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REVIEW ARTICLE

Next-Generation Platelet-Rich Fibrin: Emerging Paradigms in Periodontal Regeneration and Healing

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ABSTRACT

Platelet-rich fibrin (PRF) has evolved from a simple autologous clot into a versatile, bioactive scaffold that can be tailored through centrifugation physics, tube surface chemistry, and post-processing techniques. This narrative review synthesizes the last decade of evidence (2014–2025) on "next-generation" PRF variants—including advanced PRF (A-PRF+), injectable PRF (i-PRF), titanium-prepared PRF (T-PRF), lyophilized and compressed membranes, and emerging exosome-enriched hybrids—and evaluates their physicochemical attributes, biological performance, and clinical utility in periodontal regeneration. Compared with classic leukocyte-PRF, next-generation formulations display denser, more mature fibrin architectures, prolonged and higher-amplitude release of growth factors (PDGF-AB, VEGF, TGF-β1), and enriched leukocyte and progenitor-cell cargos that collectively enhance angiogenesis, osteogenesis, and immunomodulation. Human randomized controlled trials demonstrate that adjunctive use of A-PRF+ or i-PRF yields an additional 0.9–1.4 mm of clinical attachment gain and 20–35 % greater defect fill in intrabony lesions versus open-flap debridement alone, with reduced postoperative pain and morbidity. T-PRF membranes have shown superior tensile strength and volumetric stability for sinus-floor elevation and ridge-preservation procedures. Despite promising outcomes, heterogeneity in centrifugation parameters and a paucity of long-term histologic data limit meta-analytic certainty. Standardization of protocols, rigorous head-to-head trials, and integration with 3-D bioprinting and drug-delivery platforms are critical to unlocking the full translational potential of next-generation PRF. Collectively, these advances position PRF as a customizable, cost-effective, and chair-side biotherapeutic that bridges the gap between biological principles and predictable clinical regeneration in periodontology.

Keywords: Periodontal regeneration, Growth-factor release, Tissue engineering, Platelet-rich fibrin

1 INTRODUCTION

Wound healing represents the natural restorative response to tissue damage, a complex, well-organized sequence of events involving many cell types that are assisted by the release of soluble mediators and signals that can influence the homing of circulating cells to injured tissues[1].

Usually, there are four overlapping phases that make up wound-healing events: hemostasis, inflammation, proliferation, and remodeling[2, 3].

Underlying the restoration of hemostasis, platelets are key to closing injured vessels to prevent blood loss and enhancing fibrin-based clotting[4]. Whether to consider platelets as whole cells or as cellular fragments remains contentious. However, it has been evident that they release and activate diverse sets of essential biomolecules. The list includes specific proteins in platelets, factors such as platelet-derived growth factor (PDGF), proteins involved in blood clotting, proteins assisting in adhesion, cytokines with similar roles, and several factors involved in angiogenesis. The process promotes the action of cells participating in the healing processes in injured areas, including fibroblasts, neutrophils, macrophages, and mesenchymal stem cells (MSCs)[5]. Based on the information, platelets are involved in encouraging angiogenic processes and other essential processes in tissue repair.

Timeline of Platelet Concentrate Transformation[5]:

This 1954-2015 timeline illustrates a major regenerative medicine milestone. The discipline evolved from initial studies of blood clotting to effective regenerative therapy for clinical applications. The milestones in the process are:

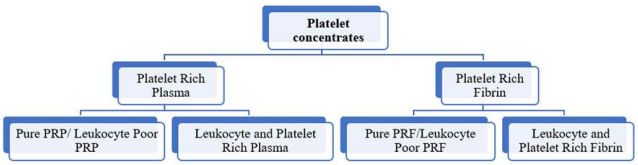
- 1954: Kingsley introduced the initial nomenclature.
- 1970: The introduction of fibrin-based healing techniques by Matras
- 1986: Clinical proof of concept by Knighton *et al*.
- 1998: Widespread clinical adoption following Marx's work
- 2000: Revolutionary PRF development by Choukroun

- 2009: Scientific classification by Dohan Ehrenfest
- 2014: Advanced formulations (A-PRF, T-PRF)
- 2015: Injectable technology breakthrough (i-PRF)

How did it evolve?

Platelet concentration without the presence of coagulation factors can be harvested (750 g) from the surface of the centrifugation tubes after one cycle of centrifugation (rep rate: 2,700 rpm, time: 12 minutes)[6]. The final composition of PRF includes a concentration of: White Blood Cells, Platelets, Fibrin matrix, and other factors present in the fibrin matrix. The concentration of Platelet rich fibrin developed by the first group (L-PRF or Leukocyte rich Platelet rich Fibrin) was reported to have a higher concentration relative to the whole blood concentration, consisting of 97% Platelets and above 50% Leukocytes in a strong fibrin matrix[6].

