REVIEW ARTICLE

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A scoping review on platelet-rich fibrin–driven bone regeneration: biological mechanisms and clinical applications in oral and maxillofacial surgery

Dong Ho Cho[1,2], Yong Seung Kim[1,2], Jun Lee[1,2], Joo-Young Park[1,2]

[1]*Department of Oral and Maxillofacial Surgery, Dental Research Institute, School of Dentistry, Seoul National University,*
[2]*Department of Oral and Maxillofacial Surgery, Seoul National University Dental Hospital, Seoul, Korea*

Abstract (J Korean Assoc Oral Maxillofac Surg 2026;52:112-127)

Platelet-rich fibrin (PRF), a second-generation platelet concentrate, has emerged as a promising autologous biomaterial in regenerative medicine. Unlike platelet-rich plasma (PRP), PRF is prepared without anticoagulants or biochemical additives, allowing natural platelet activation and fibrin polymerization. This process generates a three-dimensional fibrin matrix containing concentrated platelets, leukocytes, cytokines, and growth factors that collectively support tissue regeneration. Owing to these regenerative properties, PRF has been increasingly applied in oral and maxillofacial surgery. Despite its widespread clinical use, the precise biological mechanisms underlying PRF-mediated bone regeneration remain incompletely understood. PRF functions not only as a reservoir for growth factors, but also as a dynamic immunomodulatory scaffold that regulates inflammation, angiogenesis, cellular migration, and osteogenic differentiation. Recent evidence further suggests that leukocytes, fibrin architecture, cytokine networks, and osteoimmunological interactions within PRF play critical roles in coordinating tissue regeneration. This scoping review aims to summarize the current understanding of the biological mechanisms and regenerative potential of PRF in bone healing and oral and maxillofacial reconstruction. Particular emphasis is placed on the interplay between growth factor release, fibrin matrix structure, immune modulation, and cellular signaling pathways involved in osteogenesis. Furthermore, recent advances, limitations, and future perspectives regarding PRF optimization and clinical applications are discussed.

Key words: Platelet, Tissue engineering, Cytokines, Cell- and tissue-based therapy, Bone regeneration

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I. Introduction

Patient's own tissues have been used to boost the body's natural healing ability and to assist tissue regeneration in medical and dental clinics. Using autologous human tissue products became more popular, mainly because these tissues contain growth factors and stem cells that help repair and regenerate damaged tissue[1]. Platelet-rich fibrin (PRF), a second-generation platelet concentrate, has emerged as a promising autologous biomaterial in regenerative medicine, particularly in bone regeneration, owing to its unique structural and biological properties[2]. PRF represents an evolution in platelet concentrate technology, characterized by its simplified preparation process[3]. This autologous preparation method involves the sequestration of a fresh blood unit via centrifugation, resulting in a platelet-poor plasma (PPP) fraction, a platelet-rich stratum, and erythrocyte fractions with the fibrin matrix. One of the distinctive features of PRF is the blood borne fibrin matrix which acts as an autologous scaffold for cell migration, proliferation, and differentiation, while the concentrated platelets release a sustained supply of growth factors, cytokines, and other mediators that stimulate bone regeneration[4,5].

Additionally, unlike PRP, PRF is prepared without the use of anticoagulants, allowing for the natural activation of platelets and the formation of a fibrin network that entraps growth factors, cytokines, and cells, fostering a conducive environment for tissue repair[6]. The controlled release of these bioactive molecules from the fibrin matrix provides a sus-

Joo-Young Park
Department of Oral and Maxillofacial Surgery, Dental Research Institute, School of Dentistry, Seoul National University, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
TEL: +82-2-6256-3133
E-mail: bbyoung1@snu.ac.kr
ORCID: https://orcid.org/0000-0002-0333-6349

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tained stimulus for cellular proliferation, differentiation, and angiogenesis, crucial processes in bone regeneration[7]. Based on its known regeneration capacity, PRF can be applied to a wide spectrum of dental and oral and maxillofacial surgical scenarios, including alveolar ridge augmentation, sinus lift procedures, and the treatment of peri-implant defects, as well as periodontal regeneration, demonstrating its versatility in addressing diverse maxillofacial bone regenerative needs.

Although PRF has been widely used in clinical practice, the precise biological mechanisms and the relative contributions of its individual components to bone regeneration remain incompletely understood[8,9]. PRF contains a high concentration of platelets embedded within a fibrin matrix, which enables release of growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF), all of which are known to promote angiogenesis, osteogenic differentiation, and tissue repair[10,11]. Beyond growth factors, increasing evidence suggests that leukocytes, the three-dimensional fibrin architecture, cytokines, and immune-regulatory molecules within PRF play critical roles in modulating inflammation, cell recruitment, and osteo-immunological crosstalk during bone regeneration[9,12,13].

