HAP	rhBMP-2 + HAP versus Control group DBBM	Flaps raised, primary closure No membrane	NR	NR	Test group: superior outcomes in alveolar bone width changes* Test group: higher percentage of new bone formation*
Jo et al. (2019)[51]	Teeth to be extracted with >50% alveolar bone height	HAP/β-TCP CS	rhBMP-2 + HAP/β-TCP + CM versus Control group rhBMP-2 + CS + CM	Flaps raised, no primary closure Collagen membrane	Pain, NSSD	NR	NSSD

Abbreviations: BBD, buccal bone dehiscence; CM, bioabsorbable collagen membrane; CS, collagen sponge; DBBM, demineralized bovine bone matrix; DBM, demineralized bone matrix gel; HAP, hydroxyapatite; NR, not reported; NSSD, not statistically significant difference ($p > 0.05$); PROMs, patient-reported outcome measures; rhBMP, recombinant human bone morphogenetic protein; XBMC, xenogeneic bone mineral containing collagen; β-TCP, beta-tricalcium phosphate.

*Statistically significant difference ($p < 0.05$).

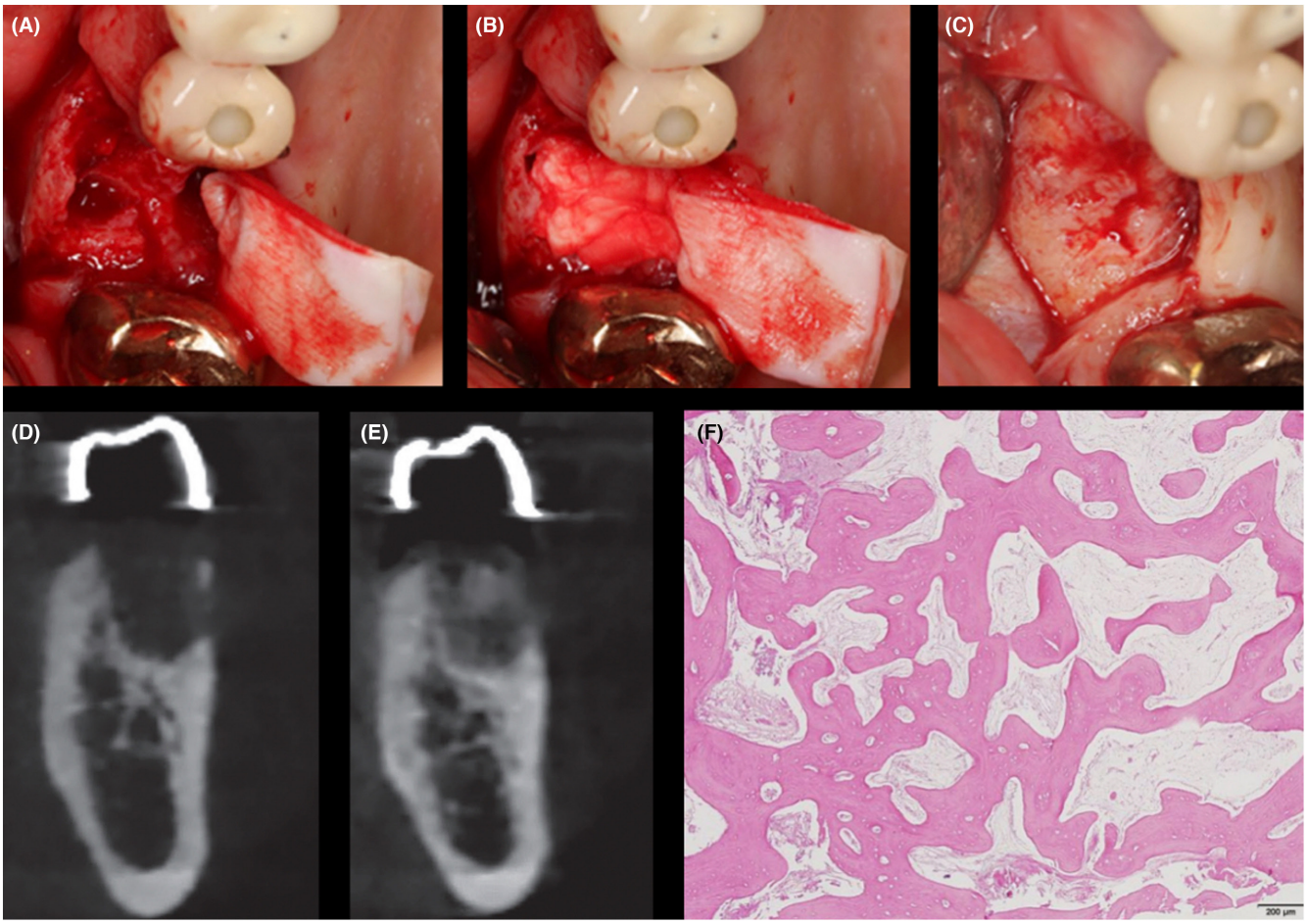

FIGURE 2 Schematic diagram representing the (A) surgical intervention, (B) application of resorbable membrane with rhBMP-2 for socket preservation, (C) grafted area after 12 weeks, (D, E) tomographic (12-week follow-up) and (F) histomorphometric analyses performed in a study evaluating the osteoinductive role of rhBMP-2 combined with a resorbable collagen sponge for alveolar ridge preservation (adapted from Jo et al.).[51]

an absorbable collagen sponge presented a significant higher bone regeneration and re-osseointegration when compared to control sites treated with collagen sponge solely. Nevertheless, peri-implant bone augmentation has been studied in limited studies. Clinical trials utilizing rhBMP-2 for peri-implant bone augmentation are summarized in Table 4. A randomized clinical trial evaluated the effect of rhBMP-2 at time of implant placement with concomitant lateral bone augmentation.[40] Peri-implant bone defects were augmented with xenogeneic bone and resorbable membranes with or without rhBMP-2 coating. This study showed through histomorphometric analyses that rhBMP-2 enhanced bone maturation process around dental implants and that also the contact between the graft and receptor bone was higher for the test group.[40] Moreover, Jung et al.[41] reported in the long-term follow-up of the aforementioned split-mouth study that implants placed with concomitant guided bone regeneration using a xenogeneic bone substitute, collagen membrane, and rhBMP-2 presented satisfactory clinical and radiographic outcomes over 17 years. However, rhBMP-2 treated sites did not seem to have an enhanced bone regenerative effect over the long term.[41] Further clinical studies reporting the long-term stability of peri-implant bone augmented with rhBMP-2 are needed. Currently, no clinical trials have proven the role of BMPs in peri-implantitis surgical augmentative therapy. Presently, there is still no gold standard treatment to regenerate peri-implant defects caused by peri-implantitis inflammatory pathogenesis, especially when considering supracrestal bony defects.[58] Thus, future clinical studies are required to test the bone regenerative potential of BMPs at peri-implantitis bone defects.

2.3 | Current recommendations for clinical applications of BMPs

Diverse BMP isoforms, specially rhBMP-2 has been tested in different clinical applications for implant site development and regeneration. The biological effects of BMPs have been shown to induce osteogenic differentiation at grafted sites in preclinical models. Additionally, several systematic reviews for alveolar ridge preservation, lateral and horizontal augmentation, and sinus floor elevation with the adjunct use of BMPs have been inconclusive regarding their

TABLE 3 Clinical, radiographic, and histomorphometric outcomes of clinical trials utilizing rhBMP-2 with diverse carriers for sinus floor augmentation.

Reference	BMP isoform	Carrier	Comparison	Complications	PROMs	Clinical, radiographic, and histomorphometrical outcomes
Boyne et al. (2005)[54]	rhBMP-2	Collagen sponge	0.75 or 1.5 mg/mL rhBMP-2 + collagen sponge versus Control group: Autograft with or without allograft	Higher edema and rash in the control group*	More patients in pain in control group*	Test group: rhBMP-2 treated site presented lower bone width gain than control group* Unambiguous bone induction by rhBMP-2. No differences among the groups
Triplett et al. (2009)[168]	rhBMP-2	Collagen sponge	rhBMP-2 + collagen sponge Control group: versus Autograft	Implant failure for control group twice than Test group. Test group: more facial edema than control group*. Control group: 17% sensory loss from donor site at 6 months. Also pain and gait disturbance in the long term at the donor site.	NR	NSSD for bone gain, but control group showed higher bone density* No marked differences between the groups
Kao et al. (2012)[169]	rhBMP-2	Collagen sponge + DBBM	rhBMP-2 + DBBM versus Control group: DBBM	NR	NR	NR
Corinaldesi et al. (2013)[170]	rhBMP-7	DBBM	rhBMP-7 + DBBM versus Control group: DBBM	Yes/NSSD	NR	More new bone on the control side than the rhBMP-7 treated side*
Froum et al. (2013)[55]	rhBMP-2	Collagen sponge + allograft	rhBMP-2 + allograft versus Control group: Allograft	NR	NR	Test group: higher amount of vital bone* at 4–5 months. Higher residual graft in the control group than test group*
Kim et al. (2015)[52]	rhBMP-2	BCP	rhBMP-2 + BCP versus Control group DBBM	NSSD	NR	NSSD for clinical, radiographic and volumetric outcomes
Kim et al. (2015)[56]	rhBMP-2	HAP	rhBMP-2 + HAP versus Control group DBBM	Yes/NSSD	NR	Test group: Higher new bone formation*
Han et al. (2022)[37]	rhBMP-2	HAP	rhBMP-2 + HAP versus Control group DBBM	NR	NR	NSSD for implant survival rate, marginal bone level changes and implant stability quotient values after 1 year of loading. Test group: implants were loaded 3 months before control group (6 months).