Classification[7]:



How PRF classified?

a. Pure platelet-rich fibrin (P-PRF)

b. Leukocyte and platelet-rich fibrin (L-PRF)

c. Injectable PRF (i-PRF)

2 MECHANISMS OF PERIODONTAL REGENERATION

Scaffold Function and Space Maintenance:

Next-generation platelet concentrates acts as a natural, biodegradable scaffold that maintains space within periodontal defects, enabling cell migration and proliferation essential for tissue regeneration[8-11]. The fibrin matrix provides a three-dimensional architecture that supports cellular adhesion and serves as a reservoir for growth factors, allowing gradual release in situ[8-11]. This structural function prevents soft tissue collapse into bony defects, preserving the regenerative environment and promoting bone and periodontal ligament formation[8-11].

Promotion of Angiogenesis and Collagen Maturation:

Angiogenesis is crucial for supplying oxygen and nutrients to healing tissues. PRF enhances neovascularization through sustained release of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), stimulating endothelial cell proliferation and migration[12]. Additionally, PRF accelerates collagen synthesis and maturation by upregulating fibroblast activity and transforming growth factor-beta (TGF-β) signaling, leading to improved soft tissue quality and attachment[13]. These biological effects accelerate wound closure and functional periodontal regeneration[14].

Modulation of Inflammatory Milieu and Microbial Load:

Leukocytes within L-PRF release anti-inflammatory cytokines, IL-4 and IL-10, and antimicrobial peptides such as LL-37 and defensins that suppress TNF-α, IL-1β, and IL-6, while disrupting microbial membranes and biofilms of P. gingivalis and F. nucleatum.[15] Neutrophil-derived LL-37 enhances innate defense, while monocyte factors restrict excessive inflammation. L-PRF lysates downregulate cytokine expression by 40 to 60%, restrain infection, and encourage healing with a balance. Clinically, L-PRF attenuates inflammation, increases collagenization, accelerates closure and attachment gain, thereby creating an immuno-modulatory environment that is conducive for periodontal regeneration[15, 16].

Synergistic Effects with Biomaterials (Bone Grafts, Membranes, Bio-Ceramics):

Next-generation PRF combined with bone grafts such as DFDBA or hydroxyapatite enhances periodontal regeneration because biological signaling mixed with bio-ceramics promotes osteoconductive support[17]. PRF acts as a bioactive binder and resorbable membrane, enhancing graft stability, vascularization, and cellular infiltration. Greater probing depth reduction, attachment gain, and bone fill have been clinically demonstrated in comparison to either grafts or membranes alone. PRF-ceramic composite "sticky bone" accelerates defect closure and meta-analyses report 30-50% superior regenerative outcomes, emphasizing its standardized use for predictable furcation and intrabony defect management[18, 19].

3 PERIODONTAL REGENERATION WITH PRF

PRF represents a platelet-derived biomaterial containing leukocytes, cytokines, glycoproteins, and growth factors such as PDGF, TGF-β, IGF-1, FGF, and VEGF, which exert an effect on endothelial cell proliferation, angiogenesis, collagen synthesis, and osteoblastic activity[20]. Its elastic fibrin matrix supports cellular infiltration, cytokine entrapment, and sustained release without anticoagulants or bovine thrombin. PRF enhances wound healing by modifying inflammation, potentiating mesenchymal stem cell activity, and improving the quality and speed of tissue repair. In periodontics, this biomaterial is widely applied for soft tissue healing, gingival recession coverage, and intrabony or furcation defects due to its excellent biocompatibility and cost-effectiveness[22]. However, small autologous yield, donor variability, and loss of structural integrity or leukocyte viability if not used immediately are all serious drawbacks of PRF preparations, along with possible contamination during storage[21].

The role of PRF in the regeneration of IBD(Intrabony defects):

Platelet-Rich Fibrin (PRF) is effective in regenerating intrabony defects (IBD) by enhancing the proliferation, differentiation, migration, and mineralization of bone-forming cells[23]. Macrophages in PRF support osteogenesis, while growth factors and cytokines released by leukocytes and platelets stimulate osteoblasts and periodontal ligament cells to promote bone regeneration. TGF-β1 in PRF promotes collagen and fibronectin production, aiding bone healing, and VEGF-driven angiogenesis supports skeletal development. PDGFs and IGF-1 also induce osteoblast proliferation and differentiation[23]. Systematic reviews

indicate that PRF combined with open flap debridement (OFD) yields outcomes comparable to OFD with bone grafts, with some studies showing OFD+PRF results more favorable than bone grafts for bone fill and defect reduction[24].

