Significance of the platelet-derived growth factor in periodontal tissue regeneration

Fawad Javed a, Mansour Al-Askar a,b, Abdulaziz Al-Rasheed a,c, Khalid Al-Hezaimi a,c,*

a Eng. A.B. Research Chair for Growth Factors and Bone Regeneration, College of Dentistry, King Saud University, Riyadh, Saudi Arabia
b Department of Periodontology, School of Dental Medicine, Tufts University, USA
c Department of Periodontics and Community Dentistry, College of Dentistry, King Saud University, Riyadh, Saudi Arabia

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A B S T R A C T
Aim: The aim was to review the significance of the platelet derived growth factor (PGDF) in periodontal tissue regeneration.
Methods and results: Databases were searched using the following terms in different combinations: "growth factors", "guided bone regeneration", "guided tissue regeneration", "periodontal", "platelet rich plasma" and "platelet derived growth factor". Titles and abstracts of articles obtained using the above-described criteria were then screened by the authors and checked for agreement. The next step was to hand-search the reference lists of original and review studies that were found to be relevant in the previous step. PDGF has a stimulatory effect on the DNA replication and chemotaxis of osteoblasts, fibroblasts, leukocytes, monocytes, neutrophils periodontal and alveolar bone cells. Proliferation of mesenchymal stem cells is also promoted by supplement treatment with PDGF. PDGF in combination with other growth factors enhances periodontal tissue repair.
Conclusions: The PDGF plays a significant role in periodontal bone and tissue regeneration.
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* Corresponding author at: Eng. A.B. Research Chair for Growth Factors and Bone Regeneration, College of Dentistry, King Saud University, Riyadh, Saudi Arabia. Tel.: +966 50 2303000; fax: +966 1 467 7326.
E-mail address: hezaimik16@gmail.com (K. Al-Hezaimi).
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1. Introduction

Tissue regeneration is a complex biological process requiring intricately regulated interactions between cells, local and systemic growth factors and the extracellular matrix components in which these entities interact.1-3 A critical issue in periodontology and dental implantology continues to be the regeneration of periodontal tissues including the alveolar bone, cementum and the periodontal ligament (PDL). In periodontology, the concept of tissue engineering initiated with guided tissue regeneration (GTR), a mechanical approach that utilizes non-resorbable barrier membranes to allow clot stabilization and selective colonization of the defect area by PDL cells, to regenerate periodontal tissues.4,5 In dental implantology, guided bone regeneration (GBR) (with or without mechanical support), is performed for bone augmentation of the proposed implant installation site.6,7 Various biological approaches have been used for the promotion of periodontal tissue regeneration. These include the use of growth factors (GFs), application of extracellular matrix proteins and use of mediators of bone grafts.

GFs are natural proteins that regulate the cellular events involved tissue repair and regeneration. Intracellular signalling pathways are induced after the GFs bind to specific cell membrane receptors of the target cells. This results in the activation of genes that may eventually alter cellular activity and phenotype. Experimental studies have shown that GFs have the potential to enhance tissue regeneration by a series of events including cell chemo-attraction, differentiation and proliferation (Fig. 1).8,9 Nevertheless, the impact of various GFs on tissue regeneration may differ from one another depending on the enzymes and binding proteins involved.

1.1. The platelet derived growth factor—structure, isoforms and biology

Within the family of GFs, the class of proteins that has been extensively investigated particularly with reference to the regeneration of periodontal tissues is the platelet derived growth factor (PDGF).10-29 The PDGF is a natural protein found abundantly in the bone matrix. It presents as dimers of A, B and C polypeptide chains linked by disulphide bonds. Four isomeric forms of PDGF, namely PDGF-AA, PDGF-AB, PDGF-BB and PDGF-CC have been identified30-32; however, more recently an additional isomer, PDGF-DD has also been verified.33 PDGF binds to two structurally related but distinct receptor types: PDGF alpha-receptors (or A-type receptors) bind all three isoforms with high affinities; however, beta-receptors (or B-type receptors) bind PDGF-BB with high affinity and PDGF-AB with a comparatively lower affinity, but do not bind PDGF-AA with any considerable affinity.34 The PDGF receptor signalling has been reported to play an important role in the regulation of proliferation and migration of cells including osteoblasts and fibroblasts (Fig. 2).30,31 Results by Nistér et al.35 showed that PDGF-AA has no chemotactic activity or ability to induce reorganization in human fibroblasts; however, it has been reported PDGF-BB stimulates the proliferation of osteoblasts and fibroblasts.36,37 All isoforms of PDGF are available in recombinant human (rh) forms.

