Application of PRP (platelet-rich plasma) in surgical periodontal therapy: overview

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ABSTRACT
Clinical and morphological manifestation of periodontitis is associated with persistent inflammation of the gingiva, loss of connective tissue attachment, formation of a periodontal pocket and loss of alveolar bone, which indicate variations in a wide range in different individuals. The main purpose of non-surgical therapy for periodontitis is to achieve long-term control of inflammation, and the ultimate goal of therapy is the regeneration of periodontal tissues affected by destruction. The unique anatomy and structure of the entire periodontal complex determine the course of more complex processes related to the restoration of periodontal structures affected by destruction, which include coordination of response by four different types of tissues: epithelial tissue, connective tissue, periodontal ligament and bone. Periodontal regeneration is defined as the regeneration of main tooth-supporting tissues: alveolar bone, periodontal ligament, cementum and attachment. Modern modalities for carrying out the periodontal regeneration include the use of bone substitutes, guided tissue regeneration with barrier membranes, treatments with flaps and a variety of additional components, such as: soft tissue grafts, root biomodifiers and growth factors, the carrier of which is platelet-rich plasma (PRP). This mini-review provides an overview of PRP applied in surgical periodontal therapy. Data of the initial experiences with this method are included, as well as brief references on its usage in the clinical practice. There is no substitute material in the modern literature shown as the gold standard in the treatment of periodontal bone defects.

Introduction
Clinical and morphological manifestation of periodontitis is associated with persistent inflammation of the gingiva, loss of connective tissue attachment, formation of a periodontal pocket and loss of alveolar bone, which indicate variations in a wide range in different individuals. The formation of periodontal pockets of variable depth, the attachment loss, as well as horizontal or vertical bone loss are pathognomonic characteristics for diagnosing periodontitis. The main purpose of non-surgical therapy for periodontitis is to achieve long-term control of inflammation and the ultimate goal of therapy is the regeneration of periodontal tissues affected by destruction. Periodontal regeneration is not only associated with obtaining a new connective tissue attachment; it involves, as well, the formation of a new functional cementum with the incorporation of new collagen fibers to that part of the root surface that has lacks periodontal ligament due to periodontitis progression. The unique anatomy and structure of the entire periodontal complex determine the course of more complex processes related to the restoration of periodontal structures affected by destruction, which include coordination of response by four different types of tissues: epithelial tissue, connective tissue, periodontal ligament and bone. Periodontal regeneration is defined as the regeneration of the main tooth-supporting tissues: alveolar bone, periodontal ligament, cementum and attachment [1–3].

Growth factors
As early as 1986, Knighton DR et al. [4] examined the ability of platelets to provide additional potential for better healing and regeneration of lost tissue by means of growth factors release from them (Table 1). This thesis was proven by the authors using platelet mass for the treatment of difficult-to-heal skin ulcers [4]. Since then, many authors have considered the
application of growth factors as biologically reactive molecules that can stimulate cells accounting for tissue regeneration. Growth factors have been shown to promote cell proliferation, migration and metabolic activity, as well as to influence chemotaxis and the production of extracellular matrix proteins [9, 17–19].

Platelets are known to be the first cells to respond to the healing site and, in addition to this pro-coagulant effect, locally release a cocktail of "growth factors" from α-granules contained in them, such as: platelet-derived growth factor (PDGF), transforming growth factor (TGF-β1 and 2), insulin-like growth factor (IGF-1 and 2) and vascular growth factor (VEGF), which

