Platelet-Rich Fibrin in Periodontal Regeneration

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***Abstract*—Platelet-rich Fibrin (PRF) has become a powerful autologous biomaterial in the field of periodontal regeneration, aiding the healing of both hard and soft tissues. This comprehensive review examines the biological mechanisms of PRF, its various forms, preparation methods, clinical uses in periodontal treatment, and its present limitations. PRF contributes to significant reductions in probing depths, gains in clinical attachment, and the filling of bone defects in both intrabony and furcation areas. While using PRF on its own provides beneficial results, its regenerative effects can be significantly improved when combined with bone grafts, bioactive biomolecules, or barrier membranes. By facilitating the gradual, sustained release of growth factors and creating a stable three-dimensional fibrin structure, PRF promotes osteogenesis, angiogenesis, and soft tissue healing. Continuous developments, including advanced PRF (A-PRF), injectable PRF (i-PRF), and standardized protocols for preparation, are anticipated to enhance its dependability and practical use in modern clinical dental practices.**

***Index Terms*—Platelet-rich fibrin (PRF), Periodontal regeneration, Intrabony defects, Bone regeneration, Growth factors, Regenerative dentistry**

I. INTRODUCTION

Regeneration of periodontal structures, including the alveolar bone, cementum, and periodontal ligament, is essential for restoring both dental function and esthetics. However, achieving predictable periodontal regeneration remains a significant clinical challenge. Conventional grafting approaches such as autografts, allografts, xenografts, and alloplastic materials are widely used in periodontal therapy. Despite their clinical utility, these techniques present several limitations, including donor-site morbidity, risk of disease transmission, and variability in osteoinductive potential.[1]

In recent years, platelet concentrates have emerged as promising biologically active alternatives in regenerative dentistry. Among the early platelet-derived products, first-generation platelet concentrates such as platelet-rich plasma (PRP) were introduced to enhance tissue healing and regeneration. However, PRP often demonstrated inconsistent clinical outcomes, primarily due to the rapid release of growth factors and the complexity of its preparation, which requires the use of anticoagulants and other biochemical additives. These limitations prompted the development of second-generation platelet concentrates, particularly platelet-rich fibrin (PRF).[1]

Platelet-rich fibrin (PRF) is a second-generation, completely autologous platelet concentrate that was first introduced in France by Choukroun et al. in 2001. Unlike earlier platelet derivatives, PRF is produced without the addition of anticoagulants or biochemical agents, allowing the formation of a natural fibrin matrix during centrifugation. This simplified preparation method contributes to the biological stability and clinical applicability of PRF.[2]

The three-dimensional fibrin network of PRF serves as a scaffold that gradually releases a variety of growth factors and bioactive molecules. These factors promote angiogenesis, stimulate bone formation, and support soft tissue healing. In addition, PRF exhibits immunomodulatory and antimicrobial properties that further enhance the healing environment. Previous studies have demonstrated that PRF can stimulate progenitor cell proliferation, facilitate osteoblast differentiation, improve alveolar bone height, and ultimately contribute to the regeneration of periodontal tissues.[2]

II. GENERATIONS OF PLATELET CONCENTRATES

First-generation: Platelet-rich plasma (PRP)
Preparation involves the double-spin technique and the addition of anticoagulants.

- Leukocyte-Rich Platelet-Rich Plasma(L-PRP): Prepared by initially centrifuging blood at 250 × g for 10 minutes, followed by a second centrifugation at 250 × g for another 10 minutes (Jia et al., 2018). An anticoagulant is added prior to centrifugation to prevent clotting.[2]
- Pure Platelet-Rich Plasma(P-PRP): Obtained by centrifuging blood first at 160 × g for 10 minutes, followed by a second spin at 250 × g for 15 minutes (Jia et al., 2018).[2]

Second-Generation: Platelet-Rich Fibrin (Prf)

- Leukocyte-Rich Platelet-Rich Fibrin(L-PRF): Produced by centrifugation at 400 × g for 12 minutes and does not require any additives (Ratajczak et al., 2018).[2]
- Horizontal Platelet-Rich Fibrin(H-PRF): Prepared using horizontal centrifugation at 700 × g for 8 minutes (Feng et al., 2020).[2]
- Titanium Platelet-Rich Fibrin(T-PRF): Generated by centrifuging blood at 2,700 rpm for 12 minutes using titanium tubes (Ercan et al., 2022).[2]
- Injectable Platelet-Rich Fibrin(i-PRF): Prepared at 60 × g for 3 minutes without the use of any additives (Ozsagir et al., 2020).[2]
- Advanced Platelet-Rich Fibrin(A-PRF): Produced by centrifugation at 100 × g for 14 minutes, also without additives (Kobayashi et al., 2016).[2]
- Lyophilized Platelet-Rich Fibrin(Ly-PRF): Prepared by freezing freshly obtained PRF at −80°C for 30 minutes, followed by overnight freeze-drying at −51°C, and then centrifuged at 400 × g for 10 minutes (Ngah et al., 2021).[2]