Since GFs play an essential role in the repair and regeneration of jeopardized periodontal tissues; the expression of their respective receptors on the injured tissues are of prime significance in maintaining the periodontal integrity and mediating healing. From the literature reviewed, it was observed that the expression of these receptors in the gingiva, periodontal ligament and regenerated periodontal tissues is weakly defined. The study by Parkar et al.38 demonstrated a weak expression of beta-receptors of PDGF in the regenerated periodontal tissues; however, alpha-receptors for this growth factor were not expressed by the periodontal tissues. This suggests that the PDGF beta-receptors (PDGF-BB) are likely to contribute in periodontal healing and regeneration to a greater extent as compared to alpha receptors for PDGF. The clinical success and safety that have been demonstrated with use of rhPDGF-BB in the treatment of periodontal osseous defects have led to the approval of this protein by the United States Food and Drug Administration for this indication.39,40

2. Rationale and objective

The aim of the present paper is to review the significance of PDGF in periodontal tissue regeneration.
In this review, we will consider the clinical applications of PDGF with reference to periodontal regeneration and provide an update for studies of clinical outcomes. The review will bring together all forms of available scientific evidences in these respects (e.g. the structure and chemistry of PDGF, the biology of PDGF and lessons learned from clinical and experimental studies on the effect of PDGF on periodontal regeneration) and consider the possible underlying mechanisms.

3. Materials and methods

3.1. Eligibility criteria

The following eligibility criteria were entailed: (1) case-reports; (2) human studies; (3) experimental studies; (4) reference list of potentially relevant original and review articles; (5) intervention: significance of the PDGF in periodontal regeneration; (6) articles published only in English-language.

Letters to the editor, historic reviews, and unpublished data were not sought.

3.2. Search strategies

The authors explored the MEDLINE/PubMed databases of the National Library of Medicine, Bethesda, Maryland for appropriate articles addressing the significance of PDGF in periodontal regeneration. Databases were searched from 1988 up to and including June 2011 using the following terms in different combinations: “growth factors”, “guided bone regeneration”, “guided tissue regeneration”, “periodontal”, “platelet rich plasma” and “platelet derived growth factor”. Titles and abstracts of articles obtained using the above-described criteria were then screened by the authors and checked for agreement. The full-text of the articles judged by title and abstract to be relevant were read and independently evaluated against the stated eligibility criteria.

Hand-searching of the reference lists of potentially relevant original and review studies was also performed. The structure of the present literature review was customized to primarily summarize the pertinent information.

4. Role of platelet derived growth factor in periodontal bone regeneration

Autogenous bone grafts have traditionally been used for the treatment of osseous defects; however, the advent of tissue matrices (such as allogenic, xenogenic and synthetic grafting materials) proved to be a turning point in periodontal regenerative therapies. These tissue matrices may either be used alone or in conjunction with a barrier membrane.

The effects of GFs on bone and soft-tissue metabolism have been intensely investigated. Nearly three decades ago, in their study on beagle dogs, Lynch et al.39 showed that the PDGF promotes new bone formation around periodontal bony defects. The results also demonstrated a continuous layer of osteoblasts lining the newly formed bone in the test-sites (sites treated with PDGF) compared to the control sites (sites without PDGF treatment).39 Since then several clinical and experimental studies have been performed to investigate role of PDGF in periodontal bone regeneration (Tables 1 and 2).

Several clinical6,10–22 and experimental studies6,23–28 have been performed to investigate the potency of PDGF in the treatment of periodontal bony defects. In their study on six adult foxhounds, Simion et al.25 investigated the outcome of vertical ridge augmentation by combining rhPDGF with a block of deproteinized cancellous bovine bone. Animals that were treated with deproteinized cancellous bovine bone (with membrane) served as controls. After 4 months of treatment, the animals were sacrificed and jaw segments (containing the test- and control-sites) were evaluated histologically. The histological results showed that the test-sites (sited treated with bovine bone and rhPDGF) displayed significantly more new bone formation both coronally and apically compared to the control-sites (sites treated with bone only and covered with membrane). The result showed that rhPDGF when used in combination with cancellous bovine bone significantly enhances new bone formation compared to when the bone mineral is used alone.25 Likewise, in clinical case-report, Urban et al.4 demonstrated that use of rhPDGF in combination with bone mineral and barrier membrane enhances new bone formation around periodontal bone defects. The PDGF has also been used for the bone regeneration around peri-implant...
Table 1 – Clinical studies on the effects of platelet derived growth factor in the treatment of periodontal osseous defects.

