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Review Article

Platelet-Rich Fibrin as a Biological Mediator of Tissue Regeneration in Dentistry: A Critical Review of Clinical and Histological Outcomes

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Abstract

Background: Platelet-Rich Fibrin (PRF) has gained importance in regenerative dentistry since it was first introduced in 2001. Unlike first-generation concentrates, its three-dimensional fibrin network forms without chemical additives, which leads to a gradual release of growth factors such as PDGF, TGF-β and VEGF. Since it comes from the patient's own blood and works as both a scaffold and a source of biological factors, PRF stands as a useful option to support tissue healing from the inflammatory phase toward regeneration.

Objective: The main objective of this review is to evaluate the role of PRF in tissue regeneration, analyzing how variability in its preparation protocols affects clinical outcomes across different treatment applications in dentistry.

Methods: This literature review analyzes the current literature on PRF, covering its biological mechanisms, the influence of different preparation protocols, including Leukocyte-rich PRF (L-PRF), Advanced PRF (A-PRF) and injectable PRF (i-PRF) and its effectiveness across different areas of dentistry such as periodontics, oral surgery, implantology and soft tissue management.

Results: PRF effectiveness depends heavily on technical standardization; the use of Relative Centrifugal Force (RCF) and horizontal centrifugation allow cell concentrations up to four times higher than traditional methods. In soft tissues, PRF improves early healing in 75% of cases and reduces postoperative pain. In hard tissue, alveolar ridge preservation can be observed, although in complex bone defects better outcomes are seen when combined with other biomaterials. In implantology, PRF helps soft tissues adapt better around the implant by increasing their thickness.

Conclusion: PRF represents an autologous and low-cost alternative that has shown good results in regeneration, especially in soft tissue healing and bone preservation. However, its effectiveness depends largely on how it is prepared; without unified centrifugation criteria, results remain inconsistent. Further long-term studies are needed for PRF to be considered a reliable protocol in routine clinical practice.

Keywords: Platelet-Rich Fibrin; Tissue Regeneration; Dentistry; Growth Factors; Centrifugation Protocols

Introduction: Platelet-Rich Fibrin as a Biological Mediator of Tissue Regeneration

Platelet-Rich Fibrin (PRF) is a second-generation autologous platelet concentrate first introduced by Choukroun, et al., in France in 2001 [1]. Unlike its predecessor, Platelet-Rich Plasma (PRP), PRF is prepared by centrifuging whole blood without the addition of anticoagulants or bovine thrombin, yielding a three-dimensional fibrin matrix that concentrates platelets, leukocytes and a variety of growth factors. This natural architecture allows for a slow, sustained release of bioactive molecules that more closely mirrors the physiological sequence of wound healing [2]. Over the past two decades, PRF has been increasingly investigated across multiple areas of dentistry, including periodontal regeneration, alveolar ridge preservation, implant therapy and soft tissue management [2]. Its autologous nature eliminates the risk of immune rejection or disease transmission and its preparation is simple and cost-effective, making it accessible in routine clinical practice. Despite promising outcomes, important questions remain regarding protocol standardization, clinical predictability and long-term efficacy [3].

The aim of this review is to critically evaluate the biological mechanisms of PRF, examine the influence of different preparation protocols on its composition and clinical performance and assess its effectiveness across key areas of dentistry including periodontics, oral surgery, implantology and soft tissue management.

Biological Mechanisms of Platelet-Rich Fibrin (PRF)

Platelet-Rich Fibrin (PRF) is a second-generation platelet concentrate that operates through two principal mechanisms. The solid fibrin mesh physically traps leukocytes and platelets, localizing these cells at the site of tissue repair. As the fibrin matrix degrades over time, it gradually releases growth factors for several days to weeks. This sustained release initially modulates cytokine activity and inflammation, subsequently stimulating cell proliferation and matrix production. Unlike first-generation platelet concentrates such as Platelet-Rich Plasma (PRP), which deliver growth factors rapidly in a single bolus, PRF provides a slow, continuous release that more closely replicates physiological wound healing. PRF thus functions both as a scaffold and as a controlled delivery system for biological signals [4,5].

