# AUGMENTATION PROCEDURES WITH RECOMBINANT HUMAN RECOMBINANT PLATELET-DERIVED GROWTH FACTOR BB FOR THE HORIZONTAL AND VERTICAL JAW RECONSTRUCTION - LITERATURE REVIEW

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**Summary**

Currently, Recombinant Human Platelet-Derived Growth Factor BB (PDGF-BB) is approved for periodontal regeneration with a bone-filling material only. Although this material needs to be used with a scaffold as a carrier, there has been considerable clinical interest in combining this growth factor with different bone grafts. This article reports literature review regarding using rhPDGF-BB with bone substitutes for implant site development. After careful evaluation of the literature data of current and emerging evidence, the off-label use of rhPDGF-BB was determined in the following reports to be consistent for the good clinical practice regarding bone augmentation.

**Key words:** recombinant human platelet-derived growth factor BB, augmentation, bone graft, dental implantation.

**Rezumat**

**PROCEDURI DE AUGMENTARE CU FACTORUL DE CREȘTERE RECOMBINANT PLACHETAR BB ÎN RECONSTRUCȚIILE ORIZONTALE ȘI VERTICALE ALE PROCESULUI ALVEOLAR - REVIUL LITERATURII**

Actualmente, factorul uman derivat plachetar recombinant BB (PDGF-BB) este aprobat pentru regenerarea periodontală numai împreună cu un material de augmentare osoasă. Din considerentele că acest material trebuie folosit pe un substrat pentru regenerare tisulară, se evidențiază un interes clinic considerabil în conbinarea acestui factor de creștere cu diverse grefe osoase. Acest articol reprezintă un reviu de literatură în vederea folosirii rhPDGF-BB cu substituiente osoase pentru reformarea regiunii de inserție a implantelor dentare. După o evaluare a datelor din literatură, utilizarea științifică a rhPDGF-BB relatează indicații bune pentru utilizarea în practică clinică referiotor la augmentarea osoasă.

**Cuvinte cheie:** factorul uman derivat platelar recombinant BB, augmentare, grefa osoasă, implantare dentară.

### Objectives

To evaluate the scientific value of the Recombinant Human Platelet-Derived Growth Factor BB (PDGF) for the horizontal and vertical jaw reconstruction according to the literature data.

### Search strategy

The Cochrane Oral Health Group's Trials Register, CENTRAL, MEDLINE and EMBASE were searched. Hand searching included several dental journals.

### Data collection and analysis

Data were extracted, in duplicate, by the present author.

### Introduction

The resorption of the alveolar ridges of the superior and inferior maxillary bones following tooth extraction, periodontal aggression and trauma is a physiologically undesirable and probably avoidable phenomenon [1]. The reconstruction of the vertical and horizontal defects and atrophies in human and animal trials has

been studied extensively by evaluating healing events via histological, radiological and clinical methods [2]. But in fact of these studies the vertical and horizontal regeneration of severe localized edentulous atrophic ridges remains a challenging procedure [3]. The available modalities for the bone reconstruction started to be compromised by different intraoperative and postoperative discomforts. With the exception of selected autogenous bone grafts and demineralized bone matrix, most bone replacement grafts are generally considered passive scaffolds providing a framework for cellular migration and tissue formation [4]. The "gold standard", the autogenous graft, requires invasive techniques for harvesting of bone from intra oral and extra oral regions. And, also in front of the well known advantages of auto grafts, like its capacity for osteoconduction as well as induction and restricted immune reaction, there are also significant drawbacks, like induction of a secondary defect at the donor site, followed by possible infection and donor-site-morbidity. The resorption of such grafts could grow up till 50% of the total volume of reconstructed site [5]. The demineralized bone matrix, which is represented on the market by the deprotenized bovine bone (DBB) showed a resistance to resorption following placement into bony defects or as an onlay graft. It has been shown to induce periodontal and periimplant bone regeneration. But these applications are recognized to assist in regeneration of the small amount of lost bone [6].

The bone splinting and horizontal alveolar distraction are an alternative technique to harvesting operations [7, 8, 9]. But this technique has limitations due to non-toleration of the devices and a small amount of bone especially when the vertical augmentation is indicated. At the moment the most common methods of ridge reconstructions include grafting procedures, with or without coverage by a barrier membrane, the guided bone regeneration (GBR). Bone replacement grafts and GBR membranes appear to function primarily through the preservation of space critical for clot development and tissue maturation. However, the barrier function and the membrane longevity may differ considerably, thereby limiting their function to a few weeks [3]. Also, the membrane placement is often associated with flap dehiscence due to compromised vascularity, which can adversely impact the regenerative outcome [10,11,12,13].