The role of PRF in recession coverage (RC):

PRF membranes enhance soft tissue healing by gradually releasing growth factors like VEGF, promoting angiogenesis and tissue regeneration. In root coverage procedures, PRF reduces matrix metalloproteinase-8 and interleukin beta while increasing tissue inhibitor levels, improving early periodontal wound healing[25]. Studies show PRF can lower postoperative pain and discomfort, elevating patient-reported outcomes. However, systematic reviews indicate that PRF's effectiveness in Miller Class I and II gingival recessions is comparable to other treatments, with no significant advantages in root coverage, mucosa width, or attachment levels[26].

The role of PRF in treating furcation defects:

Furcation involvement complicates oral hygiene due to root anatomy and is a significant risk factor for tooth loss alongside factors like age, smoking, and diabetes. Periodontal regenerative techniques aim to restore bone, cementum, and periodontal ligament in these areas. PRF activates and releases growth factors that support bone regeneration[27]. A systematic review showed L-PRF enhances clinical and radiographic outcomes in furcation-affected teeth when combined with open flap debridement (OFD) and grafting, outperforming OFD alone. However, benefits are less clear when PRF is used with osseous grafts, and limited data exist on their combined effect[27].

The role of PRF in plastic aesthetic surgery:

Fibrin-assisted Soft Tissue Promotion" using platelet-rich fibrin (PRF) is emerging as an effective alternative to traditional palatal connective tissue grafts for mucogingival recession treatment. Studies show mixed results: Aroca et al. found PRF increased keratinized tissue but with lower complete root coverage[28]. Aleksic, Jankovic, and Tunalı *et al*. reported PRF alone effectively treated Miller class I and II recessions, improving recession extent and clinical attachment by around 3 mm[29]. Keceli *et al*. achieved 89.6% root coverage using PRF with a coronally advanced flap[30], while Rajaram *et al*. observed 78.8% coverage with a double lateral sliding flap and PRF[31]. Overall, PRF enhances the speed and quality of soft tissue regeneration in gingival recession treatment.

The role of PRF in implant dentistry:

Platelet-rich fibrin (PRF) enhances osseointegration and healing of soft and hard tissues during implant placement. It effectively manages peri-implant defects like coronal bone loss from peri-implantitis and buccal gaps caused by implant positioning, improving bone-to-implant contact rates up to 73%[32]. PRF promotes bone regeneration, increases keratinized mucosa, and improves clinical attachment levels. The ideal placement is under the flap without additional tissue division to preserve soft tissue thickness. PRF releases growth factors and cytokines that facilitate hemostasis, attract macrophages, and stimulate bone remodeling through osteoclastic resorption and osteoblastic formation. Clinical studies show that PRF reduces vertical bone loss, accelerates wound closure, and, when combined with bone grafts or demineralized freeze-dried bone allograft (DFDBA), significantly improves bone density and healing in infected sockets. These findings establish PRF as a reliable and effective treatment modality for osseous defects in implant dentistry[33].

4 BIOGENESIS OF NEXT-GENERATION PRF

Centrifugation Physics and the "Low-Speed Concept" (A-PRF+/I-PRF):

Next-generation PRF variants owe much of their enhanced biological activity to refined centrifugation protocols based on the "low-speed centrifugation concept" (LSCC). LSCC reduces the relative centrifugal force (RCF) and/or time to preserve a higher proportion of leukocytes, platelets, and progenitor cells within the fibrin clot[34]. This adjustment results in a more porous and flexible fibrin network that supports sustained release of growth factors such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGF-β)[35]. Advanced PRF (A-PRF+) is produced by spinning at lower RCF (≈208 g, 8 minutes), compared to classic leukocyte-PRF (L-PRF), allowing improved cellular retention and bioactivity[35]. Similarly, injectable PRF (i-PRF) utilizes very low speed (60 g for 3 minutes) to maintain a liquid consistency suitable for injection, preserving viable cells and growth factors for early regenerative signaling[35].

Modification of Tubes & Surfaces (Titanium-PRF, T-PRF):

The idea that titanium tubes could be more efficient in activating platelets than the glass tubes employed in Choukroun's platelet-rich fibrin (PRF) process is the basis for the creation of third generation concentrate, or T-PRF. For T-PRF preparation, medical-grade IV titanium tubes are used in place of glass tubes because they provide better hemocompatibility, platelet activation comparable to silica, and the benefit of durability and reusability following appropriate sanitation. Among metals, titanium boasts one of the best strength-to-weight ratios and resistance to corrosion[36]. Titanium has outstanding biocompatibility because of its noncorrosive qualities[37]. Additionally, titanium can passivate itself in vivo by creating an adhesive oxide layer[38]. T-PRF membranes demonstrate prolonged growth factor release and improved osteogenic potential, making them advantageous for hard tissue applications such as sinus lifts and ridge preservation[39].