Abbreviations: CM, bioabsorbable collagen membrane; CS, collagen sponge; DBBM, demineralized bovine bone matrix; DBM, demineralized bone matrix gel; HAP, hydroxyapatite; NR, not reported; NSSD, not statistically significant difference ($p > 0.05$); PROMs, patient-reported outcome measures; rhBMP, recombinant human bone morphogenetic protein; XBMC, xenogeneic bone mineral containing collagen; β-TCP, beta-tricalcium phosphate.

*Statistically significant difference ($p < 0.05$).

TABLE 4 Clinical, radiographic, and histomorphometric outcomes of clinical trials utilizing rhBMP-2 with diverse carriers for peri-implant bone augmentation.

Reference	BMP isoform	Carrier	Surgical receptor condition	Comparison	Complications	PROMs	Clinical, radiographic, and histomorphometrical outcomes
Jung et al. (2003)[171]	rhBMP-2	DBBM (+ CM)	Implant placement in healed ridge requiring bone augmentation	rhBMP-2 + DBBM + CM Control group DBBM + CM	NSSD	NR	Test group: higher fraction of lamellar bone higher surface of bone substitute particles in direct contact with the newly formed bone*
Jung et al. (2009)[42]	rhBMP-2	DBBM (+ CM)			NSSD	NR	NSSD
Jung et al. (2022)[172]	rhBMP-2	DBBM (+ CM)			NSSD	NSSD	NSSD

Abbreviations: CM, collagen membrane; DBBM, demineralized bovine bone matrix; GBR, guided bone regeneration procedure; NR, not reported; PROMs, patient-reported outcome measures; rhBMP-2, recombinant human bone morphogenetic protein-2; β-TCP, beta-tricalcium phosphate.

*p-Value of 0.05. NSSD, not statistically significant difference ($p > 0.05$).

clinical and radiographic benefit. However, it has been highlighted that BMP application enhanced histological outcomes, increasing favorable results toward faster wound healing processes, favored earlier implant loading periods, and superior bone regeneration development.[45] Generally, histomorphometric analyses has demonstrated that rhBMP-2 significantly stimulated de novo bone formation, higher bone marrow growth, and promoted bone vascularity at grafted areas. Consequently, bone grafting procedures with the concomitant use of rhBMPs might be considered for patients with compromised bone healing capacity or limited donor sites, when faster healing periods are required or when large bone defects are involved. Among the limitations of rhBMPs the high cost related to the synthetic production required to extract rhBMPs, together with the encapsulation in synthetic biomaterials should be mentioned.[59] Studies addressing the cost-effectiveness of rhBMPs in bone regenerative procedures are advocated.

3 | RECOMBINANT HUMAN PLATELET-DERIVED GROWTH FACTOR-BB (RHPDGF-BB)

3.1 | Historical background and biological properties

PDGF is a dimeric molecule that was initially observed in platelets, although many other cells can release this growth factor. It has been shown that PDGF interacts with different cell types, especially with those of mesenchymal origin.[60] PDGF is a potent mitogen for fibroblasts and osteoblasts.[60–62] It also promotes the proliferation of pericytes and the activation of neutrophils and macrophages, which synthesizes growth factors playing a pivotal role on the wound healing events, including PDGF, basic fibroblast growth factor, and transforming growth factor beta.[2,63–65]

Receptors for PDGF were also detected on cells of periodontal ligament and alveolar bone.[66–70] Although all isoforms of PDGF were found to enhance the proliferation of fibroblasts from the periodontal ligament,[70,71] it was demonstrated that the isoform BB was the most potent one in promoting mitogenic and chemotactic responses of periodontal ligament cells.[72] In addition, synergistic effects of PDGF and insulin growth factor-1 (IGF-1) on the mitogenesis of periodontal and bone precursor cells were described.[68,71,73] Therefore, it is not surprising that the first preclinical and clinical applications of recombinant human platelet-derived growth factor-BB (rhPDGF-BB) for periodontal regeneration involved its combination with IGF-1.[74–77] Starting in the late 1980s, several preclinical studies have confirmed the capacity of rhPDGF-BB for promoting the formation of new bone, cementum, and periodontal ligament.[66,67,74,77] Howell and coworkers performed the first phase I/II clinical trial assessing the safety and biological response of rhPDGF-BB in combination with IGF-1, applied in a gel carrier into osseous defects (infrabony and furcation defects) during periodontal surgeries in 38 human subjects.[76]

The authors demonstrated that the application of rhPDGF-BB/IGF-1 was safe, and that the combination of high dose rhPDGF-BB (150 μg/mL) with IGF-1 resulted in a significantly greater bone formation in osseous defects compared to open flap debridement procedure after 9 months. At the clinical re-entry, a mean vertical bone gain of 2.8 and 0.75 mm was found at sites allocated to 150 μg/mL rhPDGF-BB/IGF-1 and open flap debridement, respectively. The group with high dose rhPDGF-BB and IGF-1 exhibited a mean defect fill of 42.3% at 9 months, which was significantly higher than the defect fill obtained following the open flap debridement (18.5%).[76]

Currently, the use of rhPDGF-BB is approved by the Food and Drug Administration in combination with beta-tricalcium phosphate for the treatment of intrabony periodontal defects, furcation defects and gingival recessions. Nevertheless, in the past 25 years the growth factor has been often utilized with different types of scaffolds, not only in natural dentition but also in bone augmentation procedures and around dental implants.[26,45,64,65,78,79]

3.2 | Clinical applications of rhPDGF-BB in oral tissue regeneration

rhPDGF-BB has been extensively utilized for regenerative procedures in the oral cavity. A recent review from our group, based on a systematic search in the literature until June 2019, identified 63 human clinical studies describing the outcomes of rhPDGF-BB for oral tissue regeneration.[64] Interestingly, the majority of the included studies assessed the efficacy of the growth factor when utilized for bone augmentation ($N = 22$), followed by clinical studies evaluating the regenerative outcomes of rhPDGF-BB in infrabony and furcation defects ($N = 18$). Eleven studies described the application of rhPDGF-BB for root coverage procedures and soft tissue augmentation in natural dentition, while the use of the growth factor for alveolar ridge preservation and sinus floor augmentation was reported in 9 and 3 clinical trials, respectively.[64]

Several additional clinical studies involving the clinical application of rhPDGF-BB have been published since 2019, further confirming the interest of clinicians and the scientific community on this biologic agent.[80–86]

3.2.1 | Periodontal regeneration

The first human clinical trial by Howell et al.[76] demonstrated the regenerative outcomes of rhPDGF-BB through clinical observation at the re-entry procedure, 6–9 months after the initial surgery. Further clinical studies provided histological evidence of periodontal regeneration of infrabony and class II furcation defects using rhPDGF-BB with bone allograft.[87,88] Sites previously exhibiting infrabony defects obtained a mean probing depth reduction of 6.42 mm and clinical attachment level gain of 6.17 mm after 9 months,[87] while the mean horizontal and vertical probing depth reduction observed at molars with furcation defects was 3.5 and 4.25 mm, respectively.[88] Histological analysis exhibited regeneration of new periodontal ligament, cementum, and alveolar bone, with no signs of adverse reaction, ankylosis, nor inflammation at the treated sites.[87,88]

Mellonig and coworkers further confirmed the regenerative capacity of rhPDGF-BB in 4 hopeless mandibular molars with furcation III involvement.[89] Beta-tricalcium phosphate was used as a carrier of the growth factor for the surgical procedure. After 6 months a reduction of probing depth and a gain in clinical attachment level were observed in all the treated sites, with one tooth exhibiting furcation involvement reduction from class III to class II. The molars were removed en bloc for histological analysis, where partial regeneration or new cementum was evident in all specimens.[89]

A multicenter, randomized, controlled, trial was conducted to assess on a large scale the safety and effectiveness of rhPDGF with beta-tricalcium phosphate for the treatment of periodontal intrabony defects. Eleven centers participated to the clinical study, where 180 subjects were enrolled and randomly allocated to one of the three treatment arms: (i) 0.3 mg/mL rhPDGF-BB + beta-tricalcium phosphate, (ii) 1 mg/mL rhPDGF-BB + beta-tricalcium phosphate, or (iii) beta-tricalcium phosphate alone. In line with clinical previous studies,[87,88,90] the use of rhPDGF-BB was confirmed safe. In terms of clinical outcomes, a significantly greater clinical attachment level gain was found at 3 months in the 0.3 mg/mL rhPDGF-BB + beta-tricalcium phosphate group compared to beta-tricalcium phosphate alone. At 6 months, sites treated with 0.3 mg/mL rhPDGF-BB + beta-tricalcium phosphate exhibited significantly higher linear bone gain (2.6 mm vs. 0.9 mm) and percent of defect fill (57% vs. 18%) compared to the sites that did not receive rhPDGF-BB.[91] The 0.3 mg/mL rhPDGF-BB + beta-tricalcium phosphate group also outperformed the bone graft alone group in terms of reduced postoperative gingival recession at 3 months and stability of the gingival margin from 3 to 6 months.

These outcomes were shown to be stable up to 36 months,[92] with the sites treated with 0.3 mg/mL rhPDGF-BB + beta-tricalcium phosphate exhibiting a progressive—although not statistically significant—clinical attachment level gain, probing depth reduction, percent of defect fill increase and linear bone gain.