To avoid these problems, new techniques were initiated which include combination of the GBR and tissue engineering. Tissue engineering is broadly defined as the application of engineering and life-science principles to develop biological substitutes that improve or reconstitute organs, tissues, and tissue function [14]. Early efforts to engineer periodontal and alveolar bone regeneration relied largely on matrices or scaffolds, including bone grafts and synthetic bone substitutes, or cell-exclusive materials that compartmentalize the regenerative site, as in GBR.

The regenerative process of the skeletal system is characterized by the remodeling cycle, in which cell populations are recruited and differentiated for the purposes of bone resorption or bone formation. These activities are coordinated and regulated by an elaborate system of growth factors and cytokines, several of which are either now available or in promising stages of development for clinical application through recombinant technology.

Recent attention has focused on the potential for biological mediators to improve wound healing and enhance the clinical benefits of bone replacement grafts [15]. The introduction of recombinant growth factors for osteogenic enhancement has potentiated the possibilities of bone augmentation of edentulous deformities for the purpose of implant placement. This process is dependent on the presence of 3 critical ingredients: molecular signals, responding cells with associated receptors and assembly of the extracellular matrix [16]. One of the crucial biological factors responsible for reparative osseous activity is platelet-derived growth factor (PDGF). PDGF was discovered as a major mitogenic factor present in serum but absent from plasma. It was found to be secreted from the α-granules of platelets activated during the coagulation of blood to form serum. PDGF works by binding to cell-surface receptors on most cells of mesenchymal origin, and it stimulates the reparative processes in multiple tissue types. The potent stimulatory effects of PDGF as a chemo attractant and a mitogen, along with its ability to promote angiogenesis, complementing the actions of vascular endothelial growth factor (VEGF) in vessel formation, position it as a key mediator in tissue repair [17,18]. Subsequent studies have demonstrated that PDGF is not one molecule but three, each a dimeric combination of two distinct but structurally related peptide chains designated A and B. The group PDGF polypeptide growth factors include PDGF-A, B, C, and D, encoded by four genes located on different chromosomes.

Following injury and hemorrhage, bone repair is characterized by activation of the coagulation cascade and formation of a blood clot at the site of trauma (Fig. I). Platelets aggregate and release their cytokine-laden granules, including varying amounts of PDGF-AA, PDGF-BB, and PDGF-CC, into the developing blood clot.

As a consequence of injury, alpha granules containing PDGF are jettisoned by platelets for the purpose of angiogenesis, chemotaxis, and mitogenesis. Transforming growth factor-beta (TGF-b) also appears to play a role in chemotaxis and cell proliferation during wound-healing. The attraction of osteoprogenitor cells (chemotaxis) and their increase in number (mitogenesis) provide a pool of osteo-regenerative cells that will respond to the bone morphogenetic proteins (BMP) [19].

PDGF-BB has been shown to enhance the chemo tactic and mitogenic activity of periodontal ligament cells at concentrations as low as 1 ng/mL [20, 21]. PDGF-BB delivered in a methylcellulose gel was reported to have a half-life of 4.2 hours, with greater