PRF consistently delivers essential growth factors for tissue repair, including Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor-Beta (TGF-β) and Vascular Endothelial Growth Factor (VEGF). Each growth factor fulfills a distinct role: PDGF stimulates the migration and proliferation of fibroblasts and smooth muscle cells; TGF-β regulates inflammation and promotes extracellular matrix production; VEGF facilitates angiogenesis by inducing endothelial cell proliferation and migration. Additional factors such as Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF) and Bone Morphogenetic Proteins (BMPs) may also be present depending on the preparation method [5]. The concentration and timing of growth factor release are influenced by PRF subtype and handling protocols. Certain protocols extend release for 7 to 14 days, resulting in a prolonged overlap of chemotactic and mitogenic signals [6].

The fibrin mesh serves as a scaffold, protecting proteins from degradation and concentrating signaling gradients within the wound microenvironment. VEGF released from PRF functions as the central mediator of neovascularization, binding to endothelial cell receptors and stimulating their proliferation, migration and tube formation *in-vitro* [6]. Mechanistic studies in animal models indicate that PRF increases microvascular density by providing a supportive fibrin matrix that stabilizes new vessels and improves tissue perfusion during healing. The combined effects of VEGF and fibrin cues direct endothelial morphogenesis, preventing disorganized angiogenesis and promoting stable tissue integration [7].

PRF also orchestrates the recruitment and regulation of reparative and immune cells during wound healing. It releases signaling proteins that form chemotactic gradients, attracting mesenchymal stem cells, fibroblasts and immune cells to the injury site. Leukocytes within the PRF release cytokines that modulate inflammation by either promoting or limiting it. PDGF and TGF-β specifically serve as chemoattractant to guide reparative cells to the wound. Furthermore, the three-dimensional fibrin structure supports and directs cell migration across the wound bed and into grafts or scaffolds. Together, these mechanisms accelerate the shift from inflammation to proliferation [8].

Beyond cell recruitment, PRF influences cell fate and lineage commitment through two main mechanisms: TGF-β and BMP family signals activate pathways that differentiate progenitor cells into bone-forming osteoblasts, promoting bone regeneration; and other PRF factors drive gene expression leading to fibroblastic and endothelial differentiation, supporting soft tissue repair [4,5]. Proteomic and *in-vitro* studies confirm PRF's dual action in both hard and soft tissue regeneration [5].

However, several limitations constrain its translation to clinical practice. Variability in preparation protocols; including centrifugation speed, duration and collection tube type, leads to inconsistent PRF composition and growth factor release [7]. Donor-specific factors including age, comorbidities and medication use further influence PRF quality and clinical outcomes [8]. The current evidence base is also limited by a lack of high-quality, long-term clinical trials. Addressing these limitations is a critical future direction, requiring the development of consistent protocols and expanded clinical evaluation [9].

In clinical practice, PRF can enhance outcomes in bone grafting, periodontal regeneration and soft tissue healing by accelerating repair and improving its quality. Its localized, gradual release of growth factors, along with its fibrin matrix, promotes the transition from hemostasis to proliferation and facilitates efficient tissue remodeling [8]. Protecting the natural stages of wound healing (hemostasis, inflammation, proliferation and remodeling) is a key advantage of this approach [9].

PRF Preparation Protocols and Variations

The main differences between L-PRF, A-PRF and i-PRF are centrifugation time and speed, which modify the fibrin network architecture and alter the biological properties of the material. L-PRF, also known as leukocyte-rich PRF, is centrifuged at high speeds (2700-3000 rpm, equivalent to around 400-700g), leading to rapid polymerization and generating a stiffer and denser fibrin network [10].

A-PRF uses lower centrifugation speeds between 1300-1500 rpm (approx. 200-230 g), forming a more flexible and porous fibrin network. Lower centrifugal forces allow a greater number of leukocytes and neutrophils to be incorporated, increasing the release of growth factors such as VEGF and TGF-β1 compared to the original protocol [10]. i-PRF uses approximately 700 rpm or 60 g for 3-4 minutes, keeping the concentrate in a liquid state and preserving viable platelets and leukocytes before clot formation. Although less dense, it releases factors such as PDGF in a more sustained manner, with stimulation lasting over ten days [10,11]. PRF effectiveness is not just about spin time; clotting cascade activation changes depending on the type of tube used, whether hydrophilic or hydrophobic [12]. Reporting speed in RPM is currently considered inadequate, as it does not allow results to be compared efficiently; Relative Centrifugal Force (RCF) should be used as an objective and reproducible measure [12,13]. At high speeds (~700g), L-PRF protocols cause leukocytes to migrate to the bottom of the tube outside the clot collection area. In contrast, The Low-Speed Centrifugation Concept (LSCC) uses reduced forces (~200g) to keep cells evenly distributed within the A-PRF fibrin network,[12] resulting in greater and more prolonged release of growth factors [12,13].