These clinical studies set the stage for the use of rhPDGF-BB in periodontal regenerative procedures. Since then, the growth factor has rapidly become popular among clinicians (Tables 5 and 6). Further clinical studies have confirmed that rhPDGF-BB significantly enhanced the clinical attachment level gain and probing depth reduction of beta-tricalcium phosphate following treatment of periodontal infrabony defects.[93–96] Several authors also reported promising outcomes when the growth factor was applied "off-label" with freeze-dried bone allograft, demineralized freeze-dried bone allograft, equine-derived bone matrix, or even used alone.[87,97–100] There has not been a consensus regarding the most ideal carrier for rhPDGF-BB, when utilized in periodontal infrabony defects. Most of the available randomized controlled trials involved a test group

TABLE 5 Clinical outcomes of recombinant human platelet-derived growth factor-BB (rhPDGF-BB) for the treatment of periodontal infrabony therapy.

Publication, reference	Study design	Patients (*N*), infrabony defects (*N*)	Treatment arm	Follow-up (months)	Mean PD reduction	Mean CAL gain	Mean REC change
Dhote et al. (2015)[173]	RCT	14, 24	MSCs + rhPDGF-BB + β-TCP	6	4.5 ± 1.08*	3.91 ± 1.37*	0.58 ± 0.79*
			OFD	6	3.5 ± 0.9	2.08 ± 0.90	1.41 ± 0.66
Howell et al. (1997)[76]	RCT	36, 72[a]	50 μg/mL rhPDGF-BB and rhIGF-I	6	NR	NR	NR
			150 μg/mL rhPDGF-BB and rhIGF-I	9	NR	NR	NR
			OFD	6–9	NR	NR	NR
Jayakumar et al. (2011)[174]	RCT	54, 54	rhPDGF-BB + β-TCP	6	4.3 ± 0.9*	3.7 ± 1*	0.44 ± 0.77
			β-TCP	6	3.2 ± 1.6	2.8 ± 0.9	0.54 ± 0.73
Kavyamala et al. (2019)[93]	RCT	12, 24	rhPDGF-BB + β-TCP	6	4.67 ± NR*	4.34 ± NR*	0.25 ± NR
			rhPDGF-BB	6	3.75 ± NR	3.09 ± NR	0.84 ± NR
Lee et al. (2017)[175]	RCT	32, 32	rhPDGF-BB + β-TCP	6	4.93 ± 2.86	5.56 ± 3.00	NR
			rhPDGF-BB + XBG	6	4.93 ± 1.81	4.22 ± 1.72	NR
Maroo and Murthy (2014)[176]	RCT	15, 30	rhPDGF-BB + β-TCP	9	5.46 ± 1.60*	5.33 ± 1.72*	0.07 ± 0.26
			β-TCP	9	4.13 ± 1.51	3.67 ± 1.45	0.53 ± 0.52
McGuire et al. (2006)[177]	Case series	4, 4	0.3 or 1 mg/mL rhPDGF-BB + β-TCP	24	7.00 ± 1.83	6.25 ± 1.89	0.75 ± 1.50
Mishra et al. (2013)[99]	RCT	22, 22	rhPDGF-BB	6	4.18 ± 0.60	3.00 ± 0.89	−0.82 ± 0.60
			OFD	6	3.82 ± 0.87	2.64 ± 0.67	−0.55 ± 0.52
Nevins et al. (2003)[87]	Case series	9, 11	0.5, 1 or 1.5 mg/mL rhPDGF-BB + allograft	9	6.42 ± 1.69	6.17 ± 1.94	0.25 ± 0.61
Nevins et al. (2005)[91]	RCT	177, 177	0.3 mg/mL rhPDGF-BB + β-TCP	6	NR	3.8 ± 0.2	NR
			1 mg/mL rhPDGF-BB + β-TCP	6	NR	NR	NR
			β-TCP	6	NR	3.5 ± 0.2	NR
Nevins et al. (2007)[100]	Case series	2, 2	rhPDGF-BB + allograft	8–11	7.00 ± 2.83	7.50 ± 4.95	−0.50 ± 2.12
Ridgway et al. (2008)[178]	RCT	8, 16	0.3 mg/mL rhPDGF-BB + β-TCP	6	4.6 ± 1.5	3.1 ± 1.8	1.3 ± 1.3
			1 mg/mL rhPDGF-BB + β-TCP	6	4.3 ± 1.5	3.2 ± 1.9	1.1 ± 0.9
Rosen et al. (2011)[98]	Retrosp.	50, 50	rhPDGF-BB + allograft	6	4.8 ± 1.4	4.1 ± 1.3	NR
Schincaglia et al. (2015)[179]	RCT	28, 28	rhPDGF-BB + β-TCP (with SFA)	6	4.1 ± 1.7	4.0 ± 1.9	0.1 ± 0.7
			rhPDGF-BB + β-TCP (with DFA)	6	3.6 ± 1.1	3.2 ± 1.4	0.4 ± 1.3
Thakare and Deo (2012)[94]	RCT	18, 18	rhPDGF-BB + β-TCP	12	3.82 ± 1.07*	3.42 ± 1.24*	0.42 ± 0.40
			HA + β-TCP	12	2.70 ± 0.70	2.06 ± 0.63	0.30 ± 0.38

Abbreviations: CAL, clinical attachment level; DFA, double flap approach; HA, hydroxyapatite; MSCs, mesenchymal stem cells; NR, Not reported; OFD, open flap debridement; PD, probing depth; REC, recession depth; Retrosp., retrospective study; SFA, single flap approach; XBG, xenogeneic bone graft; β-TCP, beta-tricalcium phosphate.

[a]Including both furcation and infrabony defects.

*Statistically significant difference in favor of the test group over the control group ($p < 0.05$).

TABLE 6 Radiographic outcomes of infrabony defects treated with recombinant human platelet-derived growth factor-BB (rhPDGF-BB).

Publication, reference	Study design	Patients (*N*), Infrabony defects (*N*)	Treatment arm	Follow-up (months)	Radiographic bone fill (mean) (%)	Radiographic linear bone gain (mean ± SD) (mm)
Dhote et al. (2015)[173]	RCT	14, 24	MSCs + rhPDGF-BB + β-TCP	6	88.33*	3.50 ± 0.67*
			OFD	6	52.77	1.83 ± 0.38
Howell et al. (1997)[76]	RCT	36, 72[a]	50 μg/mL rhPDGF-BB and rhIGF-I	6	NR	NR
			150 μg/mL rhPDGF-BB and rhIGF-I	9	42.3	2.08 ± NR
			OFD	6–9	18.5	0.75 ± NR
Jayakumar et al. (2011)[174]	RCT	54, 54	rhPDGF-BB + β-TCP	6	65.6*	3.7 ± 1.1*
			β-TCP	6	47.5	2.8 ± 1.2
Kavyamala et al. (2019)[93]	RCT	12, 24	rhPDGF-BB + β-TCP	6	73.59*	3.28 ± 1.71*
			rhPDGF-BB	6	45.74	2.75 ± 1.95
Lee et al. (2017)[175]	RCT	32, 32	rhPDGF-BB + β-TCP	6	NR	4.16 ± 2.08
			rhPDGF-BB + XBG	6	NR	5.91 ± 3.61
Maroo and Murthy (2014)[176]	RCT	15, 30	rhPDGF-BB + β-TCP	9	94.30*	4.05 ± 1.52*
			β-TCP	9	67.99	2.50 ± 1.21
McGuire et al. (2006)[177]	Case series	4, 4	0.3 or 1 mg/mL rhPDGF-BB + β-TCP	24	88.25	6.77 ± 1.20
Mishra et al. (2013)[99]	RCT	22, 22	rhPDGF-BB	6	36.20	1.89 ± 0.6
			OFD	6	35.02	1.85 ± 1.18
Nevins et al. (2003)[87]	Case series	9, 11	0.5, 1 or 1.5 mg/mL rhPDGF-BB + allograft	9	NR	2.14 ± 0.85
Nevins et al. (2005)[91]	RCT	177, 177	0.3 mg/mL rhPDGF-BB + β-TCP	6	57*	2.6 ± 0.2*
			1 mg/mL rhPDGF-BB + β-TCP	6	34*	1.5 ± 0.2*
			β-TCP	6	18	0.9 ± 0.1
Nevins et al. (2013)[92]	RCT	83, 83	0.3 mg/mL rhPDGF-BB + β-TCP	12, 24, 36	60.5 (at 12 months)* 68.3 (at 24 months)*	2.88 ± NR (at 12 months)* 3.32 ± NR (at 24 months)*
			1 mg/mL rhPDGF-BB + β-TCP	12, 24, 36	53.7 (at 12 months)*	2.25 ± NR (at 12 months)*
			β-TCP	12, 24, 36	32.6 (at 12 months) 41.5 (at 24 months)	1.42 (at 12 months) 1.81 (at 24 months)
Schincaglia et al. (2015)[179]	RCT	28, 28	rhPDGF-BB + β-TCP (with SFA)	6	NR	2.00 ± NR
			rhPDGF-BB + β-TCP (with DFA)	6	NR	2.1 ± NR
Thakare and Deo (2012)[94]	RCT	18, 18	rhPDGF-BB + β-TCP	12	80.99*	3.00 ± 0.81*
			HA + β-TCP	12	54.16	2.30 ± 0.67

Abbreviations: CAL, clinical attachment level; DFA, double flap approach; HA, hydroxyapatite; MSCs, mesenchymal stem cells; NR, Not reported; OFD, open flap debridement; PD, probing depth; REC, recession depth; Retrosp., retrospective study; SFA, single flap approach; XBG, xenogeneic bone graft; β-TCP, beta-tricalcium phosphate.

*Statistically significant difference in favor of the test group over the control group ($p < 0.05$).