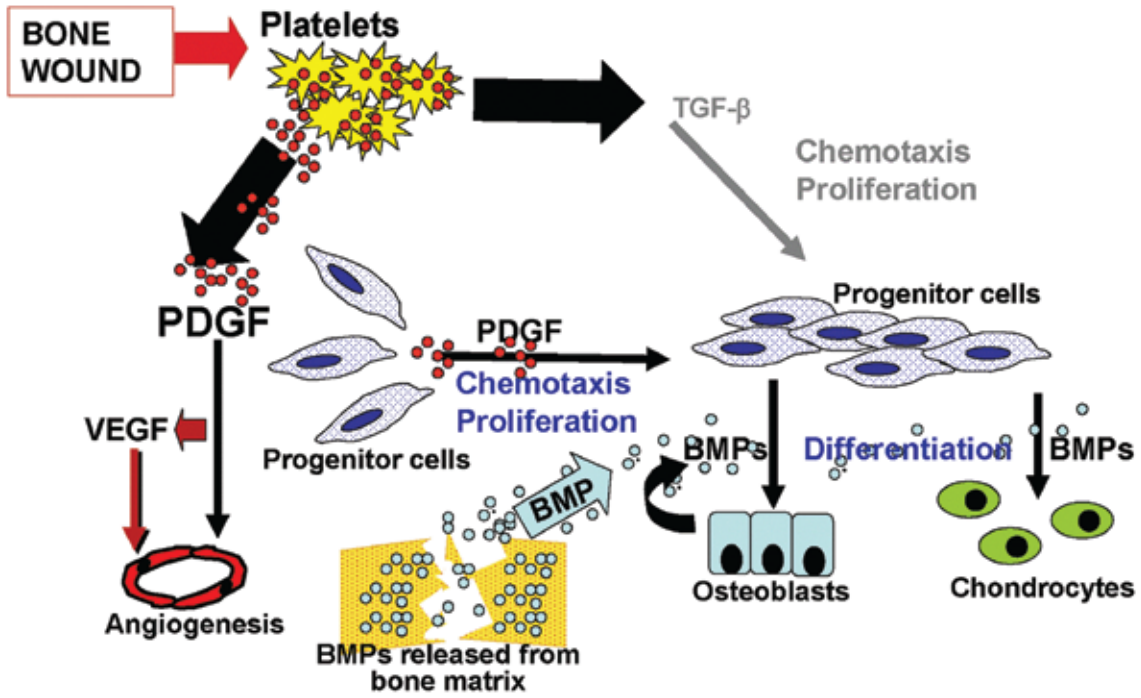


**Fig. I** Platelet-derived growth factor (PDGF): action and bone regeneration [19].

than 96% clearance of the radio labeled growth factor by 96 hours, when applied for the treatment of naturally occurring periodontal disease in beagle dogs [22]. Accordingly, following clinical application, the potent actions of this growth factor must occur early, triggering a cascade of biologic and cellular events at the surgical wound. These effects are characterized by the recruitment and differentiation of mesenchymal cell populations, as well as new vessel formation, ultimately supporting wound healing and regeneration [17]. Cooke et al [23] examined the effects of PGDF-BB on levels of VEGF and bone turnover in periodontal wound fluid in 16 patients who were randomized to receive treatment of intrabony defects with either ß-TCP carrier alone, ß-TCP plus 0.3 mg/mL rhPDGF-BB, or ß-TCP plus 1.0 mg/mL rhPDGF-BB. These patients had participated in a large clinical trial evaluating the efficacy and safety of PDGF-BB in the treatment of intraosseous periodontal defects. Pyridinoline cross-linked carboxyterminaltelopeptide of Type I collagen (ICTP) is an indicator of osseous metabolic activity and provided a marker of bone turnover. Low-dose rhPDGF-BB application was found to elicit increasing in ICTP at 3 to 5 days in the wound healing process, with the 1 mg/mL rhPDGF-BB group showing the most pronounced difference in VEGF at 3 weeks. Thus, a single dose of rhPDGF-BB exhibited demonstrable, sustained metabolic actions at the clinical site of application [24]. In a parallel study, the release of the ICTP into the periodontal wound fluid was monitored longitudinally in 47 patients for 24 weeks following regenerative surgical treatment with PDGF-BB. The 0.3 and 1 mg/mL PDGF-BB treatment groups exhibited increases in levels of ICTP for as much as 6 weeks. ICTP levels were significantly higher in defects treated with PDGF-BB and ß-TCP compared with sites grafted with ß-TCP alone at the 6-weeks point. Given the rapid biologic clearance of the growth factor, these results provide further evidence that a single administration of PDGF-BB exerts a sustained effect on periodontal bone metabolism and helps clarify the sequence and timing of signal cascades involved in periodontal wound healing [24].

Currently, PDGF-BB is clinical approved for periodontal regeneration together with bone-filling material only [24]. Although the bone-filling material uses ß-TCP as the scaffold/carrier, there has been considerable clinical interest in combining this growth factor with other bone replacement grafts, particularly bone allografts. Bone allografts, such as freeze-dried bone allograft and demineralized freeze-dried bone allograft, exhibit highly osteoconductive surfaces and support well-documented clinical improvements in periodontal parameters compared to open flap debridement [25]. These materials have also been shown to possess variable amounts of growth factors, including bone morphogenetic proteins, and the capacity for osteoinduction [26]. Because of the safety and efficacy profile of bone allografts, the potential to serve as carriers for growth factors and other biologic mediators has been extensively explored and documented in cell-culture and preclinical models. Clinical case reports also provide information on the clinical efficacy of PDGF-BB being used with bone allografts. Nevins et al [27] and Camelo et al [28], reported human histological evidence of periodontal regeneration in intra-osseous defects treated employing a combination of rhPDGF-BB and ß-TCP. Nevins et al [29] reported a case series describing the clinical and radiographic outcomes following the treatment with rhPDGF-BB and ß-TCP of severe periodontal intrabony defects. Clinical reentry and radiographs at one year showed

complete bone fill, indicating that rhPDGF combined with ß-TCP provides excellent clinical results. Preclinical studies regarding combination of an aloplastic material with a rhPDGF-BB showed the potential to support only initial stages of guided bone regeneration at chronic-type lateral ridge defects [16].