This scoping review aims to elucidate the intricate, multifaceted mechanisms by which PRF facilitates tissue regeneration, especially how PRF interplay of growth factors, cell signaling pathways, and the modulation of the immune response for bone regeneration[14,15]. Understanding these mechanisms is critical for optimizing the clinical application of PRF and designing novel strategies to enhance bone regeneration in various clinical settings.

II. Development of Platelet-Rich Derivatives and Comparative Characteristics of the Formulations

Platelet-rich derivatives have evolved substantially since their introduction in the 1980s, progressing from early PRP protocols to more advanced fibrin-based and growth-factor-focused formulations.(Table 1) First-generation products PRP, including pure and leukocyte-rich variants, rely on multi-step centrifugations to concentrate platelets and growth factors but require anticoagulants and offer only short-term release of growth factors[16,17]. However, the preparation of PRP requires a two-step centrifugation process, which not only increases the risk of contamination but also necessitates the use of anticoagulants to prevent premature clotting[18]. Such requirements complicate the procedure and may alter the natural function of platelets[19]. Therefore, second-generation derivatives PRF were developed to address these limitations by using a single-spin, anticoagulant-free protocol that produces a three-dimensional fibrin matrix capable of entrapping platelets, leukocytes, cytokines, and growth factors, enabling sustained biological activity and improved regenerative potential[3]. Importantly, the fibrin network provides a three-dimensional scaffold capable of entrapping bioactive molecules, thereby allowing the gradual and sustained release of growth factors and cytokines[10,12]. These properties extend the biological ac-

Table 1. Development of platelet-rich derivatives and comparative characteristics of the formulations

Generation	Platelet-rich derivative	Primary centrifugation	Additional centrifugation	Tube	Anticoagulant	Reference
1st	P-PRP	160 xg, 10 minutes	250 xg, 15 minutes	Plastic tube	Present	Dohan Ehrenfest et al.[10] (2009) Dhurat et al.[134] (2014)
	L-PRP	250 xg, 10 minutes	250 xg, 10 minutes			Dohan Ehrenfest et al.[133] (2009)
2nd	P-PRF	700 xg, 15 minutes	None	Glass or silica-coated plastic tube	Absent	Dhurat et al.[134] (2014)
	L-PRF	400 xg, 12 minutes				Dohan et al.[3] (2006)
	H-PRF	700 xg, 8 minutes				Feng et al.[21] (2020)
	T-PRF	2,700 RPM, 12 minutes				Ercan et al.[22] (2022)
	A-PRF	100 xg, 14 minutes				Ghanaati et al.[20] (2014)
	i-PRF	60 xg, 3 minutes				Miron et al.[75] (2017)
	Ly-PRF	400 xg, 10 minutes				Ngah et al.[26] (2021)
3rd	CGF	Acceleration 30 seconds 2,700 RPM, 2 minutes	2,400 RPM, 4 minutes → 2,700 RPM, 4 minutes → 3,000 RPM, 3 minutes → Deceleration 36 seconds	Glass or silica-coated plastic tube	Absent	Bernardi et al.[135] (2017)

(P-PRP: pure platelet-rich plasma, L-PRP: leukocyte- and platelet-rich plasma, P-PRF: pure platelet-rich fibrin, L-PRF: leukocyte- and platelet-rich fibrin, H-PRF: horizontal platelet-rich fibrin, T-PRF: titanium-prepared platelet-rich fibrin, A-PRF: advanced platelet-rich fibrin, i-PRF: injectable platelet-rich fibrin, Ly-PRF: lyophilized platelet-rich fibrin, CGF: concentrated growth factor, RPM: revolutions per minute)

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tivity of PRF beyond the immediate release profile characteristic of PRP.

Despite its clinical advantages, conventional PRF has limitations related to handling bulkiness and lack of storage capability[20], prompting the development of multiple PRF variants, including horizontal PRF (H-PRF), titanium PRF (T-PRF), advanced PRF (A-PRF) and injectable PRF (i-PRF), which aim to optimize leukocyte content, fibrin architecture, growth-factor release, injectability, and storage stability[21-24]. Because freshly prepared PRF must be used immediately, storage issues limit its application. To overcome this, lyophilized PRF (Ly-PRF) was developed using freeze-drying[25]. Ly-PRF exhibits larger pores, thicker fibrin, and a rougher surface, leading to sustained growth factor release and enhanced osteoblast adhesion[26]. Additionally, low-speed centrifugation produces PRF with higher platelet retention, more growth factor secretion, and improved regenerative potential compared with high-speed centrifugation[27].

The most recently developed generation platelet-rich derivatives is the concentrated growth factor; CGF. Unlike the steady centrifugation used in PRP and PRF, CGF is obtained by alternating acceleration and deceleration cycles[28]. This generates a denser fibrin network with greater tensile strength and higher cytokine content, supporting both bone and soft tissue regeneration[29].