[a]Including both furcation and infrabony defects.

with rhPDGF-BB and a control group without the growth factor, with one study only comparing two different bone graft carriers for rhPDGF-BB.[97] Another open question regarding rhPDGF-BB is related to its effectiveness compared to other biologic agents and treatment approaches (e.g., guided tissue regeneration, open flap alone, bone graft alone, etc.). Currently, there is a lack of clinical trials providing data from direct head-to-head comparisons between treatment arms assessing rhPDGF-BB with different scaffolds, nor rhPDGF-BB versus other biologics. Conventional qualitative systematic reviews and pairwise meta-analyses are, therefore, inadequate to analyze the data from the existing literature.

Our group recently conducted a systematic review on the efficacy of biologics for the treatment of periodontal infrabony defects, where 150 randomized clinical trials reporting the outcomes of more than 7000 infrabony defects were included.[79] A mixed model network meta-analysis was employed to gather all the available evidence from randomized controlled trials using rhPDGF-BB, enamel matrix derivative, or autogenous blood-derived products, separating and isolating the specific components of the utilized surgical approaches among studies, through additive and interactive models, to explore the relative impact of the different bone graft materials, alone, or in combination with biologics, as well as the application of a barrier membrane on different therapeutic outcomes.[79] This approach allowed for obtaining direct and indirect comparisons among the stated treatment constituents, together, and in separation, all of which are vital for an evidence-based quality synthesis with the ultimate goal of improving daily clinical decision-making and patient-care.[101–105] It was observed that rhPDGF-BB was the biologic agent exhibiting the largest effect size for clinical attachment level gain, pocket depth reduction, less gingival recession and radiographic linear bone gain.[79] In addition, it was demonstrated that the type of bone graft may play a key role on the surgical outcomes of infrabony defects. Allogenic bone graft displayed the highest treatment effect compared to the other bone graft types in terms of clinical attachment level change and radiographic linear bone gain, while xenogeneic bone graft obtained the largest effect size for probing depth reduction and stability of the gingival margin.[79] Interestingly, rhPDGF-BB was found to have the highest treatment effect in terms of stability of the gingival margin following regenerative surgical procedures compared to other treatment approaches.[79] It was also observed that there are overall no benefits when adding barrier membranes to a regenerative approach utilizing a bone graft in combination with a biologic agent,[79] supporting the assumption that the barrier membranes may jeopardize the angiogenic, cell recruitment and wound healing capacities of biologic agents.[88,91,92,106]

Therefore, clinicians should be aware that the type of scaffold can also affect the outcomes of rhPDGF-BB for the treatment of infrabony defects, and that barrier membranes are overall not recommended when utilizing the growth factor. Figure 3 depicts a case of periodontal infrabony defect treated with rhPDGF-BB in combination with xenogeneic bone allograft as a scaffold and connective tissue graft for obtaining simultaneous root coverage and gingival phenotype modification.

3.2.2 | Root coverage of gingival recessions in natural dentition

McGuire and Scheyer[107] published in 2006 the first report describing a rhPDGF-BB-mediated approach for root coverage procedure. Avoiding palatal harvesting and the possibility of regenerating the lost bone and periodontium associated with the gingival recession defects were among the reasons that led the authors to investigate root coverage outcomes using rhPDGF-BB. After elevating a full-thickness flap and conditioning the root surface with EDTA for 2 min followed by a saline rinse, the rhPDGF-BB solution was applied to the exposed root surface and to the coronal ligament fibers. Then, in order to prevent the collapse of the flap against the root surface that could probably prevent new bone formation, a small amount of beta-tricalcium phosphate, previously saturated with rhPDGF-BB, was positioned on the root surface and on the adjacent bone. A collagen membrane soaked in rhPDGF-BB was applied over the bone graft material, and sutured to the de-epithelialized papillae, prior to coronally advancing and suturing the flap.[107]

The positive preliminary outcomes of this pilot study led the authors to design a split-mouth randomized controlled trial comparing this novel rhPDGF-BB-based treatment approach to autogenous connective tissue graft[108]; considered the gold standard for root coverage procedures.[12,104,109] After 6 months, the connective tissue graft group exhibited a significantly higher recession reduction and percentage of mean root coverage, while the sites allocated to the growth factor treatment obtained significantly greater probing depth reduction compared to the connective tissue graft group. Similar keratinized tissue width gain, esthetic results, and patient satisfaction were observed between the two groups. The study also evaluated histologic and microcomputed tomographic data on 6 treated teeth requiring extraction for orthodontic therapy. Recession defects were created in these teeth, that were then treated with connective tissue graft or rhPDGF-BB-mediated therapy. After 9 months, en bloc resections were performed to assessing the histological and tomographic outcomes of the two procedures. The sites treated with the autogenous graft exhibited healing with long-junctional epithelium and connective tissue fibers running parallel to the root surface, while the sites that received rhPDGF-BB showed evidence of periodontal regeneration. The microcomputed tomography displayed regenerated bone coronal to the notch performed prior to the treatment, while the histological analysis allowed to appreciate osteocytes and cementocytes entombed in the newly formed bone and cementum. The newly regenerated periodontal ligament exhibited Sharpey fibers obliquely inserting into the newly formed cementum and bone. This study demonstrated that rhPDGF-BB can promote root coverage of gingival recession defects together with regeneration of the periodontium.[108] In a following publication, the authors also reported the 5-year follow-up data from the same cohort, showing that the sites treated with the autogenous graft had a small but nonsignificant reduction in the mean root coverage from 6 months to 5 years (97.90% vs. 89.35%), while the contralateral sites treated

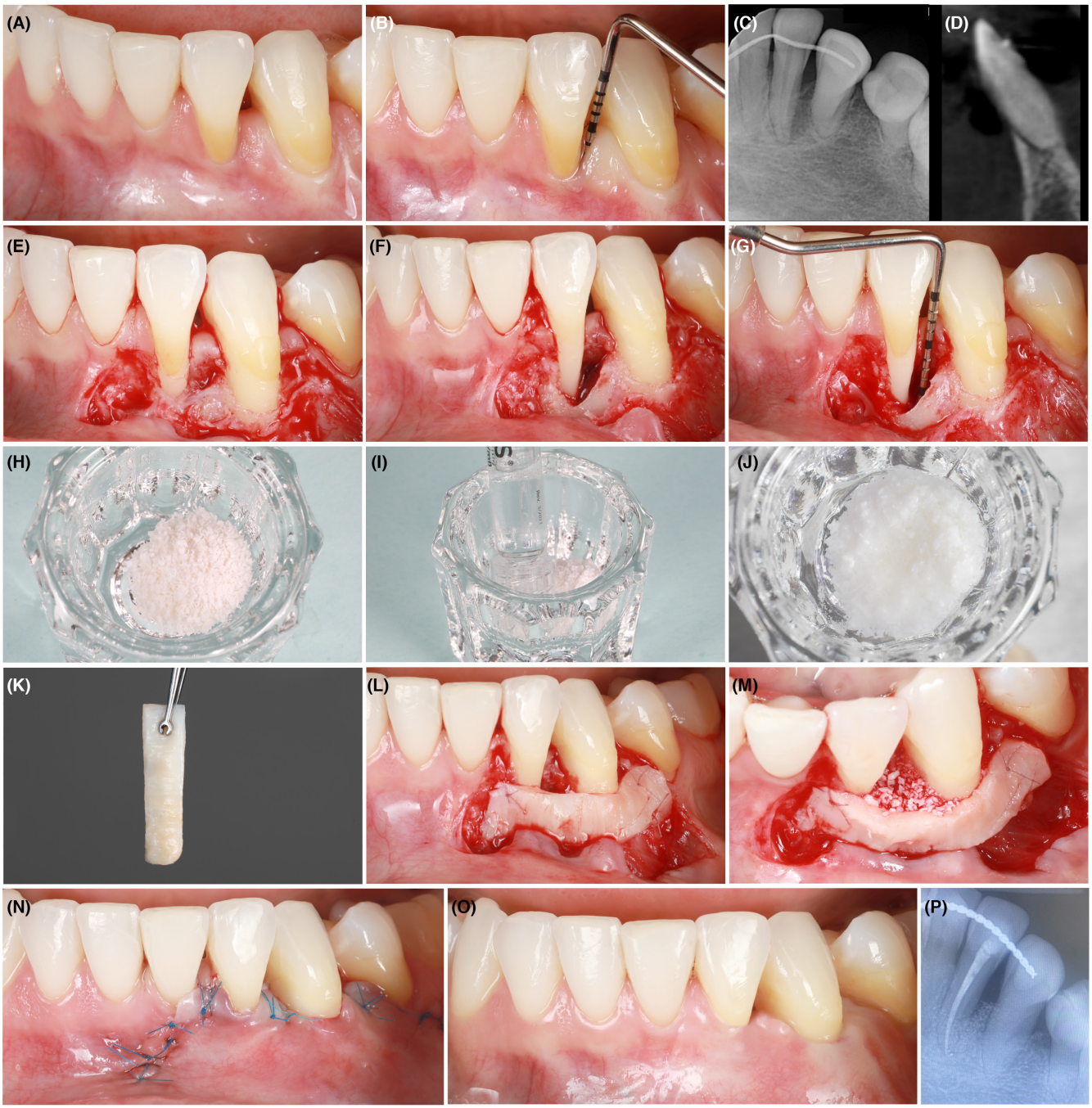

FIGURE 3 Regenerative treatment of an infrabony defect using rhPDGF-BB. (A, B) Clinical presentation at baseline. (C) Periapical x-ray at baseline. (D) Sagittal view from the cone beam computed tomography scan. Note that the tooth received root canal treatment prior to periodontal regenerative therapy. (E) Flap design. (F, G) Flap elevation and visualization of the defect. Mechanical and chemical root conditioning was performed on the root surface after the degranulation of the defect. (H) Xenogeneic bone graft (Bio-Oss, Geistlich Pharma North America, Princeton, USA). (I, J) Bone graft soaked with rhPDGF-BB (GEM21, Lynch Biologics, Franklin, USA). (K) Connective tissue graft harvested from the palate. (L) Suturing of the connective tissue graft on the buccal aspect to create a wall.[181,182] The graft was used to obtain simultaneous root coverage and gingival phenotype modification at the level of the canine and incisor. (M) After applying rhPDGF-BB in direct contact to the root, the bone graft previously soaked with the growth factor was applied into the defect. (N) Flap closure. (O, P) Outcomes at 9 months.

with the growth factor exhibited a significant reduction in mean root coverage (89.85% at 6 months and 74.10% at 5 years).[110] It can be speculated that the modification of the soft tissue phenotype may be more important than the regeneration of the periodontium and buccal bone in preventing the relapse of the gingival margin over time. Regenerating the lost periodontium and buccal bone at sites exhibiting thin gingival thickness may not guarantee the long-term stability of the gingival margin, since thin soft tissue is more prone to recede in case of inflammation and traumatic toothbrushing, regardless of the level of the buccal bone.