Injectable & Liquid PRF (i-PRF):

i-PRF is a relatively recent innovation that maintains the regenerative benefits of PRF in a liquid injectable form, which allows for minimally invasive application and easier mixing with biomaterials[40, 41]. Prepared by very low-speed centrifugation in plastic tubes without anticoagulants, i-PRF retains a rich concentration of platelets and leukocytes with higher levels of cytokines and growth factors released rapidly after application[1, 2]. Its liquid consistency allows for precise delivery in peri-implant soft tissue augmentation and non-surgical periodontal therapy[40, 41].

Lyophilized / Compressed Membranes:

Freeze-drying (lyophilization) and compression techniques have been explored to enhance the storage, handling, and clinical application of PRF membranes. Lyophilized PRF retains the biological activity of growth factors and cellular components for prolonged periods, improving shelf-life and enabling off-the-shelf availability[1-3]. Compressed PRF membranes also exhibit greater tensile strength and ease of manipulation while maintaining porosity and bioactive molecule release[42, 43]. These modifications aim to overcome the temporal limitations of fresh PRF, expanding its clinical utility[42, 43].

Exosome-Enriched and Bio-Engineered PRF Hybrids:

Recent advances focus on enriching PRF with exosomes and bioengineered materials to enhance regenerative potential. Exosomes derived from platelets or mesenchymal stem cells (MSCs) incorporated into PRF scaffolds improve cell proliferation, angiogenesis, and immune modulation[44]. Hybrid PRF constructs combining nanoparticles, growth-factor-loaded hydrogels, or gene therapy vectors offer controlled release and targeted delivery, bridging tissue engineering with autologous biomaterials[45]. These innovations promise customizable, next-level biomimetic scaffolds for periodontal and maxillofacial regeneration[45].

5 TRANSLATIONAL INNOVATIONS & FUTURE DIRECTIONS

3-D Bioprinting with PRF Bio-Inks:

Emerging advances in tissue engineering integrate next-generation PRF with 3-D bioprinting technologies to fabricate patient-specific scaffolds with precise architecture. PRF bio-inks, composed of platelet-rich fibrin combined with hydrogels or polymer matrices, provide a bioactive milieu that promotes cell proliferation and vascularization in printed constructs[46, 47]. This approach enables simultaneous delivery of cells, growth factors, and structural support, potentially revolutionizing periodontal and craniofacial regeneration[46, 47].

Drug-/Gene-Delivery PRF Composites:

Functionalization of PRF scaffolds with drug molecules or gene vectors is under investigation to achieve controlled and localized therapeutic delivery[48, 49]. Antibiotics, anti-inflammatory agents, or osteoinductive genes loaded into PRF matrices enhance infection control and tissue repair. This strategy exploits the inherent sustained release capabilities of PRF and its autologous origin to improve safety and efficacy in regenerative medicine[48, 49].

Allogeneic/Cryopreserved PRF Platforms for Large-Scale Use:

While autologous PRF is widely used, cryopreservation and development of allogeneic PRF products are being explored to enable off-the-shelf availability and broader clinical application[30]. Cryopreserved PRF retains biological activity post-thaw, addressing limitations of fresh PRF such as short shelf life and preparation constraints[50]. Regulatory challenges remain in ensuring safety and immunocompatibility for allogeneic applications.

Standardization Issues: Tube Materials, RPM ↔ RCF Conversions, Regulatory Landscape:

Lack of standardized centrifugation protocols and tube materials remains a critical barrier to reproducibility and regulatory approval. Variability in relative centrifugal force (RCF) despite similar revolutions per minute (RPM) across different centrifuge models leads to inconsistent PRF quality . Moreover, disparities in glass vs. plastic vs. titanium tubes affect clot architecture and growth factor release[51]. Harmonizing preparation protocols and establishing regulatory guidelines are imperative for clinical translation and commercialization.

6 CONCLUSION

Next-generation platelet-rich fibrin (PRF) variants—including A-PRF+, i-PRF, and T-PRF—represent significant advances in periodontal regeneration, offering improved biological activity, sustained growth factor release, and enhanced scaffold properties compared to classic PRF and conventional therapies. Clinical studies consistently report meaningful gains in clinical attachment level and defect fill, with reduced patient morbidity and favorable handling characteristics. Their autologous nature, cost-effectiveness, and minimal chair-side preparation requirements make these biomaterials practical options for routine periodontal and implant-related regenerative procedures.

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