The most recent evidence also highlights that horizontal centrifugation for variants like i-PRF achieves cell concentrations up to four times higher than standard fixed-angle devices [12].

All these protocol variations directly affect outcomes. The lack of standardization has led to contradictory conclusions about PRF's effectiveness [14,15]. For results to be reliable, handling time must also be controlled: if more than 60 seconds pass between blood draw and the start of centrifugation, fibrin polymerization is altered and clot quality drops. Patient-specific factors such as hematocrit levels can also drastically change the separation of cell layers [14].

There is solid clinical evidence showing that PRF improves probing depth reduction and clinical attachment gain in intrabony defects. The best results come when it is combined with other materials; mixing it with bone grafts, bioactive glasses or agents like metformin has shown greater bone fill capacity compared to conventional techniques [15]. Although there is still no consensus on the ideal protocol, controlling these variables ultimately makes the difference in long-term regenerative outcomes [14].

Feature	L-PRF	A-PRF	i-PRF
Full name	Leukocyte-Rich PRF	Advanced PRF	Injectable PRF
Centrifugation speed	2700-3000 rpm (~400-700g)	1300-1500 rpm (~200-230g)	~700 rpm (~60g)
Duration	10-12 min	8-14 min	3-4 min
Physical form	Solid membrane/clot	Flexible, porous membrane	Liquid (injectable)
Fibrin network	Dense, stiff	Flexible, porous	Not yet polymerized

Feature	L-PRF	A-PRF	i-PRF
Leukocyte content	Moderate (migrate to bottom)	High (evenly distributed)	High (preserved in suspension)
Growth factor release	Rapid initial release	Greater and prolonged release	Sustained (>10 days)
Key growth factors	PDGF, TGF-β, VEGF	VEGF, TGF-β1 (higher than L-PRF)	PDGF (sustained)
Main clinical use	Membranes, socket coverage	Periodontal/soft tissue procedures	Mixing with grafts, injection
Tube type	Glass or silica-coated	Plastic (hydrophobic)	Plastic (hydrophobic)
Key advantage	Well-documented, widely used	Better cell incorporation	Flexible delivery, mixable
Key limitation	Leukocyte loss at high speed	Less structural rigidity	Shorter working window

Table 1: Main differences between PRF preparation protocols [10-13].

Effectiveness of PRF in Soft Tissue Healing

From a clinical point of view, PRF is an autogenous material that has been used as a tool to improve the healing of soft tissues in different dental procedures. Its use in the clinical field focuses mainly on its direct placement in the surgical area, such as post-extraction sockets or during oral surgery procedures, where it is currently used as a biomaterial that favors tissue repair [3,16]. In addition, it can be used in the form of a membrane or clot, which facilitates its adaptation to different clinical techniques of soft tissue management [3]. Different studies have shown that PRF can improve early healing of soft tissues compared to spontaneous healing. A systematic analysis reported that nearly 75% of the included studies showed better healing at the first week in sites treated with PRF [16]. Another analysis indicated that PRF is associated with a significant improvement in soft tissue healing and a reduction in the incidence of postoperative complications [17].

These findings suggest that PRF exerts a positive effect especially in the early phases of the healing process. It has also been demonstrated that PRF contributes to reducing pain and inflammation after surgical procedures. Patients treated with PRF present less postoperative pain during the first days, favoring a faster and more comfortable recovery [16,17]. Hajibagheri, et al., in 2024 reported a lower incidence of alveolar osteitis and other difficulties linked to the healing process [17].

A randomized clinical trial conducted by Ghanaati, et al., showed that PRF favors a faster sealing of the alveolar ridge compared to the natural healing process [18]. This result has great clinical relevance, as faster healing protects the surgical area and favors optimal conditions for subsequent treatments. Furthermore, in 2024, Calle, et al., reported that PRF helps to reduce edema and inflammation while favoring soft tissue evolution during healing [19].