A recent study from our group assessed the long-term (10 years) outcomes of different root coverage procedures in 83 subjects (for a total of 157 teeth) that previously participated in six randomized clinical trials.[111] The Akaike information criterion-driven model selection and regression analyses allowed to demonstrate that the amount of keratinized tissue width and gingival thickness obtained at 6 months significantly affected the long-term stability of the gingival margin. In particular, irrespective of the approach performed, in the presence of at least 1.5 mm of keratinized tissue, gingival thickness at 6 months was found to be the main determinant on the long-term behavior of the gingival margin, which showed stability over time if gingival thickness at 6 months was at least 1.46 mm.[111]

Therefore, it can be hypothesized that a regenerative, growth factor-based treatment for gingival recessions should also aim at increasing gingival thickness at sites with thin gingival phenotype. It is reasonable to assume that using soft tissue matrices as scaffolds for rhPDGF-BB rather than bone grafts may be more indicated for root coverage procedures. Previous studies described the use of autogenous connective tissue graft,[112–114] collagen membrane,[115–117] acellular dermal matrix,[118] and xenogeneic cross-linked collagen matrix,[119,120] as carriers for rhPDGF-BB. Collagen membranes are designed for acting as barriers preventing the migration of epithelial cells into the area to be regenerated, and therefore, due to their properties and characteristics do not promote gingival phenotype modification. On the other hand, connective tissue graft has been shown to be a predictable treatment for gingival recessions, with a very high rate of mean and complete root coverage that has been reported for type 1 recession defects.[104,109,121–123] One of the goals of rhPDGF-BB, and overall biomaterials, is to mimic the root coverage outcomes of autogenous connective tissue graft, without requiring a donor site. The combination of rhPDGF-BB with connective tissue graft may be beneficial in very challenging cases; however, in most case scenarios, autogenous connective tissue graft alone is sufficient for treating recession defects and promoting phenotype modification. The ability of rhPDGF-BB to induce chemotaxis and mitogenesis of the host cells, and to accelerate angiogenesis and the rate of wound healing[124–126] makes this growth factor particularly attractive for soft tissue scaffolds such as porous collagen matrices and acellular dermal matrices. A clinical study failed to find differences in root coverage outcomes at sites treated with human acellular dermal matrix, with or without rhPDGF-BB. Nevertheless, it should be considered that the type of decellularization processes that human acellular dermal matrices undergo for being immunologically inert has a strong impact on the characteristics of the graft, with consequences also on cell migration and proliferation within the matrix.[127–129] This type of dermal matrix may have had a favorable structure for promoting a synergistic effects when soaked with rhPDGF-BB.

On the other hand, it may be assumed that a recently introduced xenogeneic collagen matrix, which has undergone chemical cross-linking to enhance its mechanical stability, and which is characterized by a porous structure, may represent a more ideal carrier for rhPDGF-BB for growth factor-mediated root coverage procedures.[119,130] In particular, Agis and coworkers reported an increased cellular population and metabolic activity in this collagen matrix when utilized as a scaffold for rhPDGF-BB.[131] A recent triple-blind randomized, placebo-controlled trial tested the hypothesis that rhPDGF-BB could enhance the outcomes of a cross-linked collagen matrix for the treatment of multiple gingival recessions.[120] Thirty subjects were randomized and equally distributed to receive collagen matrix soaked with saline or with rhPDGF-BB. After 6 months, the sites treated with the growth factor showed significantly superior mean root coverage (88.25% vs. 77.72%), frequency of complete root coverage (59.57% vs. 20.45%), and esthetic outcomes (root coverage esthetic score[132] of 8.17 vs. 6.98 points) compared to the control group. Intraoral optical scanner and ultrasonography were employed to assess volumetric changes over time.[120] The three-dimensional analysis of the digital impressions showed a significantly greater volume gain in the rhPDGF-BB group over the control group (75.39 mm^3 vs. 58.67 mm^3, respectively). Regarding the ultrasonographic outcomes, the longitudinal analysis assessing the rate of change in soft tissue thickness with respect to time from baseline throughout the healing period, up to 6 months, demonstrated significantly lower changes (less "shrinkage" of the tissue) for the rhPDGF-BB group over time compared with the control group.[120] These findings are consistent with the mechanism of action of rhPDGF-BB that may have promoted a faster revascularization of the graft, a rapid resolution of the inflammatory phase and more complete ingrowth of host cells within the matrix, all leading to reduced soft tissue shrinkage (Figures 4 and 5).[120]

The authors also published a case report of two subjects with multiple gingival recessions treated with the tunneling coronally advanced flap and a cross-linked collagen matrix enriched with rhPDGF-BB, where complete root coverage and increased soft tissue thickness were obtained, together with ultrasonographic evidence of buccal bone dehiscence reduction at 18 months compared to baseline.[119] While only histology can confirm true periodontal regeneration, readers should be aware that several studies have demonstrated ultrasonography to be a reliable and reproducible method for assessing the level of the buccal bone.[133–135] Nevertheless, further studies with a larger sample size, multiple treatment arms, and longer follow-ups, are required for further evaluating this technique for the treatment of gingival recessions.

Table 7 summarizes the outcomes of the currently available studies that utilized rhPDGF-BB-mediated root coverage approaches.

3.2.3 | Alveolar ridge preservation

Few studies have described the outcomes of rhPDGF-BB for alveolar ridge preservation,[85,136–139] and, therefore, a comprehensive assessment and quantitative analysis on its efficacy for this purpose is not currently feasible.[45,140] The rationale for utilizing rhPDGF-BB for alveolar ridge preservation is the possibility of promoting a quicker wound healing of the extraction socket and earlier remodeling of the bone graft particles that are utilized as carriers of the growth factor (Figures 6 and 7).[136–139,141,142]

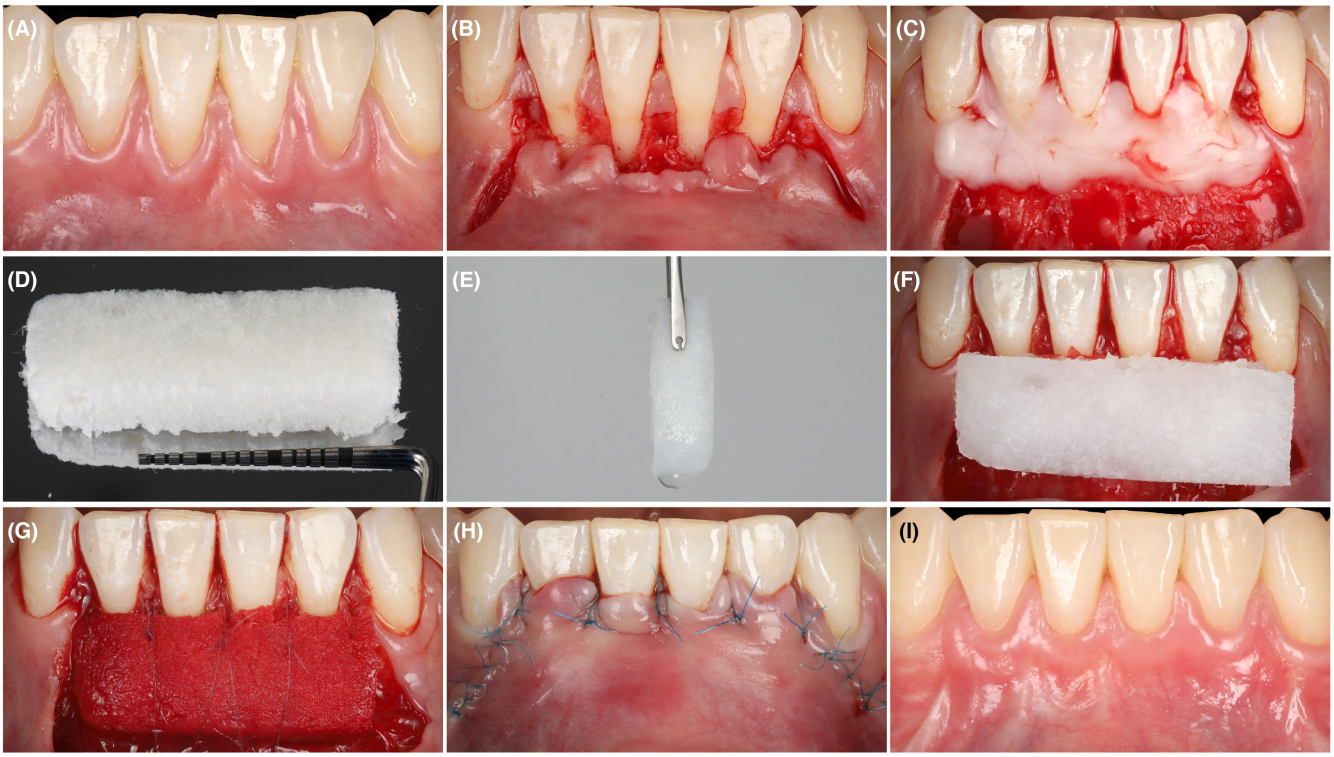

FIGURE 4 Treatment of multiple gingival recessions using a collagen matrix soaked with rhPDGF-BB. (A) Baseline. (B) Coronally advanced flap performed. (C) Mechanical and chemical root conditioning of the roots with 24% EDTA for 2 min. (D) Xenogeneic collagen matrix (Geistlich Fibro-Gide, Geistlich Pharma North America, Princeton, USA), (E) Collagen matrix soaked with rhPDGF-BB (GEM21, Lynch Biologics, Franklin, USA). (F, G) Stabilization of the collagen matrix to the recipient bed. (H) Flap advancement and closure. (I) 2-year outcomes. (Adapted from Tavelli et al.).[120]