III. Microstructure and Biological Properties of Platelet-Rich Fibrin

During centrifugation for fabricating PRF, whole blood is separated into three distinct layers: PPP in the most upper layer, the PRF clot in the intermediate layer, and red blood cells at the bottom[30]. From a standard 10 mL blood sample, approximately 2 to 3 mL of PRF can be harvested, retaining nearly 97% of circulating platelets and more than 50% of leukocytes[31]. Histological analyses of freshly prepared PRF have demonstrated heterogeneous architecture consisting of two distinct zones: a platelet-rich region characterized by dense aggregates of intensely stained platelets, and a fibrin-rich region containing entrapped blood cells within a reticular fibrin network[32]. This organized microstructure enables PRF to function as an effective scaffold, providing a supportive niche for sustained cytokine secretion and facilitating both soft- and hard-tissue regeneration[33].

The fibrin and fibronectin networks within PRF play critical roles in coagulation, wound healing, and cell–matrix interactions by promoting cellular adhesion, proliferation, and differentiation[34]. Fibronectin is particularly important in angiogenesis and bone regeneration; its β15-42 domain interacts with endothelial receptors such as calmodulin to stimulate capillary formation, especially in the presence of fibroblast growth factor-2 (FGF-2) and VEGF[35]. Fibrin has been shown to enhance osteogenic differentiation of mesenchymal stem cells (MSCs) by upregulating osteocalcin expression[36]. In addition, fibrinogen-mediated integrin signaling activates the SMAD1/5/8–RUNX2 pathway, thereby promoting osteogenesis in both embryonic and induced pluripotent stem cells[37]. Importantly, fibrin components also protect growth factors from proteolytic degradation, enabling their sustained release over time[38].

During PRF formation, platelet activation triggers the release of α-granules containing a wide range of growth factors and cytokines, including platelet-derived growth factor (PDGF-AA, -AB, and -BB), transforming growth factor-β1 (TGF-β1), insulin-like growth factor-1 (IGF-1), VEGF, interleukins (IL-1β, IL-4), and tumor necrosis factor-α (TNF-α)[3,10,39]. Quantitative proteomic analyses have demonstrated that PRF releases more than 9,000 ng/mL of proteins over a 10-day period, with PDGF-AA being the most abundant, followed by TGF-β1, PDGF-BB, VEGF, epidermal growth factor (EGF), and IGF-1[12]. Release kinetics studies indicate that growth factors and matrix metalloproteinases (MMPs) are released most rapidly within the first 6 hours, followed by an exponential decline, whereas cytokine release typically peaks between 6 and 24 hours[40]. In contrast to PRP, which exhibits a bimodal release pattern of TGF-β1, PRF demonstrates a single release peak around day 7, with IGF-1 showing a gradual release over approximately 3 days and IL-1β peaking on day 1[41]. Additional studies have reported that EGF release peaks at approximately 7 hours, while VEGF, TGF-β1, PDGF-BB, and MMP-9 reach maximal levels around day 7 before declining substantially after 7-10 days[42]. Collectively, these findings suggest that PRF exhibits its highest biological activity during the first postoperative week, underscoring the clinical importance of strategies aimed at delaying PRF degradation to prolong growth factor availability.

Finally, the biomechanical properties of PRF also contribute to its regenerative potential. Mechanical testing of leukocyte-PRF (L-PRF) membranes has demonstrated an elastic modulus of approximately 0.07 MPa, an ultimate tensile strength of 0.29 MPa, and an elongation at break of 2.78, with anticoagulation protocols significantly influencing these mechanical characteristics[43]. These observations highlight

the importance of both biological composition and mechanical integrity in determining the regenerative performance of PRF-based biomaterials.

IV. Mechanisms of Platelet-Rich Fibrin–Mediated Tissue Regeneration

1. Coupling of angiogenesis and osteogenesis in bone healing

Bone regeneration relies on the tightly coordinated interaction between angiogenesis and osteogenesis, as early vascularization is essential for delivering oxygen, nutrients, and osteoprogenitor cells to the defect site[44]. PRF facilitates this coupling by providing a fibrin-based scaffold enriched with angiogenic growth factors, including VEGF, PDGF, and EGF[10,11]. These factors stimulate endothelial cell proliferation, migration, and capillary formation through signaling pathways such as extracellular signal-regulated kinase (ERK), EGFR, and Notch, thereby creating a vascular niche that supports subsequent osteogenic activity. Experimental models have demonstrated that PRF and i-PRF upregulate angiogenic markers and adhesion molecules in endothelial–osteoblast co-culture systems, while *in vivo* studies suggest the recruitment of circulating endothelial progenitor cells contributes to PRF-induced neovascularization[45]. Insufficient function of the HIF-1α/PDGF-β axis has been implicated in poor neovascularization[46]. VEGF is a key angiogenic driver; its overexpression in osteoprogenitors enhances vascularization of bone grafts, and during osteogenesis, VEGF couples angiogenesis with osteogenesis—partly via Notch signaling[47,48]. In co-cultures of endothelial cells and primary osteoblasts, i-PRF enhances angiogenic activation, including upregulation of VEGF, E-selectin, and ICAM-1[45]. These effects may be mechanistically related to the ability of fibrin and activated platelets to recruit circulating CD34+ progenitor cells and promote endothelial differentiation, a process relevant to neovascularization[49,50]. VEGF released from PRF matrices activates endothelial mitosis via ERK signaling, enhancing trabecular endothelial proliferation and angiogenesis[51]. L-PRF also boosts human umbilical vein endothelial cell (HUVEC) proliferation/migration and tube formation through EGFR-related signaling[52,53]. PRF prepared at different centrifugal forces supports neovascularization, but medium-force protocols outperform high-force settings in vessel number, density, and percent vascularization[54]. Importantly, the angiogenic efficacy of PRF is strongly influenced by centrifugation protocols, with low- to medium-speed centrifugation preserving platelet and leukocyte content and yielding superior vessel density and maturation compared with high-speed protocols[55].