<table>
<thead>
<tr>
<th>Authors et al., year</th>
<th>Participants</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
</table>
| Jayakumar et al., 2011 | 54 Patients | Group 1: rhPDGF and βTCP  
Group 2: β-TCP + xenograft | At 6-months, new bone formation was significantly more amongst patients in Group 1 compared to those in Group 2 |
| McAllister et al., 2010 | 11 Patients | Group 1: rhPDGF, βTCP  
and NBM  
Group 2: rhPDGF, xenograft | Use of rhPDGF either with βTCP or with a xenograft promotes new bone formation in extraction socket defects |
| Urban et al., 2009 | 30-Year-old female | rhPDGF + NBM + membrane | rhPDGF + NBM + membrane supports guided bone regeneration at severe alveolar bone defects |
| Mellonig et al., 2009 | 4 Patients | rhPDGF + NBM + membrane | Clinical signs of periodontal inflammation were significantly reduced following treatment with BM soaked in rhPDGF |
| Fagan et al., 2008 | 52-Year-old male | rhPDGF + NBM + membrane | rhPDGF + NBM + membrane supports GBR at alveolar bone defects around delayed and immediate implants |
| Nevins et al., 2009 | 8 Patients | rhPDGF + NBM without membrane | New bone formation was observed at 4- and 6-month specimens |
| Nevins et al., 2009 | 12 Patients | rhPDGF + NBM without membrane | The treatment resulted in new bone formation which was in close contact with graft particles |
| Simion et al., 2008 | One patient | rhPDGF + NBM + membrane | Bone had regenerated throughout the whole area and the xenograft particles were embedded in bone |
| Ridgway et al., 2008 | 8 Patients | rhPDGF-BB, βTCP and BM  
Patient 1: NBM and rhPDGF  
Patient 2:NBM embedded in collagen matrix soaked in rhPDGF | In 81.25% cases, new bone formation was observed |
| Simion et al., 2007 | 2 Patients | Patient 1: NBM and rhPDGF  
Patient 2: NBM and rhPDGF | Significant amount of new bone formation around the defects was observed in both cases. Clinical signs of periodontal inflammation were also reduced following PDGF treatment |
| Nevins et al., 2005 | 180 Patients | Test sites: rhPDGF and βTCP  
Control sites: βTCP and buffer | The test-sites showed significantly more bone refill compared to the control sites |
| Nevins et al., 2003 | 9 Patients | Test sites: rhPDGF and allograft  
Control sites: A graft material and membrane | Test sites showed a complete regeneration of periodontal apparatus including new bone compared to the control sites |
| de Obario et al., 2000 | 5 Patients | Platelet rich plasma and NBM | Significant amount of new bone formation around the defects was observed as early as 2-months following PDGF treatment |
| Howell et al., 1997 | 38 Patients | Test sites: rhPDGF-BB and rhIGF-1  
in a vehicle  
Control sites: Conventional flap surgery | The test-sites showed significantly more new bone formation around periodontal defects compared to the control sites |

βTCP: beta-tricalcium phosphate; BCP: biphasic calcium phosphate; GBR: Guided bone regeneration; IGF-1: insulin like growth factor-1; NBM: natural bone mineral; PDGF: platelet derived growth factor-BB; rh: recombinant human.

defects. McAllister et al.11 assessed the significance of the PDGF-BB in bone regeneration around dental implants following tooth extraction. In this study, twelve premolar extraction sockets were randomly assigned for treatment with PDGF-BB in combination with either a collagen containing deproteinized bovine bone (xenograft) or a beta-tricalcium phosphate (β-TCP). After 3 months, a histological assessment of extraction socket healing was performed and the results showed that the use of rhPDGF-BB with either a xenograft or a β-TCP resulted in uneventful socket healing. At the phase of final phase of implant treatment (restoration phase), all implants demonstrated 100% osseointegration.11

In an in vitro study, Sanchez-Fernandez et al.40 tested the hypothesis that osteoclasts can regulate the chemotaxis of osteoblasts. The results showed that mature osteoclasts produce factors including the PDGF that attract osteoblasts towards the injured or inflamed sites thereby promoting new bone regeneration in the target tissues.40 Similarly, the Park study36 also reported that PDGF-BB promotes the proliferation of osteoblasts around periodontal defects. It is therefore apparent that rhPDGF exerts a chemotactic effect on osteoblasts around the infected periodontal and peri-implant tissues (that have increased osteoclastic activity41) thereby promoting new bone formation in the jeopardized areas (Figs. 3 and 4).