In 2009 Nevins and coworkers described for the first time clinical and histological outcomes of 0.3 mg/mL rhPDGF-BB utilized with a mineralized collagen bone substitute for alveolar ridge preservation.[141] The healing was uneventful in all subjects, with the bone at the time of implant placement (4–6 months after alveolar ridge preservation) that appeared firm, with minimal graft particulate detected. Primary stability of the dental implants was obtained in all the sites. Microcomputed tomographic and histological analyses of the core biopsy samples obtained with a trephine demonstrated robust new bone formation throughout the extraction sockets, with intimate contact between the new formed bone and the few residual particles of the bone graft substitute (9.5% at 4 months, and 17.1% at 6 months). The new percentage of the new bone at 4 and 6 months was, on average, 23.2% and 18.2%, respectively.[141]

An early study from McAllister and coworker described for the first time the histological outcomes of extraction sockets 3 months after grafting with either rhPDGF-BB + beta-tricalcium phosphate (group 1) or rhPDGF-BB + anorganic deproteinized bovine bone (group 2).[138] Similar histological findings were observed within the two groups in terms of vital bone formation (on average, 21% for the group 1 and 24% for the group 2), and residual graft particles (on average, 24% for the group 1 and 17% for the group 2), with all implants that were placed without the need for further bone augmentation.[138] On the other hand, Wallace and coworkers obtained a greater new bone formation at extraction site previously treated with rhPDGF-BB + mineralized allograft compared to allograft alone (41.8% vs. 32.5%, respectively, after 4 months), suggesting that the growth factor could accelerate bone regeneration in extraction socket, possibly allowing for early implant placement.[142]

A pilot study investigated the histological and histomorphometric outcomes of the following four different treatment approaches in 16 subject of extraction socket defects lacking buccal wall: (i) mineral collagen bone substitute alone, (ii) mineral collagen bone substitute with rhPDGF-BB, (iii) mineral collagen bone substitute with enamel matrix derivative, and (iv) bone ceramic with enamel matrix derivative.[139] The graft was completely closed by the flap, with the alveolar ridge that was allowed to heal for 5 months. At this point, a trephine core biopsy was obtained during implant therapy. Histological and histomorphometric analyses revealed a superior trend for new bone formation at sites treated with rhPDGF-BB + bone graft compared to enamel matrix derivative + bone graft or bone graft alone, although these differences were not statistically significant, probably due to the limited sample size.[139] The samples from the sites treated with rhPDGF-BB showed robust bone formation with minimal residual bone graft particles and some native bone at the periphery, while the other three groups exhibited substantial amounts of bone particles after 5 months.[139] A more recent study demonstrated that the combination of rhPDGF-BB with bone allograft was able to significantly reduce the amount of residual bone particles in

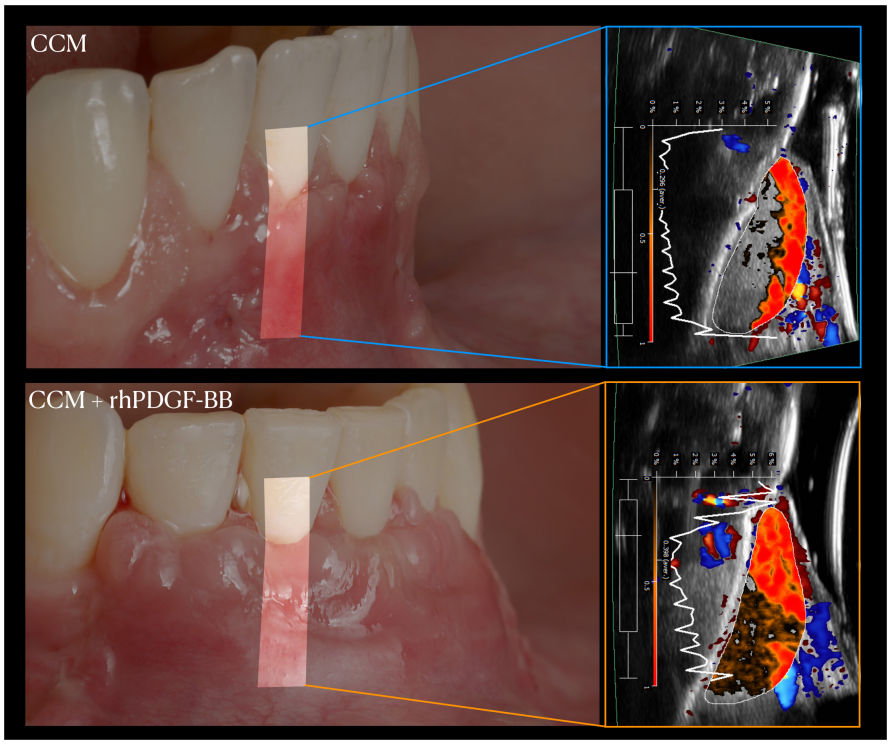

FIGURE 5 Ultrasonographic dynamic tissue perfusion assessment performed 2 weeks after root coverage procedures at sites grafted with a xenogeneic cross-linked collagen matrix (CCM) with or without rhPDGF-BB. The blood flow analysis shows the local distribution and intensity of tissue perfusion within the CCM. It is possible to appreciate an enhanced early vascularization at the site that received the growth factor-mediated approach.

the histological samples, while also providing a higher percentage of organic matrix compared to using bone graft alone for alveolar ridge preservation.[136,137] Mendoza-Azpur and coworkers further highlighted the possible benefits of utilized rhPDGF-BB for alveolar ridge preservation.[85] The authors reported that the extraction site treated with rhPDGF-BB and anorganic bovine bone significantly outperformed the control group (no biomaterials) in terms of buccolingual width after 4 months. Furthermore, histological findings revealed a significantly higher vascular microdensity in the rhPDGF-BB group compared to the control group. The Musashi-1 positive cells in the nonmineralized tissues were also significantly elevated at the sites treated with rhPDGF-BB. These findings, together with the substantially higher number of osteoblasts observed in the rhPDGF-BB group, led the authors to speculate that the sites treated with the growth factor may benefit from a transformation of mesenchymal stromal cells to osteoblasts.

Although more clinical studies exploring the outcomes and benefits or rhPDGF-BB for alveolar ridge preservation are needed before drawing convincing conclusions regarding the effects of this growth factor on extraction site healing, it should be highlighted that the recent American Academy of Periodontology Best Evidence Consensus statement recommended the use of biologics, including rhPDGF-BB, in challenging and compromised extraction sockets.[26]

3.2.4 | Horizontal and vertical bone augmentation

Currently, most of the available evidence on the use of rhPDGF-BB for ridge augmentation comes from case series or case reports[82,84,143–156] and, therefore, assessing the benefits of adding rhPDGF-BB to conventional bone augmentation procedures is not feasible.[64] Overall, rhPDGF-BB was utilized with autogenous bone graft,[144,157] bone allograft,[143,148–150,152,153] beta-tricalcium phosphate,[147] anorganic bovine bone particles,[144–146,151,155,157] xenogeneic bone block,[154,156] or a combination of different bone grafts.[82,84,144,145] (Figure 8). No complications related with the use of the growth factor have been reported, and therefore, the use of rhPDGF-BB should be considered safe also in these scenarios.[64] In a study comparing rhPDGF + beta-tricalcium phosphate to autogenous bone graft, it was found that the two approaches resulted in similar outcomes in all the assessed parameters.[147] Simion et al. described two cases of bone augmentation (one horizontal and the other vertical ridge augmentation) treated with a deproteinized bovine infused with rhPDGF-BB, without addition of barrier membranes. Histological analysis from biopsy specimens at the augmented sites showed areas of ongoing bone remodeling with alternately occurring demineralization and remineralization, with the authors speculating that rhPDGF-BB has the potential for promoting bone regeneration at large defects sites without the need for barrier membranes.[146] An animal study from the same group, comparing the regenerative capacities of xenograft alone, xenograft + rhPDGF-BB and xenograft + rhPDGF-BB + barrier membrane for vertical bone augmentation found that the greatest amount of newly formed bone was obtained at sites treated with xenograft + rhPDGF-BB, without the addition of a barrier membrane.[158] These findings led the authors to speculated that the periosteum may play a crucial role as a source of osteoprogenitor cells in growth factor-mediate regenerative therapies, and that using barrier membranes may limit the blood supply of the graft and chemotaxis of key cells for bone regeneration.[158]

TABLE 7 Root coverage outcomes of rhPDGF-BB-mediated approaches as alternatives of autogenous connective tissue graft.