Although these effects have been observed in studies with a lower level of evidence, they agree with the findings of systematic reviews, supporting PRF as a valuable option for soft tissue healing. However, certain studies show variable results, indicating that effectiveness may depend on clinical factors such as the technique used or the patient's individual conditions [17]. In general, the available evidence suggests that PRF is a promising tool to improve soft tissue healing, especially in the initial stages of the repair process [20].

Role of PRF in Hard Tissue Regeneration

Bone loss following dental extraction remains a major challenge in dentistry, as it affects potential future treatments such as implants. López-Valverde, et al., report that alveolar bone resorption occurs early and progressively, affecting bone dimensions [20]. Socket preservation techniques have been developed to reduce these changes and recent studies highlight the use of biomaterials such as PRF to promote bone regeneration [21].

The use of PRF in sockets after dental extraction has shown favorable results compared to spontaneous healing. Yan, et al., suggest a reduction in bone loss and an increase in bone formation during the first months after extraction [21]. Wang, et al., found a significant increase in bone formation and greater preservation of alveolar width [22]. However, López-Valverde, et al., noted that conventional techniques using bone graft and membranes are still widely used, with outcomes varying depending on the case [20]. Although studies indicate positive results, PRF displays some osteogenic potential but tends to produce less new bone than traditional graft material and is therefore not sufficient to entirely replace it. Alfaraj, et al., reveal that in larger bone

defects, the volume regenerated with PRF is reduced compared to that obtained with conventional grafting materials [23]. Variability in protocols and outcomes also limits the standardization of PRF use [24].

In complex procedures such as maxillary sinus augmentation, PRF revealed variable results showing a trend towards greater bone formation, although without reaching statistical significance in some parameters [24]. Other clinical studies demonstrated increased bone formation when PRF was combined with materials such as Deproteinized Bovine Bone Mineral (DBBM) [25].

The combined use of PRF with synthetic biomaterials may enhance bone formation and stability at the regenerated site [26]. Other studies have shown increased bone volume and quality when PRF is used as a complement to synthetic grafts, suggesting a synergistic effect in the regenerative process [25]. Current evidence indicates that PRF can improve bone regeneration particularly in small bone defects and socket preservation procedures [20-22]. However, its effectiveness as a standalone material is limited in complex alveolar defects. In these cases, combined use with conventional bone graft offers better clinical outcomes, although additional studies are still needed to establish standardized protocols [25].

PRF in Implant Dentistry: The Influence of Soft Tissues on the Stability of the Peri-implant Bone Margin

The thickness of the soft tissues around implants plays a fundamental role in the stability of the bone margin around dental implants. A thin biotype, less than 2 mm, is associated with greater marginal bone loss, while a thick biotype helps to preserve the peri-implant bone crest [27]. This phenomenon is related to the body's need to establish an adequate biological width, which can cause bone remodeling when soft tissue is insufficient [27].

The soft tissue forms a seal around the implant that acts as a barrier against bacteria. A good and adequate seal protects the marginal bone; if the seal is weak or insufficient, the risk of inflammation and bone loss increases. Implant stability does not depend only on the bone but also on the interaction between hard and soft tissues. Primary stability is influenced by mechanical factors, while secondary stability depends on tissue growth factors that promote angiogenesis and cell proliferation [28].

PRF improves soft tissue healing, strengthening the biological seal and promotes peri-implant bone formation, potentially reducing marginal bone loss. Clinical studies have shown that PRF can increase both tissue thickness and the width of keratinized gingiva [29]. PRF acts as an autologous material, improving healing and favoring soft tissue management in immediate implants. It also serves as a minimally invasive alternative to connective tissue grafts, with studies reporting comparable results to the connective tissue graft gold standard through a less invasive approach. This increase in soft tissue volume is clinically relevant, as it can help reduce bone resorption and improve the stability of peri-implant tissues [29].

PRF has also been evaluated in comparison with other biomaterials in alveolar ridge preservation [30]. It showed similar results to allogeneic bone graft in terms of marginal bone loss but with less gingival recession, suggesting an additional soft tissue benefit. Less gingival recession means a better peri-implant biological seal, which can prevent bacterial microleakage and peri-implant inflammation [30].