Third-Generation: Platelet-Rich Derivatives

- Concentrated Growth Factor (CGF): Produced using alternating acceleration and deceleration cycles, including acceleration for 30 seconds, followed by centrifugation at 2,700 rpm for 2 minutes, 2,400 rpm for 4 minutes, 2,700 rpm for 4 minutes, 3,000 rpm for 3 minutes, and finally deceleration for 36 seconds.[2]
- Platelet-derived extracellular vesicles (pEVs): Isolated through sequential centrifugation steps, typically at 300–2,000 × g for 20 minutes, 5,000–10,000 × g for 10 minutes, and 1,000,000 × g for 1–3 hours.[2]

Fourth Generation:

- Coupling partner cells of prf which is still under investigation[3]

Preparation Protocols:
First generation:
Method:10mLof blood is drawn into anticoagulant-containing tubes (e.g., CPDA or sodium citrate) and subjected to a double-spin centrifugation to concentrate platelets.[4]

Second generation:
Method:10 mL of blood was drawn without anticoagulant into glass tubes and centrifuged immediately.[4]

Third generation:
Method:Collection of autologous venous blood (usually 9–10 mL per tube) and usage of sterile, additive-free, silica-coated tubes without anticoagulants. CGF is fully autologous and avoids biochemical additives.[5]

III. FACTORS AFFECTING PRF QUALITY:

Several variables influence the biological and structural quality of PRF,including:
Time to Centrifugation: Coagulation begins within seconds after venipuncture; delays beyond 60–90 seconds may result in premature fibrin polymerization, reducing PRF yield.[6]

Centrifugation Speed and Time: Alterations in g-force and duration change fibrin density, cellular composition, and growth factor release kinetics.[6]

Tube Material: A significant difference was observed between PRF membranes produced using glass tubes and those produced using plastic tubes. Clot size varied by up to 200%, while differences between the centrifugation devices themselves were minimal.[7]

Relative centrifugal force influence on PRF: Relative centrifugal force (RCF) is the force exerted on a sample during centrifugation and is expressed as multiples of gravitational force (g). It depends on factors such as rotational speed (RPM) and rotor radius and can be calculated using the formula $RCF = 11.18 \times r \times (RPM/1000)^2$, where r is the radius in centimeters[8]

Patient-Related Factors: Age, systemic health, platelet count, and hematocrit levels can significantly affect PRF's regenerative potential.[9]

IV. BIOLOGICAL PROPERTIES OF PRF:

During PRF preparation, freshly drawn blood (without any anticoagulant) is centrifuged under specific conditions, which leads to separation into three layers: the bottom layer of red blood cells, a middle layer containing the PRF clot (buffy coat), and a top layer of platelet-poor plasma.[8] The PRF clot consists of a tightly cross-linked three-dimensional fibrin network that physically traps platelets, leukocytes, and a variety of cytokines (such as TGF-β1, PDGF, VEGF). It also provides a microenvironment that supports stem cells, making PRF not just a clot but a bioactive scaffold for tissue regeneration.[11]

PRF serves multiple biological functions critical for bone regeneration:

- Growth Factor Reservoir: PRF releases multiple growth factors, including PDGF, TGF-β1, VEGF, EGF, and IGF, in a sustained manner, facilitating osteoblast proliferation, differentiation, and angiogenesis.[2]
- The fibrin matrix present in platelet-rich fibrin forms a three-dimensional scaffold that facilitates cellular migration and attachment. This structural network supports extracellular matrix production and provides a favorable environment for tissue organization, thereby contributing to bone regeneration and structural stability in dental applications.[12]
- Leukocytes incorporated within the PRF matrix contribute significantly to its immunomodulatory properties. Through the secretion of various cytokines, they regulate inflammatory processes and enhance antimicrobial defense mechanisms, which are essential for maintaining infection control and supporting effective bone healing.[13 14]

Platelet-rich fibrin (PRF) promotes the chemotactic migration and recruitment of mesenchymal stem cells (MSCs) to sites of tissue injury. The presence of numerous growth factors within its fibrin matrix stimulates MSC proliferation and enhances their differentiation into osteogenic lineages. As a result, PRF functions as a bioactive scaffold that supports both bone and soft tissue regeneration.[2 15]

V. HARD TISSUE AUGMENTATION:

The application of PRF in bone regeneration spans multiple clinical scenarios:

• Intra-bony Periodontal Defects: Platelet-rich fibrin has demonstrated considerable efficacy in promoting periodontal regeneration within intrabony defects. PRF, whether used alone or in combination with bone graft materials, enhances clinical attachment gain, contributes to significant reductions in probing depth, and facilitates increased bone defect fill. These findings highlight PRF's role as an effective adjunct in periodontal tissue repair.[16 17]

• Alveolar Ridge Preservation: PRF accelerates bone fill and preserves ridge volume after tooth extraction, thereby facilitating future implant placement.[18 19]

• Sinus Lift Procedures: When used in combination with bone graft materials, platelet-rich fibrin improves the stability of the graft, promotes neovascularization, and facilitates new bone formation in sinus augmentation procedures.[20]

• Socket Healing: The use of PRF enhances soft-tissue healing and thereby reduces post-extraction bone loss.[21]

VI. SOFT TISSUE REGENERATION:

PRF in Periodontal Ligament Regeneration:

Platelet-rich fibrin not only promotes bone regeneration but also supports the healing of the periodontal ligament. It stimulates fibroblast proliferation and enhances collagen production, creating a favorable environment for PDL repair. The cytokines and growth factors released from PRF facilitate the reattachment of periodontal ligament fibers to the root surface and promote cementum formation, thereby contributing to comprehensive periodontal regeneration.[22]

PRF in Dental Implantology:
PRF is frequently employed in dental implant procedures to support osseointegration and improve soft tissue healing.[17] Platelet-rich fibrin has been shown to accelerate bone regeneration and soft-tissue healing around dental implants, enhancing peri-implant tissue quality and potentially lowering the risk of peri-implantitis.[23]

Combinational Approaches with PRF:
Platelet-rich fibrin (PRF), which alone has limited mechanical strength and rapid degradation, is frequently combined with bone grafts to form "sticky bone," enhancing graft handling and stability.[24] This combination also promotes osteoconduction and osteoinduction, leading to improved clinical outcomes compared with graft materials used alone.[25] Moreover, incorporating PRF with barrier membranes or bioactive agents such as enamel matrix derivative (EMD) has demonstrated encouraging results in both periodontal and bone regeneration.[26]

Advantages & Biological Rationale:

- Platelet-rich fibrin (PRF) is autologous, cost-effective, easy to prepare, and does not require exogenous additives.[2]
- Its three-dimensional fibrin matrix supports cellular migration, retains cytokines, and enables.[2]
- sustained growth factor release.[2]
- PRF enhances angiogenesis, osteogenesis, and immunomodulation, which are crucial for effective periodontal regeneration.[2]
- When combined with graft materials, PRF forms "sticky bone," improving handling and stabilizing the graft during placement.[24]

Limitations:

- Differences in PRF preparation protocols, including centrifugation speed, duration, and equipment, can affect the composition and quality of the final product. This variability may impact biological activity and lead to inconsistent clinical outcomes.[9]
- Platelet-rich fibrin has limited mechanical stability and does not maintain space. When used alone, it may not adequately manage large defects, so it is often combined with scaffold materials to improve regenerative outcomes.[27]

VII. FUTURE DIRECTIONS & INNOVATIONS

Future research is focused on enhancing the mechanical stability and durability of platelet-rich fibrin. Modified preparations such as titanium-prepared PRF (T-PRF) have demonstrated a more compact and densely organized fibrin network, which may contribute to improved clinical performance and regenerative outcomes.[28]Lyophilized PRF and its combination with nanomaterials, stem cells, or bioprinted scaffolds are currently being investigated to enhance regenerative potential, as these approaches have been shown to support stem-cell viability and promote osteogenic gene expression for bone regeneration.[29] Establishing standardized PRF preparation protocols and conducting large-scale, well-controlled clinical studies are necessary to determine its clinical effectiveness and refine its application in regenerative dentistry.[30] Recent advances in regenerative medicine have expanded the applications of platelet-based products such as platelet lysates and platelet-derived extracellular vesicles. These biologically active components are being explored for their potential roles in cell therapy, tissue regeneration, and targeted drug delivery due to their rich content of growth factors and signaling molecules.[31]

VIII. CONCLUSION

Platelet-rich fibrin (PRF) is a promising autologous biomaterial for periodontal regeneration, offering a three-dimensional fibrin matrix and sustained release of growth factors that support angiogenesis, osteogenesis, and soft-tissue healing. Clinical evidence shows that PRF significantly improves periodontal outcomes, including probing depth reduction, clinical attachment gain, and radiographic bone defect fill, especially in intrabony defects.[32] [33]Combining PRF with bone grafts or other regenerative materials may further enhance results. However, differences in preparation protocols and patient biology can affect clinical effectiveness, underscoring the need for standardized techniques and additional long-term randomized clinical studies.[32]

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