Publication, reference	Study design	Patients (*N*), Gingival recessions (*N*), recession type	Follow-up (months)	mRC (%) and CRC (%)	Mean KTW change (mm)	Mean GT change (mm)	PROMs
Root coverage procedures with rhPDGF-BB + β-TCP							
Deshpande et al. (2014)[180]	RCT	NR, 28, RT1	6	87.8 and 71.4	0.8	NR	NR
McGuire et al. (2006)[107]	Case series	7, 7, RT1	6	NR	NR	NR	NR
McGuire et al. (2009)[108]	RCT	30, 30, RT1	6	90.8 and NR	1.0	NR	No differences in terms of pain and esthetics compared to CTG
McGuire et al. (2014)[110]	RCT	20, 30, RT1	60	74.1 and 60	1.0	NR	No differences in terms of esthetics and satisfaction compared to CTG
Singh and Suresh (2012)[117]	Case series	7, 7, NR	6	70.24 and NR	NR	NR	NR
Root coverage procedures with rhPDGF-BB + ADM							
Carney et al. (2012)[118]	RCT	17, 12, RT1 and RT2	6	84.1 and NR (for RT1 defects)	0	NR	NR
Root coverage procedures with rhPDGF-BB + barrier membrane							
Dandu and Murthy (2016)[116]	RCT	15, 15, RT1	9	87.37 and NR	NR	NR	Lower postop discomfort compared to the control group
Zadeh (2011)[115]	Case report	2, 8, RT1	12	NR	NR	NR	NR
Root coverage procedures with rhPDGF-BB + CCM							
Barootchi et al. (2022)[119]	Case report	2, 6	18	91.6 and 83.3	NR	0.64	Mean patient's rated satisfaction and esthetics (using 1–100 VAS) of 100 and 96.49, respectively
Tavelli et al. (2022)[120]	RCT	15, 47	6	88.25 and 59.57	0.32	0.80	Lower early morbidity and time to recovery compared to the group without rhPDGF-BB

Abbreviation: RCT, randomized, controlled, clinical trial.

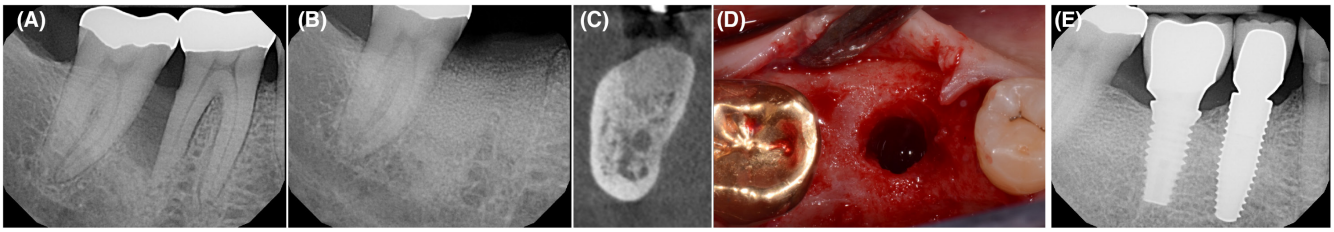

FIGURE 6 Implant site development with freeze-dried bone allograft (FDBA) and rhPDGF-BB. (A) Baseline. (B, C) The extraction socket was grafted with FDBA soaked with rhPDGF-BB. (C) Cone beam computed tomography scan taken after 4 months. (D) Re-entry and implant placement after 8 months. (E) Follow-up at 10 years.

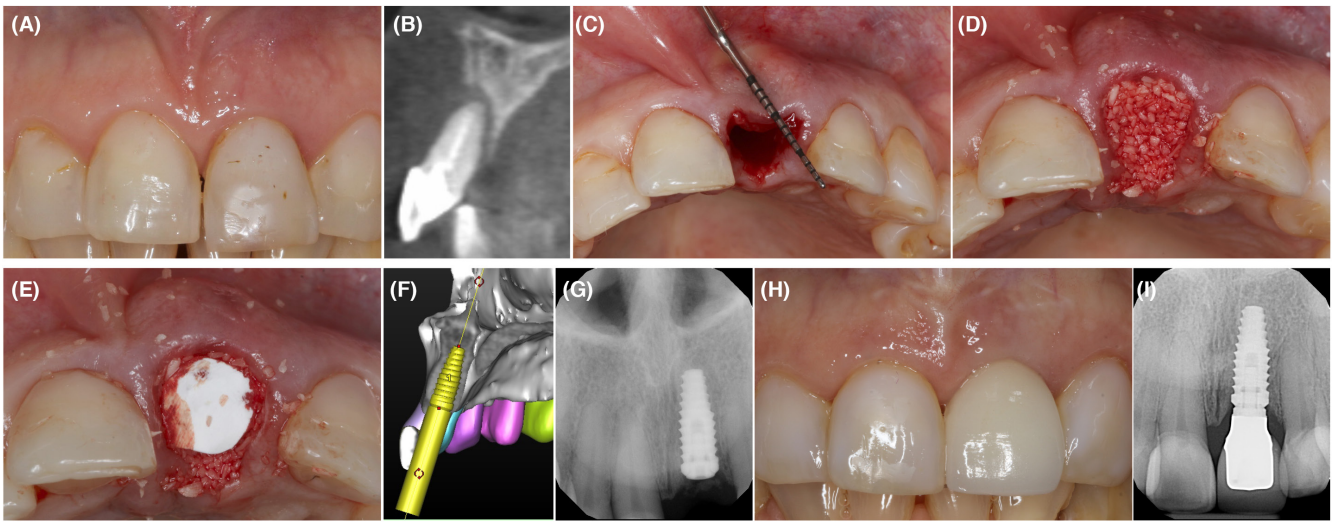

FIGURE 7 Flapless alveolar ridge preservation with freeze-dried bone allograft (FDBA) and rhPDGF-BB. (A) Baseline. (B) Cone beam computed tomography scan at baseline. (C) Clinical view after the extraction showing the lack of buccal bone of the extraction socket. (D) The socket was grafted with FDBA soaked with rhPDGF-BB. (E) A collagen membrane was applied on top of the bone allograft. (F) Digital planning of implant therapy after 4 months. (G) Implant placement 5 months after alveolar ridge preservation. (H, I) Clinical and radiographic outcomes at 5 years.

3.2.5 | Sinus floor augmentation

rhPDGF-BB has also been evaluated for maxillary sinus floor augmentation.[159–161] The first proof-of-principle study assessing rhPDGF-BB for this application was conducted by Nevins and coworkers, who aimed to investigate the adjunctive benefits of the growth factor when combined with particulate anorganic bovine bone mineral.[161] From a clinical point of view, all treated sites exhibited adequate bone for implant placement 6–8 months after the sinus augmentation. Core biopsies were also obtained at the at the time of implant placement. The authors observed large areas of dense lamellar bone with abundant numbers of osteoblasts secreting significant quantities of osteoid, indicating ongoing osteogenesis.[161] Froum and coworkers described a more rapid formation of vital bone in sinuses augmented with xenograft + rhPDGF-BB compared to xenograft alone.[159] After 4–5 months, the mean vital bone at sinuses augmented with bone graft alone was 11.8%, while at sinuses grafted with bone graft + rhPDGF-BB, the mean vital bone was nearly double (21.1%). These findings led the authors to speculate that the addition of the growth factor may allow for earlier implant placement following sinus augmentation.[159] In line with this hypothesis, Kubota et. al reported that combining deproteinized bovine bone graft with rhPDGF-BB reduced the healing time for sinus floor augmentation to 4 months, with a mean vertical bone height of 13 mm after 4 months.[160]

3.2.6 | Peri-implant hard and soft tissue reconstruction

Currently, few studies have described the use of rhPDGF-BB at implant sites.[86,162–164] Amorfini and coworkers observed that sites that received rhPDGF-BB for lateral bone augmentation—either with block allograft or guided bone regeneration—preserved better bone volume at 1 year compared to sites augmented without the growth factor. The difference between the two groups (augmented sites with and without rhPDGF-BB) was at the limit of significance ($p = 0.052$).[162]

In a split-mouth prospective, controlled, clinical study, Santana et al. investigated the outcomes of rhPDGF-BB in combination with beta-tricalcium phosphate for buccal bone reconstruction at the