| Authors | Literary source | Results |
|---------|-----------------|---------|
| Knighton et al. 1986 [4] | Classification and treatment of chronic no healing, cutaneous wounds. Successful treatment with autologous platelet-derived wound healing factors (PDWHF).Ann Surg 1986; 204:322-330. | Consider the possibility of Platelet to provide additional potential for healing process, by separating growth factors from them. |
| Kawamura, M. Urist R. 1988 [5] | Human fibrin is a physiologic delivery system for bone morphogenetic protein. Clin Orthop Relate Res 1988; 235:302-310. | The authors report that PRF may act as a supportive matrix for bone morphogene proteins (BMP). So trapped BMPs in the fibrin matrix are released progressively and if transplanted intramuscularly lead to bone formation. |
| Tuan TL, Song A et al. 1996 [6] | In vitro fibroplasia: matrix contraction, cell growth and collagen production of fibroblasts cultured in fibrin gels. Exp Cell Res 1996; 223:127-134. | The authors describe the role of fibrin in tissue recovery. Their research shows that fibroblasts can actively reorganize fibrin matrix and begin collagen synthesis. |
| Whitman DH et al. 1997 [7] | Platelet gel: an autologous alternative to fibrin glue with applications in oral and Maxillofacial surgery. J Oral Maxillofac Surg 1997;55;1294–1299. | The authors report on their experience with Platelet gel in oral and Maxillo facial surgery and comment on the healing qualities of Platelet. |
| Marx RE et al. 1998 [8] | Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:638-646. | The authors explain the key role of Platelet concentrates, in which they believe the term (platelet-rich plasma PRP) is best suited to the nature of these biomaterials. |
| Anitua E et al. 2007 [9] | The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. Biomaterials, 2007; 28: 4551-4560. | Described a new PRP modification called Plasma rich in growth factors (PRGF), which does not contain leukocytes and has a low platelet concentration compared to PRF, but the material has powerful osteoconductive qualities and has no proven antigenic action. |
| Van Hinsbergh W, Colleen A et al. 2001 [10] | Role of fibrin matrix in angiogenesis. Ann NY Accad Sci 2001; 936:426-437. | The authors assess the growth of human muscular vascular endo-cells in 3D fibrin matrix. Their study shows that circulating mesenchymal stem cells fall from the blood into the places of damage tissues and differentiate into different types of cells. |
| Choukroun J et al. 2001 [11] | PRF: an opportunity in perio- implantology (in French).Implan- todontie 2001; 42:55-62. | The authors develop a new generation of autogenic platelet concentrates, which is called Platelet-rich fibrin (PRF). This is a material that contains concentrates of platelets and leukocytes, together with their growth factors in fibrin. PRF can be used directly after compression and drying as a fibrin membrane. |
| Choukroun J et al. 2006 [12] | Platelet-rich fibrin (PRF): a second generation platelet concentrate. Part IV: clinical effects on tissue healing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod.2006; 101:56-60. | According to the authors, PRF can be seen as a natural fibrin and a basic biomaterial capable of directing epithelial cells to migrate to its surface. During the phenomenon, hemostasis and healing fibrin clot retain circulating stem cells, which, once fastened, can be transformed into a secreting phenotype, allowing vascular and tissue regeneration. |
| Tsai CH, Sheen SY, Zhao JH et al. 2009 [13] | Platelet-rich fibrin modulates cell proliferation of human periodontally related cell in vitro. J Dent Sci, 2009; 4:302-310. | The authors report in their study that PRF can stimulate cell proliferation of osteoblasts, gingival fibroblasts, periodontal ligament cells and suppress epithelial growth in an in vitro model. These results determined the use of PRF in periodontal surgery as an independent graft material for the treatment of periodontal intrabony defects. |
| Dohan Ehrenfest DM et al. 2010 [14] | The dimensional architecture and cell composition of a Choukroun’s platelet-rich fibrin clot and membrane. J Periodontol 2010; 81(4):546-555. | The authors found that 97% of platelets and more than half of leukocytes are implanted in the fibrin network. They observed a major cluster of cellular elements in the so-called "buffycoat". Under an electron-microscope this layer is divided into two zones: the first zone is made up of thick fibrin fibers and little erythrocytes, and the second zone contains platelets and fibrin, which form a dense and well-organized 3 D fibrin network. |
| Douglas TE et al. 2012 [15] | Enzymatically induced mineraliza- tion of platelet-rich fibrin. J Biomed Mater Res A, 2012; 100(5):1335-1346. | The authors in their in vitro study have shown that PRF under the action of alkaline phosphatase may be mineralized. |
| Solakoglu Ö, Heydecke G, Amiri N et al.2020 [16] | The use of plasma rich in growth factors (PRGF) in guided tissue regeneration and guided bone regeneration. A review of histological, Immunohistochemical, histo- morphometrical, radiological and clinical results in humans. Annals of Anatomy-2020;vol.231; september151528 | The authors summarize that the use of platelet concentrates for tissue regeneration is increasingly used in periodontal and maxillofacial surgery. Data from the study show that the use of plasma rich in growth factors (PRGF) significant improves tissue healing, reduces postoperative complication, accelerates the processes of recovery of soft and hard tissues. It is also used in the treatment of various complications arising during the healing process. |

Table 1. An overview of fibrin and platelet biomaterials and their application in clinical dental practice.
promote healing processes by stimulating fibroblast proliferation, output regulation and differentiation of extra-cellular matrix proteins and local vascularization [6, 20]. Being considered independently, each of the growth factors has a definite role in the healing and regenerative processes:

- **Platelet growth factor (PDGF)** - stimulates increased formation of cell adhesion molecule fibronectin that activates cell proliferation; influences the differentiation of osteoprogenitor cells, which affect the healing processes in connective tissue; binds to endothelial cells of blood vessels and stimulates local vascularization.