2. Regulation of mesenchymal stem cell osteogenic differentiation

PRF-derived preparations promote bone regeneration by supporting the proliferation, migration, and osteogenic differentiation of MSCs. The three-dimensional fibrin matrix of PRF provides a favorable microenvironment for cell attachment, while platelet- and leukocyte-derived mediators released from the matrix activate osteogenic signaling pathways. Among these pathways, BMP/SMAD and ERK/MAPK signaling appear to play central roles. PRF has been shown to activate BMP2/SMAD signaling in bone marrow-derived MSCs, increasing SMAD1/5/8 phosphorylation and the expression of osteogenic markers such as RUNX2, ALP, and osteocalcin[56]. PRF lysates also contain biologically active TGF-β, which can induce BMP2 expression and downstream BMP-responsive genes through TGF-β receptor 1 kinase activation[57,58]. In addition, PRF-conditioned media and i-PRF enhance ERK1/2 activation, and inhibition of ERK signaling reduces PRF-induced osteogenic differentiation[40,59]. Similar osteogenic effects have been reported in dental progenitor cells, including periodontal ligament cells, periodontal ligament stem cells, and dental pulp stem cells[60-62].

3. Modulation of osteoblast function and bone matrix formation

Beyond stem cell differentiation, PRF directly enhances osteoblast function during bone formation and remodeling. Osteoblasts exposed to PRF exhibit increased adhesion, proliferation, and extracellular matrix (ECM) synthesis, accompanied by activation of ERK1/2 and PI3K–Akt signaling pathways[63,64]. PRF also improves osteoblast adhesion/spread on titanium—counteracting zoledronic-acid–induced impairment—thereby favoring osseointegration[65]. Among PRF types, A-PRF+, L-PRF, and i-PRF all enhance osteoblast osteogenesis *in vitro*; A-PRF+ shows the greatest mineralization, while i-PRF tends to favor early osteogenic events[66]. PRF also upregulates collagen-related proteins such as HSP47 and LOX in human osteoblasts, thereby supporting collagen maturation and ECM assembly[64]. In addition, PRF increases the osteoprotegerin (OPG)/RANKL ratio, indirectly inhibiting osteoclastogenesis and favoring net bone forma-

tion[63]. These effects are particularly relevant in implant-related applications, as PRF has been shown to improve osteoblast adhesion and spreading on titanium surfaces, even under compromised conditions such as bisphosphonate exposure, thereby supporting osseointegration[65,67].

4. Inhibition of osteoclastogenesis and regulation of bone remodeling

Balanced bone regeneration requires not only osteogenesis but also controlled osteoclast activity to enable proper remodeling[68]. PRF exerts an inhibitory effect on osteoclast differentiation by downregulating osteoclastogenic marker genes, including NFATc1, TRAP, cathepsin K, DCSTAMP, and OSCAR[69]. PRF combined with biphasic calcium phosphate has been shown to impair osteoclast differentiation and promote osteoclast apoptosis through the intrinsic mitochondrial pathway, while also suppressing NF-κB and MAPK signaling cascades[70,71]. When combined with osteoconductive graft materials, PRF further enhances anti-resorptive effects, suggesting a synergistic role in conditions characterized by excessive bone resorption, such as periodontal disease. These findings underscore the importance of PRF in maintaining osteoblast–osteoclast coupling during bone regeneration.

5. Regulation of fibroblast activity and soft-tissue healing

In addition to its effects on bone cells, PRF plays a critical role in soft-tissue healing by regulating fibroblast behavior. Fibroblasts play a pivotal role in wound healing and tissue regeneration by producing ECM components, secreting cytokines, and regulating angiogenesis. Fibroblasts exposed to PRF demonstrate enhanced proliferation, migration, and adhesion, driven in part by the sustained release of growth factors such as PDGF, TGF-β, and VEGF from the fibrin matrix[10,72-74]. Moreover, the three-dimensional fibrin network of PRF provides a natural scaffold that facilitates cell attachment and spatial organization[31,32]. This structural microenvironment not only supports cell survival but also stimulates fibroblasts to increase the synthesis of collagen type I and other ECM proteins, leading to enhanced matrix remodeling. The gradual degradation of PRF further ensures a controlled release of bioactive molecules, allowing fibroblast activity to be sustained over an extended period compared with PRP, which releases factors more rapidly[75].