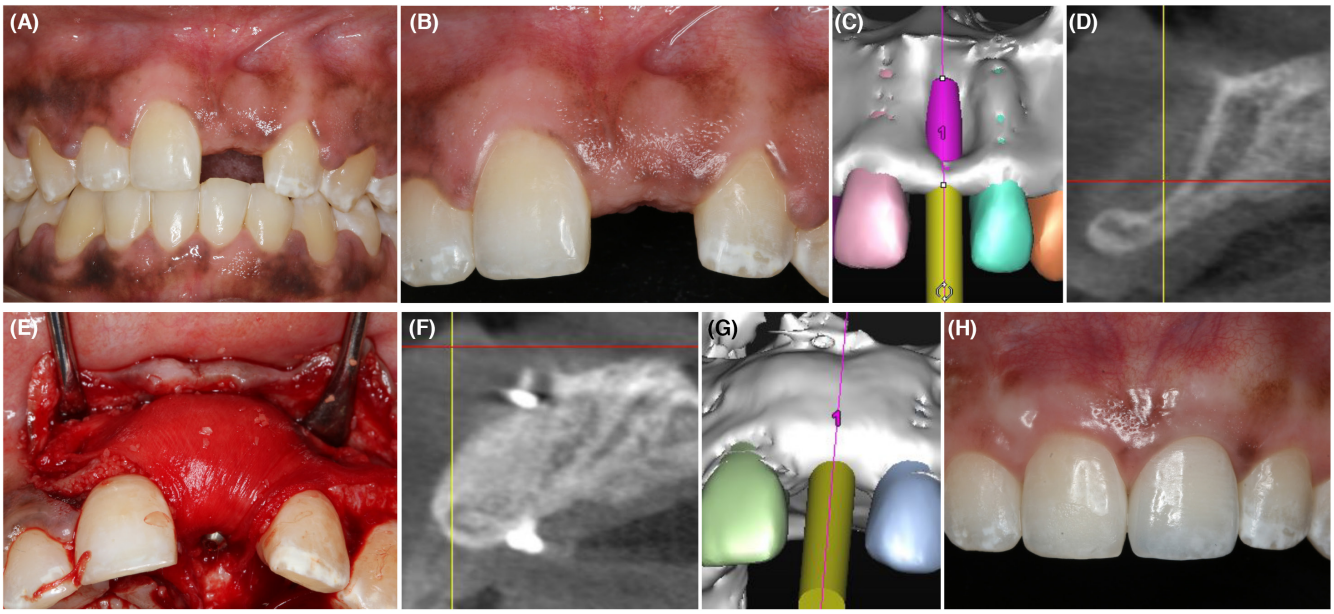

FIGURE 8 Horizontal bone augmentation with freeze-dried bone allograft (FDBA) and rhPDGF-BB. (A, B) Clinical view at baseline. (C) Digital implant planning visualizing the buccal bone deficiency. (D) Cone beam computed tomography scan. (E) A staged guided bone regeneration with FDBA soaked with rhPDGF-BB was performed. A collagen barrier membrane was stabilized on the palatal and buccal aspects on top of the bone allograft. (F) Cone beam computed tomography scan obtained 6 months after the augmentation procedure. (G) Digital planning for implant therapy. (H) Final outcome of implant rehabilitation at 1 year.

time of immediate implant placement, compared to dental implants placed in fully healed ridges not requiring bone augmentation. The authors demonstrated that immediate implant therapy at sites where the deficient buccal bone was reconstructed with rhPDGF-BB and beta-tricalcium phosphate was as effective as conventional implant therapy, in terms of survival rate (100% in both groups), clinical, and radiographic outcomes at 1 year.[163]

In a recent case report, Urban et al. described the use of rhPDGF-BB at different stages of bone reconstruction after a removal of a failed implant.[86] A patient presented with an anterior implant with advanced peri-implantitis and with the adjacent tooth showing deep probing depth in proximity of the implant. Four months after implant removal, vertical bone augmentation and simultaneous periodontal regeneration was performed using autogenous bone chips saturated with rhPDGF-BB. Additional rhPDGF-BB was applied over the root surface of the tooth prior to flap closure. After 7 months, the site was re-opened and a significant bone gain was noticed at the edentulous site and at the mesial aspect of the tooth. A dental implant was placed in an adequate prosthetic position. Autogenous bone chips from an apical region were combined with rhPDGF-BB to address the peri-implant bone deficiency. A nonresorbable membrane was utilized to augment the buccal and crestal bone, with additional bone graft that was added on the crest. The nonresorbable membrane was covered by a collagen membrane, with a connective tissue graft that was positioned on top of the collagen membrane to increase the supracrestal tissue height of the implant and to gain interproximal attachment at the level of the tooth. The flaps were reapproximated for obtaining primary closure. After several months of healing, and further soft tissue augmentation procedures, the implant was rehabilitated with satisfactory esthetic outcomes.[86]

Simion et al.[164] also described the application of rhPDGF-BB in combination with a collagen matrix for peri-implant soft tissue augmentation. The study included six patients that were previously treated with guided bone regeneration for hard tissue deficiencies in the anterior maxilla. Implants were placed either at the same time of bone augmentation, or at the time of membrane removal. At the time of second stage, the authors utilized a collagen matrix was infused with rhPDGF-BB and placed buccally and occlusally over the bone crest to augment peri-implant keratinized mucosa and soft tissue thickness.[164]

Future applications of rhPDGF-BB-mediated approaches at implant sites may include treatment of peri-implantitis. Figure 9 depicts a case of peri-implantitis treated with bone allograft and rhPDGF-BB.

3.3 | Current recommendations for clinical applications of rhPDGF-BB

There is robust evidence supporting the safety and the clinical benefits of rhPDGF-BB for periodontal regeneration and for the treatment of gingival recessions in the natural dentition.[26,64,78,79,120] Its application for implant site development and peri-implant augmentation has been demonstrated safe, yet the limited number of randomized controlled clinical trials aiming to evaluate the efficacy of rhPDGF-BB prevent definitive conclusions. Nevertheless, it has been advocated that rhPDGF-BB may enhance osteogenesis when combined with bone graft scaffolds for implant site development, and should be particularly considered in complex/large bone

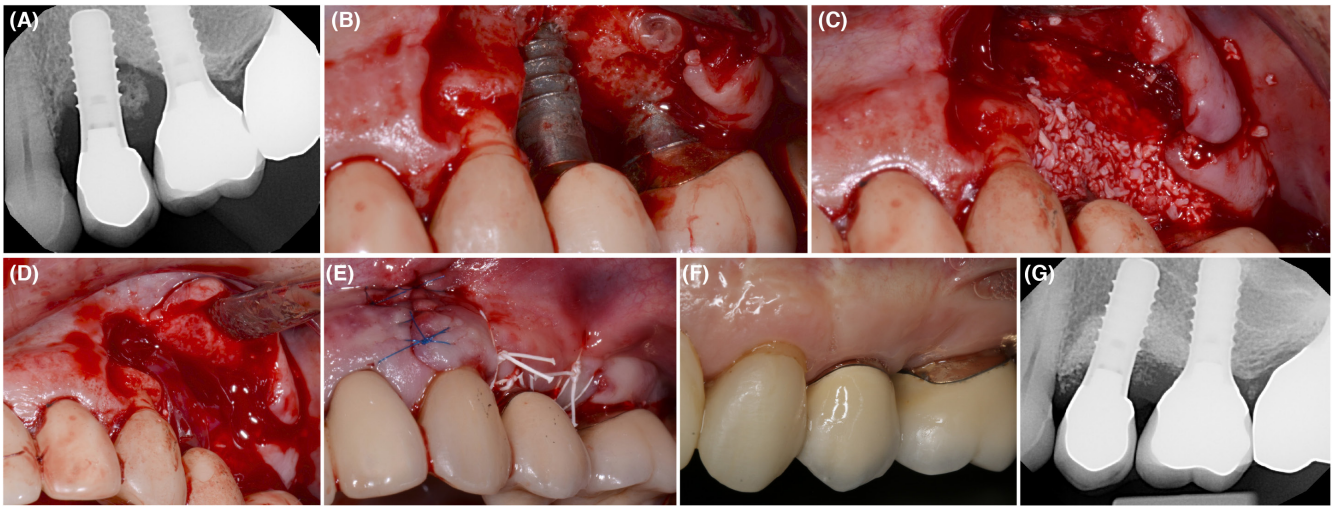

FIGURE 9 Treatment of peri-implantitis using freeze-dried bone allograft (FDBA) and rhPDGF-BB. (A) Periapical x-ray. (B) Flap elevation and defect degranulation. (C) Application of demineralized bovine bone mineral graft (Bio-Oss, Geistlich, Wolhusen, Switzerland) soaked with rhPDGF-BB into the defect. (D) Amniotic membrane positioned over the graft material and stabilized with absorbable pins. (E) Flap closure. (F, G) Clinical and radiographic outcomes at 8 years.

defects.[26] Studies addressing the cost-effectiveness of rhBMPs in oral regenerative procedures are advocated.

4 | FUTURE DIRECTION

The future—if not present—path of periodontology is without doubt in the direction of minimal invasiveness. Subjectively informed patient-reported outcomes are becoming more prominent than ever in determining our daily treatment decisions. The days of clinicians performing whichever surgical technique "necessary" to obtain a certain result are limited. Firstly, the concept of "necessity" in treatment outcomes is not a fixed construct, and depends on a variety of situations and considerations. Clinical endpoints, measurable with simply a ruler or a probe, do not reflect the entire outcomes. A major portion of our treatment outcomes are more and more geared toward patient satisfaction, and not just a surgical result. Thus, clinicians should rather consider the entire treatment experience. As such, reducing surgical and procedure chair time, patients' intra- and postoperative discomfort, their postoperative healing time, reducing the disruption of their daily activities and routine behaviors, and adjustments they need to make in their lives for accommodating the healing process, all heavily impact the overall perception of our treatments and, therefore, the overall result. Undoubtedly along this path lies the development and employment of novel surgical techniques, less-invasive approaches, utilization of microsurgical instruments, and certainly the application and use of biologics, bioactive mediators, and nonautogenous grafting substitutes, whenever possible. As healthcare providers through the lens of periodontology, we must strive to treat patients as a whole, and not merely their teeth/implants/tissues.

5 | CONCLUSIONS

The present review depicts the clinical application of rhBMPs and rhPDGF-BB over the past 25 years, highlighting their safety, clinical, radiographic, histologic, and patient-reported outcomes in different case scenarios. While more evidence is needed toward the additional clinical benefits of rhBMPs for bone regenerative procedures, a large body of studies supports the application of rhPDGF-BB for periodontal regeneration and root coverage procedures. Further studies assessing the efficacy of rhBMPs and rhPDGF-BB for implant site development and peri-implant augmentation are advocated. Future research should focus on the development of novel carriers and customized scaffolds for an optimal and sustained delivery of these growth factors.

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DATA AVAILABILITY STATEMENT

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