5. Role of the platelet derived growth factor in the regeneration of periodontal ligament and cementum

Cell migration, differentiation and proliferation are amongst the prerequisites for a successful wound healing. Besides osteoblasts, the periodontal wound also requires proliferation of various other cells including gingival- and PDL fibroblasts in order to facilitate tissue repair and regeneration. Studies have shown that following injury, several GFs including the PDGF are released from the blood and cells

adjacent to the wound site. The PDGF-BB has been reported to enhance the proliferation of human gingival fibroblasts thereby promoting stimulate periodontal soft tissue repair. Similarly, Pountos et al. investigated the effect of PDGF-BB on the proliferation and osteogenic differentiation of mesenchymal stem cells (MSCs) derived from patients with osteoporosis. The results showed that the proliferation of MSCs was stimulated by supplementation with the PDGF-BB in comparison to other proteins including bone morphogenetic protein-7 and parathyroid hormone. This study concluded that the PDGF-BB enhances the proliferation and osteogenic differentiation of MSCs; however, controversial results have also been reported. Results from the Kumar study reported that

![Diagram](image)

**Fig. 3** - Impact of various growth factors on periodontal tissue regeneration (modified from reference numbers 46–53). BMP-2: bone morphogenetic protein-2; EMD: enamel matrix derivative; PDGF: platelet derived growth factor; PDL: periodontal ligament; TGF-β: transforming growth factor-beta.

### Table 2 - Experimental studies on the effects of platelet derived growth factor in the treatment of periodontal osseous defects.

<table>
<thead>
<tr>
<th>Authors et al., year</th>
<th>Study animals</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwarz et al., 2010</td>
<td>4 Dogs</td>
<td>rhPDGF + NBM + membrane</td>
<td>rhPDGF soak-loaded on BM supports bone formation at chronic-type lateral ridge defects</td>
</tr>
<tr>
<td>Schwarz et al., 2009</td>
<td>4 Dogs</td>
<td>rhPDGF + BCP + membrane</td>
<td>rhPDGF + BCP supports guided bone regeneration at chronic-type lateral ridge defects</td>
</tr>
<tr>
<td>Rocchietta et al., 2007</td>
<td>6 Dogs</td>
<td>Group 1: rhPDGF, NBM and membrane; Group 2: rhPDGF, NBM without membrane</td>
<td>Bone regenerated via non-autogenous grafts displays composition, structure, and physical properties very similar to those of native bone. There was no difference in bone composition or structure between the groups. Animals in Group B showed significantly more new bone formation compared to animals in Groups A and C</td>
</tr>
<tr>
<td>Simion et al., 2006</td>
<td>12 Minipigs</td>
<td>Group 1: NBM and membrane; Group 2: NBM and rhPDGF; Group 3: NBM, rhPDGF and membrane</td>
<td>Platelet concentrate had no impact on bone formation</td>
</tr>
<tr>
<td>Jensen et al., 2005</td>
<td>8 Rats</td>
<td>Platelet concentrate and autograft</td>
<td>rhPDGF induced only a limited amount of new bone formation in both groups.</td>
</tr>
<tr>
<td>Park et al., 1995</td>
<td>4 Dogs</td>
<td>Test sites: rhPDGF with vehicle; Control sites: vehicle only</td>
<td>At 8 weeks, new bone formation was significantly higher at the test sites compared to the control sites; Alveolar bone refill was significantly higher in the test-sites compared to the control sites</td>
</tr>
<tr>
<td>Rutherford et al., 1993</td>
<td>4 Monkeys</td>
<td>Test sites: rhPDGF-BB + dexamethasone + membrane; Control sites: Membrane only</td>
<td>rhPDGF of BMP-2 enhances the proliferation and osteogenic differentiation of MSCs; however, controversial results have also been reported. Results from the Kumar study reported that</td>
</tr>
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</table>