- **Transforming growth factor (TGF-β1 and β2)** - mainly affects osteoblasts and stem cell proliferation associated with the process of osteogenesis. It is involved in stimulating fibroblast, osteoprogenitor and endothelial cells, as well as in the production of collagen.

- **Insulin-like growth factor** (IGF-1 and 2) - stimulates the proliferation and differentiation of osteoblasts, as for the processes of periodontal regeneration IGF-1 turns out to be of greater significance - it stimulates the proliferation of fibroblasts and the synthesis of extracellular proteins. Insulin-like growth factor-1 has a chemotaxis effect on progenitor cells of the periodontal ligament, as well.

**Platelet-rich plasma (PRP)**

PRP (platelet-rich plasma), i.e. plasma rich in platelets, acts by degranulation of platelet α-granules, which contain a number of platelet-specific proteins (β-thromboglobulin) and platelet- nonspecific proteins (fibronectin, fibrinogen), coagulation factors, fibrinolysin, immunoglobulins and synthesized growth factors [21, 22]. Their active secretion begins in the first few minutes. More than 95% of the growth factors are secreted during the first hour and therefore, the use of an anticoagulant is necessary. Its application should be carried out within 10 min from the coagulum activation. The isolated growth factors immediately bind to the outer surface of the cell membranes of graft cells or flap cells, by means of the so-called transmembrane receptors. They, in turn, have a role to activate an endogenous intrinsic signaling protein that induces the expression of a gene stimulus on cells, which is expressed in: cell proliferation, extracellular matrix formation, osteoid production and collagen synthesis [23–25].

Conventional periodontal therapy involves primarily non-surgical treatment, but also various surgical approaches. The most common effect of non-surgical therapy is the formation of a long connecting epithelium between the instrumental root surface and the adjacent alveolar bone. Histological evidence is provided that the results lead to reparation rather than true regeneration. More unfavorable and complicated ways of healing related to external root resorption and ankylosis are possible, as well [1].

Modern modalities for carrying out the periodontal regeneration include the use of bone substitutes, guided tissue regeneration with barrier membranes, treatments with flaps and a variety of additional components, such as: soft tissue grafts, root bio-modifiers and growth factors, the carrier of which is PRP [16, 18, 26, 27]. There is no substitute material in the modern literature shown as the gold standard in the treatment of periodontal bone defects.

The introduction of PRP usage in oral and maxillofacial surgery was done by Whitman et al. [7], who proposed this method in 1997. The first clinical data from the use of PRP were reported by Marx et al. [8], who used PRP in the incorporation of a bone graft to reconstruct a patient’s mandible after removal of a tumor formation. The outcomes obtained by the authors indicated that the addition of PRP significantly accelerated the process of formation of new bone structure (Table 1). Similar results were observed afterwards by other authors who used a combination of PRP with a bone allograft and a membrane to regenerate intraosseous bone defects [28–35].

Over the last few years, the literature data on combined use of bone substitutes and barrier membranes with growth factors have been increasing, as well as those on the higher regenerative potential related to growth factors, expressed in stimulating the formation of mineralized and non-mineralized tissues [9, 18, 23]. In the initial stages of healing process, platelet-derived growth factors in platelet-enriched plasma attract undifferentiated mesenchymal cells to the fibrin matrix and activate cell division. In this way, they activate tissue regeneration: by proliferation of connective tissue progenitor cells, stimulation of fibroblast and osteoblast activity, as well as angiogenesis [10, 17, 19]. Blood coagulation is considered to be the main link in initiating the healing processes of all soft tissues, as well as in bone regeneration. Normally it contains approximately 94% erythrocytes and 6% platelets, and less than 1% leukocytes in the fibrin network [20]. In contrast to blood coagulation, PRP was found to contain 5% erythrocytes, 94% platelets and 1% leukocytes.
The main components of platelet-rich plasma are: growth factors, leukocytes, phagocytes, native fibrinogen, vasoactive and chemotactic agents, as well as a high concentration of platelets [6, 25].