Aldommari, et al., demonstrated that PRF, especially in its modified form, can improve the preservation of alveolar ridge dimensions, increase bone density and promote soft tissue healing after tooth extraction [31]. The efficacy of T-PRF (Titanium-Prepared Platelet-Rich Fibrin) for alveolar bone preservation and optimization of the peri-implant environment has also been demonstrated [31]. Conversely, Naeimi Darestani, et al., found that PRF did not produce significant improvements in implant stability or marginal bone loss compared to the control group, indicating that its benefits may depend on specific clinical factors [32]. Overall, the evidence suggests that soft tissue thickness is a key factor in the preservation of peri-implant bone. PRF can improve soft tissue conditions and contribute to bone margin stability, although its effects may vary depending on the clinical context [33].

Clinical Outcomes and Patient-Centered Benefits

Platelet-Rich Fibrin (PRF) has shown consistent clinical benefits in dentistry, particularly in improving patient-centered outcomes such as postoperative pain, inflammation and healing time [33,34]. These effects are mainly related to its autologous nature and its ability to release growth factors gradually, supporting a more stable and organized healing process [35].

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One of the most relevant findings across the literature is the reduction in postoperative pain [33,34]. Clinical studies report that patients treated with PRF after tooth extractions or periodontal procedures tend to experience less discomfort and require fewer analgesics compared to conventional approaches [34]. This may be explained by the presence of leukocytes and cytokines within the fibrin matrix, which help regulate the inflammatory response during the early stages of healing [35].

PRF has also been associated with improved soft tissue healing and reduced postoperative swelling [35,36]. The sustained release of growth factors such as PDGF, TGF-β and VEGF promotes angiogenesis and cellular proliferation, contributing to faster epithelialization and better wound closure [35]. Several studies have reported improved early healing indices in sites treated with PRF compared to traditional methods [36].

In implant and periodontal therapy, PRF has demonstrated favorable clinical outcomes as an adjunctive treatment [37]. It has been associated with improved early implant stability and better peri-implant tissue response [37]. In periodontal procedures, PRF may enhance tissue integration and support the regenerative process, although results can vary depending on the clinical situation and technique used [35,37].

Another advantage of PRF is its practicality and cost-effectiveness [38]. As an autologous biomaterial, it reduces the need for additional grafting materials and minimizes the risk of adverse reactions. Its preparation is relatively simple and can be performed chairside, making it a convenient option in everyday clinical practice [38].

Limitations and Methodological Concerns

One of the main limitations of the current evidence on PRF is its high degree of heterogeneity. Differences in centrifugation parameters, tube types, blood handling time and patient-specific factors such as hematocrit and systemic health make it difficult to compare studies and draw definitive conclusions [38,39]. The lack of standardized preparation protocols remains a central methodological challenge, as it directly affects PRF composition and its biological and clinical outcome [39].

Most of the available studies are also limited by small sample sizes, short follow-up periods and variable outcome measures. High-quality, long-term randomized clinical trials are still scarce, which limits the strength of the evidence base [38,41]. Additionally, donor-specific variables including age, systemic disease and medication use introduce biological variability that further complicates interpretation of results.

Controversies

Despite a growing body of literature, the effectiveness of PRF compared to conventional treatments remains contested. Some studies demonstrate improved clinical outcomes with PRF, while others report no significant difference relative to control groups [40,41]. This inconsistency is particularly evident in complex bone defects and implant stability studies, where PRF's benefits appear to be context-dependent rather than universal [32,40,42]. The absence of a clear consensus on ideal centrifugation parameters and the continued use of RPM rather than RCF as a reporting measure further perpetuate contradictory findings across the literature [12,13].

Conclusion and Future Directions

PRF represents an autologous, low-cost biological tool that has demonstrated meaningful benefits in regenerative dentistry, particularly in soft tissue healing, socket preservation and as an adjunct to bone grafting procedures. Its ability to gradually release growth factors within a fibrin scaffold supports a more physiological wound healing response compared to earlier platelet concentrates.

However, its clinical effectiveness depends heavily on how it is prepared. Without standardized centrifugation protocols based on RCF rather than RPM, results will continue to vary and remain difficult to compare. Future research should prioritize well-designed randomized clinical trials with adequate follow-up periods, standardized preparation criteria and consistent outcome reporting to establish PRF as a reliable and reproducible option in routine clinical practice. Emerging variants and combination approaches such as the use of i-PRF mixed with bone grafts or the application of horizontal centrifugation, represent promising directions that warrant further investigation.

Conflict of Interest
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The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement
The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement
Informed consent was obtained from all participants included in the study.

Authors' Contributions
All authors contributed equally to this paper.

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