**βTCP**: beta-tricalcium phosphate; **BCP**: biphasic calcium phosphate; **BMP-2**: bone morphogenetic protein-2; **GFR**: guided bone regeneration; **IGF-1**: insulin like growth factor-1; **NBM**: natural bone mineral; **PDGF**: platelet derived growth factor-β; **rh**: recombinant human; **TGF-β**: transforming growth factor-beta.
Platelet derived Growth Factor and Periodontal Tissue Regeneration

Lessons learned from clinical and experimental studies

<table>
<thead>
<tr>
<th>Clinical studies</th>
<th>Studies on animal models</th>
<th>In vitro studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone formation, 4,7,10,11,14-17,19,21</td>
<td>Bone formation around periodontal osseous defects, 6,23-25,28,29</td>
<td>Proliferation of fibroblasts, osteoblasts, periodontal ligament cells and mesenchymal stem cells, 39-44</td>
</tr>
<tr>
<td>Regeneration of periodontal apparatus, 20</td>
<td></td>
<td>Collagen synthesis, 45</td>
</tr>
<tr>
<td>Periodontal inflammation, 12,18,22</td>
<td></td>
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</table>

Fig. 4 – Lessons learned from clinical and experimental studies (studies on animal models and in vitro studies) on the effect of platelet derived growth factor on periodontal regeneration.

PDGF-BB signalling is not involved in osteogenic differentiation of human MSCs. Studies49–57 have also reported that PDGF, when used in combination with other GFs (such as transforming growth factor-beta 1, insulin-like growth factor-1 [IGF-1], bone morphogenetic protein-2 and enamel matrix derivative [EMD]) (Fig. 3). For example, results by Chong et al.54 demonstrated that the use of PDGF in combination with EMD augments the production of new fibroblasts in the PDL compared to when EMD is used alone. Similarly, Howell et al.22 investigated the effect of combining rhPDGF with rhIGF-1 for periodontal tissue regeneration. The results demonstrated that local application of rhPDGF-BB and rhIGF-1 to periodontal lesions is safe and promotes periodontal regeneration.22 This suggests that there might be an interaction between the receptors of various GFs on target cells such as fibroblasts. For example, in an experimental study, Novosyadlyy et al.57 demonstrated that the PDGF-BB helps in stabilizing the receptors of IGF thereby preventing their downregulation. These results are summarized in Fig. 4.

Although traditional periodontal surgical therapies (using bone grafts and barrier membranes) may assist in the treatment of mild to moderate periodontal bony defects, they may still be insufficient in the regeneration of the severely jeopardized periodontal tissues. In this regard, the use of growth factors such as the platelet-derived growth factor-BB with biocompatible matrices represents a promising approach in promoting tissue regeneration. For example, in the study by Laurell et al.54 a limited bone gain of 1–2 mm may be achieved when bone grafts were used alone for the treatment of periodontal infrabony defects. Similar results were reported by Yukna et al.59. On the contrary, several studies14–20 have shown that using rhPDGF-BB in combination with bone grafts can regenerate bone up to 5 mm as compared to when bone grafts are used alone.

6. Outlook for future research

The previous studies4,6,7,10–29 that explored the effect of PDGF on periodontal regeneration mainly focused on healthy humans and animals. Several studies60–63 have reported that medically compromised individuals (such as those with poorly controlled diabetes) are more susceptible to periodontal inflammation and alveolar bone loss as compared to individuals with well-controlled diabetes and healthy individuals. It may therefore be hypothesized that treatment of periodontal inflammatory conditions with PDGF in patients with well-controlled diabetes may also support periodontal regeneration in a manner similar to that in healthy individuals by mimicking the proliferation of pluripotential cells to form tissues resembling the lost periodontal structures. This may help in the formation of new periodontal tissues that may be similar to the devasted periodontal apparatus. To our knowledge from indexed literature, this relationship is yet to be investigated.

7. Conclusion

From the literature reviewed, it is concluded that:

- PDGF plays an important role in promoting GBR around teeth and dental implants with osseous defects.
- PDGF treatment enhances the proliferation of gingival and PDL fibroblasts and cementum formation around teeth with periodontal defects.
- Combining PDGF with other GFs such as IGF-1, BMP-2 and EMD augments periodontal tissue regeneration compared to when other GFs are used alone.

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Competing interests

The authors declare that they have no conflicts of interest.
Ethical approval

Not required.

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