An additional aspect to consider is the role of leukocytes embedded within PRF. These immune cells secrete cytokines such as IL-1β and IL-6, which can indirectly modulate fibroblast activity by creating a balanced inflammatory milieu[9,10]. This controlled inflammatory response is believed to favor fibroblast recruitment and functional activation without inducing excessive scarring or fibrosis.

From a clinical standpoint, these fibroblast-mediated effects are relevant to periodontal regeneration and soft-tissue wound healing, although differences in PRF preparation protocols and cell culture conditions make direct comparison between studies difficult[9,74,76]. Enhanced fibroblast proliferation and ECM deposition contribute to faster closure of surgical sites, reduced postoperative complications, and improved esthetic outcomes[77]. Nevertheless, the literature remains heterogeneous, with variations in PRF preparation protocols and fibroblast culture conditions making direct comparisons challenging. Future studies employing standardized methodologies and advanced molecular profiling techniques, such as single-cell RNA sequencing, will be critical to further elucidate the precise signaling pathways by which PRF regulates fibroblast biology.

Taken together, the evidence indicates that PRF provides a favorable microenvironment that stimulates fibroblast proliferation, migration, and matrix production, thereby supporting both hard- and soft-tissue regeneration. This biologic activity highlights PRF's clinical potential not only as a scaffold but also as a biologically active modulator of wound healing.

6. Immunomodulatory effects of platelet-rich fibrin (anti-inflammation)

During bone repair, immune cells regulate inflammation, debris clearance, angiogenesis, and osteogenic cell recruitment, thereby shaping a pro-regenerative immune microenvironment[78]. PRF exerts anti-inflammatory effects on macrophages by attenuating pro-inflammatory mediator expression and shifting macrophage polarization from an M1-like toward an M2-like phenotype[58,69,79]. In LPS-challenged macrophages, PRF reduces IL-1β release and downregulates pyroptosis-related mediators, including NLRP3, caspase-11, and IL-18[80]. PRF may also modulate adaptive immune responses, as iPRF has been shown to induce regulatory CD4+ T cells through a GARP-related mechanism[81]. Transcriptionally, PRF reduces IL-1β, NLRP3, CASP11, and IL-18 in LPS-challenged macrophages, limits ROS, and curbs pyroptosis[80]. PRF can neutralize hydrogen peroxide-induced cytotoxicity through the release of heat-sensitive catalase/peroxidase-like activity, thereby protecting gingival fibroblasts from oxidative cell

death[69]. Conversely, PRF patches can release sCD40L from activated platelets, limiting regulatory T cell (Treg) infiltration in glioma microenvironments and impacting antitumor immunity[82].

T lymphocytes are central regulators of immune responses and play a decisive role in the balance between inflammation and tissue regeneration. While the biological effects of PRF have traditionally been attributed to platelets and growth factors, increasing evidence suggests that its leukocyte content, including T cells, also contributes significantly to its regenerative potential[8]. *In vitro* studies have demonstrated that PRF can influence T cell viability and cytokine secretion. Dohan et al.[3] reported that T cells entrapped within the PRF matrix remain metabolically active and capable of releasing signaling molecules over time. This sustained activity may contribute to the modulation of the local immune microenvironment at surgical sites. Specifically, PRF has been shown to upregulate anti-inflammatory cytokines such as IL-4, IL-10 while attenuating pro-inflammatory mediators like TNF-α and IFN-γ, thereby favoring a regenerative milieu[12,83].

Another important aspect about PRF immunomodulatory function is the interaction between T helper subsets. Although direct evidence that PRF broadly shifts Th1/Th17 responses toward Th2/Treg polarization remains limited, iPRF has been reported to support regulatory CD4+ T cell conversion through a GARP-related mechanism[81]. This immunomodulatory effect could reduce excessive inflammation while simultaneously enhancing angiogenesis and soft-tissue healing. Furthermore, experimental evidence indicates that PRF-derived extracellular vesicles may exert additional immunoregulatory effects on T cells, although their clinical significance remains to be clarified[84,85]. Several studies have highlighted the pivotal role of monocytes and macrophages in mediating the biological effects of PRF. Experimental data indicate that PRF and liquid PRF can modulate macrophage activation and polarization, attenuating pro-inflammatory responses and shifting macrophages toward a more anti-inflammatory or pro-regenerative phenotype[79,86]. *In vitro* studies have shown that PRF-conditioned media promotes monocyte migration and survival[20]. This chemotactic effect has been attributed to the release of PDGF, VEGF, and stromal-derived factor-1 (SDF-1), which collectively guide monocytes toward the healing site. Moreover, once recruited, monocytes exposed to PRF display an increased tendency to differentiate into macrophages with a pro-regenerative M2 phenotype[9]. This is consistent with findings by Kobayashi et al.[12], who demonstrated that PRF releases IL-4 and IL-10 cytokines known to drive M2 polarization.