Platelet-rich plasma is considered to be the most accessible in terms of obtaining these factors in a physiological manner. The use of PRP is essentially an autologous transplant treatment: the product applied is the patient’s own plasma. Therefore, it is reckoned that there is no risk of sensitization, disease transmission or genetic intervention. PRP therapy is a safe method, without any risk of infection, rejection, with long-lasting effect and without known side effects [20].

Platelet-rich plasma (PRP) is usually gel-like and is obtained after centrifugation of autologous blood and subsequent mixing of the separated plasma layer (PPP) with a portion of the fibrin-rich underlying layer (PRF), which is centrifuged again to obtain a yellow supernatant serum to which sterile bovine thrombin and 10% calcium chloride, dissolved in saline, are added. The plasma obtained as a final product has a high concentration of platelets: 3-4 times higher concentration compared to baseline level [15, 26, 27, 36]. The platelet count in PRP can exceed 2,000,000 in 1 μL of plasma, while the normal concentration of platelets in blood is 150,000 to 350,000 in 1 μL [26]. When platelet-rich plasma is used for treating mineralized and non-mineralized tissues, the fact that is relied on is that platelets are activated and release "growth factors" that can stimulate collagen and elastin synthesis from fibroblasts, improve blood supply and metabolism of damaged tissues by means of influencing the process of angiogenesis (formation of new blood vessels), and thus bring about healing and restoration of the affected tissues.

The antimicrobial effect of platelet-rich plasma is determined by the presence of a high concentration of leukocytes therein. The concentration of the growth factors and matrix glycoproteins (glycosaminoglycans) contained in plasma enhances substantially during the first 7 days and the success of recovery is considered to be proportional to the number of platelets in the blood clot, which have a significantly higher concentration at the end of the procedure of preparation of PRP compared to the beginning [15, 19].

Data from clinical trials have shown that the combined use of bone substitutes and PRP result in better clinical indicators (attachment gain and depth reduction on probing) in the treatment of periodontal bone defects [17]. PRP has the advantage of affecting osteoprogenitor cells in bone and bone replacement materials (autogenous bone) and is applied in procedures, such as sinus lift, techniques of vertical and horizontal augmentation of alveolar bone, periodontal and peri-implant bone defects [8, 35, 37–44].

**Plasma rich in growth factors (PRGF)**

In 1999, Anitua [44] described a new modification of PRP, called Plasma rich in growth factors (PRGF). In this modification, the author used a 10% solution to activate the polymerization of fibrinogen in fibrin. PRGF, unlike PRP, does not contain leukocytes and has a low platelet concentration. Studies with mono and polyclonal antibodies have indicated the presence of high concentration of growth factors [44]. The suspension obtained that way and used as a solution for injection, showed good osteoconductive properties and a lack of antigenic activity.

**Platelet-rich fibrin (PRF)**

In 2001, Choukroun J et al. [11] developed an even newer generation of autogenous platelet concentrate, without biological and chemical additives. This concentrate is called Platelet-rich fibrin (PRF) [11]. PRF is an autogenous fibrin matrix wherein platelets and leukocytes are concentrated together with their growth factors. PRF is defined by researchers as the second generation of PRP [45]. The fact that no additional anticoagulant is added results in the activation of a larger number of platelets upon contact with the tube walls during centrifugation, which, in turn, triggers the coagulation cascade within only a few minutes. Most platelets and leukocytes remain trapped in the fibrin clot and its 3D structure is similar to naturally polymerized fibrinogen [14]. Natural polymerization of fibrinogen in PRF determines the formation of a very stable fibrin structure, which allows the formation of a stable fibrin membrane accordingly. The platelets and leukocytes trapped in it are in high concentration, and the leukocytes remain unchanged during centrifugation. Platelets in turn are activated, which leads to the significant incorporation of the released growth factors and other biologically active molecules inside the fibrin matrix [36].