Preclinical studies and case reports provide proof of principle that rhPDGF-BB, when combined with other graft matrices, can support improved bone formation and wound healing in alveolar ridge reconstruction and implant therapy. Lynch et al [30] found that the direct application of a combination of rhPDGF-BB and IGF-1 around dental implants produced two to three times more new bone at earlier periods in dogs. Becker et al [31] reported an increase in the percentage of implant surface in contact with bone and total length of the implant surface in contact with bone in dehiscence defects treated with expanded-polytetrafluoroethylene membranes (ePTFE) plus PDGF/IGF-I compared with the defects receiving ePTFE membranes alone in dogs. Simion et al. [3] reported a canine study that demonstrated the potential for a deproteinized cancellous bovine block, when infused with rhPDGF-BB, to regenerate significant amounts of new bone in severe mandibular vertical ridge defects without placement of a barrier membrane. The xenogenic block grafts were infused with rhPDGF-BB and stabilized in alveolar defects using two dental implants with or without collagen membranes. The alveolar ridge defects treated with the combination of rhPDGF-BB plus xenograft without a collagen membrane demonstrated the greatest bone formation based on radiographic and histologic outcome measures. The histologic findings revealed robust osteogenesis throughout the block grafts, with significant graft resorption and replacement. In contrast, alveolar ridge defects treated with traditional GBR without the growth factor supported little or no bone formation. Simion et al. [3] reported similar findings using rhPDGF-BB in combination with a novel equine hydroxyapatite and collagen (eHAC) bone block in the canine model. Moreover, recent case reports demonstrate that anorganic bovine bone can serve as effective scaffolds to deliver rhPDGF-BB for lateral ridge augmentation and reconstruction, following extraction for implant placement [27,29]. The scientific base is that during bone regeneration by osteoinduction of the graft (anorganic bovine bone - DBB), pluripotent cells differentiate underinfluence of humoral and bone morphogenetic proteins into osteoblasts, which can thanproduce osteocytes [32]. By the other way the DBB regulates micro RNA which represent a class of small, functional, noncoding RNAs of 19 to 23 nucleotides that regulate the transcription of messenger RNAs in proteins [33]. The benefit of this combination is advocated by the presence of the rhPDGF-BB as an interface between graft and anatomical site. In this way the osteoconductive and osteoinductive process could be induced and mentained byrhPDGF-BB.

**Results**

Recombinant growth factor technology has increased the options for combinatorial approaches to reconstructive oral surgery. Graft matrices that are space maintaining and osteoconductive support in preventing soft-tissue collapse and provide a scaffold for cellular migration and stabilization of the blood clot. Graft matrices, such as ß-TCP and deproteinized cancellous bovine substitutes, can also serve as delivery devices for drugs and biologics, although the release kinetics can differ among scaffolds. The clinical potent effect of rhPDGF-BB on both bone and soft-ti ssue healing expands the ability to manage cases with bone atrophy and soft tissue dehiscence. For cases in which bone preservation is required, the tissue contours can be maintained with minimally invasive protocols. For sites requiring hard- and soft-tissue augmentation, these procedures can be combined to reduce the number of surgical procedures for patients. Although highly favorable clinical outcomes have been achieved using PDGF-BB in combination with deproteinized cancellous bovine bone grafts. Deproteinized cancellous bovine bone combined with PDGF-BB appear to stimulate more robust bone formation and rapid wound closure, enhancing the development and preservation of bony and gingival contours critical for achieving esthetic implant outcomes. The use of this growth factor in combination with scaffolds for therapeutic indications other than periodontal defects must be based on firm scientific rationale and sound medical evidence.

The clinical goals of growth-factor enhanced therapy include less invasive surgical procedures with more robust and predictable treatment outcomes [19,34]. Although autogenous grafts remain widely considered the gold standard for the correction of localized ridge deformities [35], constraints in the volume of available autogenous bone and morbidity associated with graft harvest often limit treatment recommendations and patient acceptance. The ability to achieve optimal and predictable bone and soft tissue for the implant site development without the use of autogenous grafts offers great advantage to the clinician and patient.

The clinical application of bone xenografts for the development of extraction sites, lateral and vertical ridge augmentation is well documented in implant therapy [36,37]. Clinical evidence supports the use of xenogenic grafts for ridge augmentation for dental implant placement [38,39]; however, the extent of bone regeneration appears variable and dependent on factors such as graft form—particulate versus block—and defect location.

The literature overviews presented in this article illustrate the application of growth-factor enhanced grafts and highlight the favorable clinical results achieved with this therapeutic approach. Controlled pre clinical experiments are necessary to establish the relative effectiveness of rhPDGF-BB combined with xenogenic deproteinized cancellous bovine scaffolds

for early bone formation in case of vertical and horizontal augmentation. The secondary studies should be addressed to determine the value of the resorbable barrier membranes to improve these procedures.

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