The immunomodulatory capacity of PRF has also been supported by co-culture models, where macrophages in contact with PRF scaffolds exhibited reduced expression of pro-inflammatory mediators such as TNF-α and IL-1β, while simultaneously upregulating anti-inflammatory markers including arginase-1 and CD206[75,78]. These findings suggest that PRF not only attenuates excessive inflammation but also actively contributes to the establishment of a pro-healing immune microenvironment. *In vivo* studies further corroborate these observations. Animal models of bone regeneration have revealed that PRF application accelerates macrophage recruitment at early stages of healing, followed by a rapid shift from M1 to M2 dominance, coinciding with enhanced angiogenesis and new bone deposition[87]. Such temporal regulation of macrophage phenotype appears crucial for orchestrating the transition from inflammation to regeneration.

V. Application of Platelet-Rich Fibrin in Regenerative Medicine for Oral and Maxillofacial Surgery

1. Platelet-rich fibrin in guided bone regeneration (GBR)

GBR uses a barrier membrane to exclude rapidly migrating epithelial and connective tissue cells from bone defects, thereby allowing osteogenic cells to repopulate the defect and support undisturbed bone formation[88,89].(Table 2) In this context, PRF has been investigated as an adjunctive biomaterial to improve graft handling, soft-tissue healing, growth factor delivery, and early bone regeneration. Clinical studies suggest that PRF may enhance GBR outcomes when combined with bone graft materials. In simultaneous GBR, A-PRF mixed with deproteinized bovine bone mineral (DBBM) showed clinical and radiographic outcomes comparable to autogenous bone mixed with the same xenograft[90]. Similarly, L-PRF combined with DBBM in severely atrophic anterior maxillae resulted in high implant survival and substantial horizontal ridge gain after 1 year[91]. The addition of liquid PRF to bovine-derived xenograft has also been associated with greater buccal bone thickness and reduced marginal bone changes compared with xenograft alone[92].

PRF membranes have shown favorable bone healing and reduced fibrosis in experimental GBR models compared with resorbable collagen membranes[93]. However, because PRF membranes have limited mechanical stiffness and relatively rapid degradation, they should be regarded mainly as bio-

Table 2. Application of PRF in oral and maxillofacial surgery

Category	Reference	Biological rationale	Reported outcome
Guided bone regeneration	De Angelis et al.[90] (2022)	PRF may improve graft handling, growth factor delivery, and early regenerative activity	A-PRF+DBBM showed clinical and radiographic outcomes comparable to autogenous bone mixed with the same xenograft
	Caramês et al.[91] (2022)	L-PRF may enhance graft integration, soft-tissue healing, and early bone regeneration	High implant survival and substantial horizontal ridge gain after 1 year were reported
	Işık et al.[92] (2021)	Liquid PRF may improve biological activity of xenograft and promote early vascularized healing	Greater buccal bone thickness and reduced marginal bone changes compared with xenograft alone
	Tayşi et al.[93] (2018)	PRF membrane may provide growth factors and biologic activity during bone healing	Favorable bone healing and reduced fibrosis compared with collagen membrane
Alveolar ridge preservation	Kargarpour et al.[69] (2020)	Anti-inflammatory and osteoclastogenesis-inhibitory effects may reduce bone remodeling	Supports the rationale that PRF may modulate early extraction socket healing
	Ouyyamwongs et al.[95] (2019)	PRF may support early socket healing and improve tissue response around dentin-derived matrix	Reduced horizontal ridge loss compared with controls at 8 weeks
	De Angelis et al.[96] (2019)	PRF may enhance early healing, while xenograft provides volume stability	L-PRF+xenograft improved dimensional stability compared with L-PRF alone; outcomes were closer to xenograft alone
	Castro et al.[97] (2021)	PRF may enhance clot stability, soft-tissue healing, bone maturation, and postoperative comfort	Improved socket bone density, new bone quality, soft-tissue healing, postoperative comfort, socket fill, and trabecular mineralized tissue formation
	de Almeida Barros Mourão et al.[98] (2020)	PRF may enhance socket fill and mineralized tissue formation in early healing	Improved socket fill and trabecular mineralized tissue formation compared with spontaneous healing
Maxillary sinus floor elevation	Xuan et al.[100] (2014)	PRF may enhance early bone formation and osseointegration around grafted sinus sites	DBBM+PRF showed higher osseointegration and new bone formation at 6 months than tissue glue+DBBM
	Pichotano et al.[101] (2019)	L-PRF may accelerate bone regeneration and maturation within DBBM-augmented sinus	Increased histologic new bone formation and enabled earlier implant placement
	Barbu et al.[102] (2018)	PRF may enhance graft healing and soft-tissue closure over lateral window	Approximately 10.1 mm vertical gain at 6 months and no implant loss over about 44 months
	Wang et al.[59] (2022)	PRF promotes MSC proliferation, migration, and osteogenic differentiation via ERK1/2 signaling	Biological support for expedited bone regeneration and improved tissue quality
	Wang et al.[103] (2021)	PRF may support clot stabilization, bone formation, and peri-implant bone densification	95.65% 1-year implant survival, approximately 6.72 mm mean sinus lift, and progressive bone densification around implants
	Lv et al.[104] (2022)	PRF may support vertical bone gain through fibrin matrix-mediated healing and growth factor release	Randomized clinical trial reported mean vertical gain of approximately 7.67 mm at 18 months
	Karagah et al.[105] (2022)	PRF may improve implant stability through enhanced early bone healing	Higher ISQ gains, indicating improved implant stability, compared with allograft/collagen membrane
Soft tissue/periodontal healing	Rosamma Joseph et al.[110] (2012)	PRF may enhance periodontal wound healing through growth factor release and fibrin-mediated tissue regeneration	Improved probing depth and attachment gain compared with conventional therapy
	Sharma and Pradeep[109] (2011)	PRF may promote periodontal regeneration and soft-tissue healing	Improved probing depth and clinical attachment gain
	Panda et al.[111] (2016)	PRF may reduce inflammation and support connective tissue regeneration	Histological confirmation of new connective tissue and reduced inflammation
Soft tissue/periodontal healing	Paolantonio et al.[112] (2020)	L-PRF may support gingival soft-tissue healing and periodontal regeneration	L-PRF+autologous bone was not inferior to enamel matrix derivative+autologous bone at 12 months
	Aroca et al.[113] (2009)	PRF may enhance gingival thickness, soft-tissue maturation, and root coverage stability	Higher root coverage and greater gingival thickness than flap alone
	Simonpieri et al.[114] (2009)	PRF membrane may accelerate epithelial closure and reduce postoperative morbidity	Accelerated epithelial closure, reduced pain, and lower complication rates
	Choukroun et al.[115] (2006)	Sustained release of angiogenic and fibrogenic growth factors	Provides mechanistic basis for soft-tissue healing and regeneration
	Miron et al.[116] (2017)	PRF may enhance angiogenesis, inflammation control, and tissue regeneration	Short-term benefits are consistent across several applications