The obtained fibrin clot consists of three main parts: yellow fibrin part, red part located at the opposite end of the clot (composed of erythrocytes) and an intermediate whitish layer (buffy coat) between them. This layer is electronically microscopically divided into two areas. The first area is composed of maturing fibrin network, thick fibrin threads and a small number
importance of fibrin, fibronectin, PDGF and TGF-

migration at the site of tissue damage has been dem-
modulating fibroblast proliferation and fibroblast
factors are included in the fibrin network, with FGF-b
a major role in angiogenesis, as well. These growth
(Platelet-derived growth factor) and angiopoietin play
of the fibrin network obtained by PRF. Growth factors,
angiotensin properties have the unique 3D structure
and phenotypic change of endothelial cells. Such
fibrin matrix is needed to allow the migration, division
ability of the capillary structures obtained
the resulting fibrin structure affects the range and sta-
work is observed, capable of supporting the intrinsic
platelets in it are activated. In PRF, in contrast to PRP,
lets and fibrin, which form a dense network and the
platelets in it are activated. In PRF, in contrast to PRP,
formation of a finer and more flexible fibrin net-
work is observed, capable of supporting the intrinsic
cytokines incorporated in it and cell migration [12, 37].
Such a configuration of the fibrin network has been
proven to provide better survival of platelet-derived
growth factors, which are available for a longer period
time among other cells and have sufficient time to
stimulate healing and regenerative processes.

The resulting 3D structure gives greater strength
and elasticity to the obtained fibrin matrix, which is
confirmed by the clinically observed properties of the
PRF membrane: elasticity, strength and ability to
be sutured.

The issue that has given rise to much controversy is
the significance of platelet-rich fibrin. For example,
Tuan et al. [6] describe the role of fibrin in tissue re-
stitution. Their study shows that fibroblasts can
actively reorganize the fibrin matrix in order to initiate
collagen synthesis [6] (Table 1). Van Hinsbergh et al.
[10] examined the growth of human vascular endothe-
lium cells in the 3D structure of the fibrin matrix
obtained from PRF. The authors’ study points out that
the resulting fibrin structure affects the range and sta-
ibility of the capillary structures obtained in vivo (Table
1). Circulating mesenchymal stem cells from the blood
to enter the available fibrin matrix, then they differenti-
ate into different cell types and this ensures a more
rapid course of the healing processes in damaged tis-
sues [10, 36]. Kawamura and Urist [5] demonstrate
that PRF can also act as a supporting matrix for bone
morphogenetic proteins (BMP), while other authors,
Douglas et al. [15], prove in their in vitro study that it
is possible for PRF to be mineralized by the action of
alkaline phosphatase [5, 12, 15, 46] (Table 1).

For the process of angiogenesis, an extracellular
fibrin matrix is needed to allow the migration, division
and phenotypic change of endothelial cells. Such
angiotensin properties have the unique 3D structure
of the fibrin network obtained by PRF. Growth factors,
such as FGF-b (Fibroblast grown factor - b), PDGF
(Platelet-derived growth factor) and angiopoietin play
a major role in angiogenesis, as well. These growth
factors are included in the fibrin network, with FGF-b
and PDGF showing high affinity for fibrin [14]. The
importance of fibrin, fibronectin, PDGF and TGF-β
for modulating fibroblast proliferation and fibroblast
migration at the site of tissue damage has been dem-

According to Choukroun et al. [47] PRF can be
regarded as natural fibrin and a basis for the develop-
ment of micro vascularization. It has the ability to di-
rect epithelial cells to migrate on its surface and the
content of leukocytes is of particular importance to
ensure faster healing of affected tissues [47, 48]. Tsai
et al. [13] reported in their study that PRF can stimu-
late cell proliferation of osteoblasts, gingival fibro-
blasts, and periodontal ligament cells and inhibits
epithelial outgrowth in an in vitro model. These results
lead to the use of PRF in periodontal surgery as an
independent graft material for treatment of periodon-
tal infraosseous defects [13] (Table 1). In recent years,
many authors have supported the idea that PRF
should be regarded as a fibrin biomaterial with very
high potential [36, 49–51].

Conclusions

It is of high significance to emphasize that the addi-
tional use of PRP or PRF is one of the latest innova-
tions for tissue regeneration in surgery. This is
associated with rapid onset of osteogenesis, early con-
solidation of soft tissue and bone grafts due to growth
factors initiation of osteocompetent cellular activity
and subsequent early mineralization of extracellular
matrix proteins.

Disclosure statement

No potential conflict of interest was reported by
the author(s).

Funding

This review was supported by project “Stimulating research in areas with high achievements” - Medical University of
Sofia, Contract № D 237/2019.

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