Table 2. Continued

Category	Reference	Biological rationale	Reported outcome
Osteoradionecrosis and medication-related osteonecrosis of jaw	Giudice et al.[117] (2018)	PRF may enhance mucosal healing and reduce postoperative symptoms in compromised bone	Earlier clinical evidence suggested improved mucosal healing and short-term clinical resolution
	Muñoz-Salgado et al.[118] (2023)	Autologous platelet concentrates may support soft-tissue healing and inflammatory modulation	Systematic review-level support for potential adjunctive role
	Ramos et al.[119] (2025)	Intended to improve mucosal healing and clinical resolution	Recent randomized trial showed no statistically significant additional benefit over surgery alone, despite numerically higher 6-month complete resolution rates
	Chen and Chang[120] (2019)	PRF may support mucosal coverage and angiogenesis in irradiated tissues	Faster mucosal coverage and reduced wound dehiscence reported in case-based evidence
	Law et al.[122] (2021)	Growth factor release and leukocyte-mediated immunomodulation may improve irradiated wound healing	Improved mucosal healing and reduced wound complications reported
	Maluf et al.[121] (2020)	PRF may promote angiogenesis and improve local wound environment	Case series suggest favorable mucosal healing and reduced dehiscence
	Del Fabbro et al.[123] (2015)	VEGF and TGF-β may stimulate angiogenesis, especially in vascularly compromised tissues	Supports potential adjunctive role in necrotic jaw conditions
	Strauss et al.[74] (2020)	Leukocytes in PRF may modulate chronic inflammation and create a favorable healing microenvironment	Provides biological rationale for L-PRF in inflammatory or necrotic bone conditions
Temporomandibular disorders	Işık et al.[125] (2022)	i-PRF may reduce joint inflammation and support intra-articular tissue repair	Reduced pain and improved mandibular function compared with arthrocentesis alone in selected patients
	Işık et al.[126] (2023)	Growth factor-rich fibrin matrix may improve post-lavage joint healing	Improvement in pain and maximal mouth opening reported
	Ghoneim et al.[127] (2022)	i-PRF may improve joint lubrication, inflammation control, and tissue repair after lavage	Safe and effective approach with improvements in pain and joint function
	Manafikhi et al.[128] (2022)	i-PRF may reduce intra-articular inflammation and improve disc-condyle functional environment	Preliminary evidence suggests reduction in articular clicking
	Vingender et al.[129] (2023)	i-PRF may provide biologic anti-inflammatory and regenerative effects similar to other injectables	Similar clinical improvement in pain reduction; superiority over other injectables remains uncertain

(PRF: platelet-rich fibrin, A-PRF: advanced platelet-rich fibrin, L-PRF: leukocyte- and platelet-rich fibrin, i-PRF: injectable platelet-rich fibrin, DBBM: deproteinized bovine bone mineral, MSC: mesenchymal stem cell, ERK1/2: extracellular signal-regulated kinase 1/2, ISQ: implant stability quotient, VEGF: vascular endothelial growth factor, TGF-β: transforming growth factor-beta)

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logically active adjuncts rather than complete substitutes for conventional space-maintaining barrier membranes. Overall, PRF may support GBR by enhancing soft-tissue healing, graft integration, and early regenerative activity, although further standardized clinical studies are needed to define its optimal indications and protocols.

2. Platelet-rich fibrin for alveolar ridge preservation (ARP)

Tooth extraction induces local inflammation, transient osteoclast activation, and loss of biomechanical loading, leading to post-extraction ridge resorption; ARP aims to reduce these dimensional changes[94]. Based on its anti-inflammatory and osteoclastogenesis-inhibitory effects, PRF has been used as a biologically active adjunct for socket preservation[69]. Clinically, aDTM combined with PRF reduced horizontal ridge loss compared with controls at 8 weeks[95], while L-PRF combined with a bone xenograft showed improved dimensional stability compared with L-PRF alone, with outcomes closer to those of bone xenograft alone[96]. PRF alone may also enhance socket bone density, new bone quality, soft-tissue healing, and postoperative comfort[97]. In multiple anterior maxillary extractions, L-PRF or A-PRF improved socket fill and trabecular mineralized tissue formation compared with spontaneous healing, although it did not completely prevent ridge resorption[97,98]. Overall, PRF appears to support early socket healing and bone maturation, but should be regarded as a regenerative adjunct rather than a complete substitute for volume-stable grafting materials in ARP.(Table 2)

3. Platelet-rich fibrin in maxillary sinus floor elevation

DBBM is a standard graft for posterior maxillary deficiency[99]. In canine lateral sinus lifts, DBBM plus PRF achieved higher osseointegration (≈43.5%) and new bone (≈41.8%) at 6 months than the tissue glue plus DBBM (≈30%-31%)[100]. Clinically, adding L-PRF to DBBM increased histologic new bone (≈44.6% vs. 30.0%) and enabled earlier implant placement[101]. Using PRF with bone substitute material and covering the buccal window with a PRF membrane yielded ≈10.1 mm vertical gain at 6 months and no implant loss over about 44 months follow-up[102]. Overall, bovine-derived substitutes combined with PRF constitute a predictable approach for posterior maxillary height augmentation. PRF promotes MSC proliferation/migration and osteogenic differentiation via ERK1/2, expediting bone regeneration and improving tissue quality[59]. As a sole filler in endoscope-assisted transcrestal elevation with simultaneous implant placement, PRF achieved a 95.65% 1-year implant survival, ≈6.72 mm mean lift, and progressive bone densification around implants[103]. Other ramdomized controlled trials report mean vertical gains ≈7.67 mm at 18 months[104] and higher implant stability quotient gains (better stability) than allograft/collagen membranes in split-mouth designs[105]. Use of PRF alone is best reserved for cases with sufficient residual height/density to secure primary stability.(Table 2)

In addition to its role as a graft adjunct, PRF has been clinically useful for managing accidental Schneiderian membrane perforations during sinus floor elevation. Membrane perforation is one of the most common intraoperative complications of sinus floor elevation from lateral approach and may compromise graft containment and sinus healing if not properly managed[106]. Owing to its cohesive fibrin architecture, autologous origin, and biologically active growth factor content, PRF membrane can be adapted over small-to-moderate tears as a resorbable sealing barrier. This approach may help stabilize the graft material, isolate the sinus cavity, and support soft-tissue repair and angiogenesis during early healing. Recent clinical reports and observational studies suggest that L-PRF or PRF-based approaches can simplify the management of Schneiderian membrane perforations and provide predictable healing outcomes[107,108], although further controlled trials are needed to define indications according to perforation size and location.

4. Platelet-rich fibrin for soft tissue healing

Evidence indicates that PRF enhances soft tissue healing in various clinical contexts. In periodontitis, adjunctive PRF with flap surgery improves probing depth and attachment gain compared to conventional therapy[109,110], with histological confirmation of new connective tissue and reduced inflammation[111]. In a randomized non-inferiority trial, L-PRF plus autologous bone was not inferior to enamel matrix derivative plus autologous bone at 12 months, improving clinical parameters related to the gingival soft tissue healing[112]. Overall, PRF-based strategies significantly improve clinical and radiographic outcomes in periodontal soft tissue regeneration. For gingival recession, apically repositioned flaps combined with PRF achieve higher root coverage and greater gingival thickness than flap alone[113]. In wound dehiscence, PRF membranes accelerate epithelial closure, reduce pain, and lower complication rates[114]. These effects are linked to sustained release of angiogenic and fibrogenic growth factors[115].

While short-term benefits are consistent, heterogeneity in protocols and limited long-term data remain concerns[116]. Overall, PRF supports soft tissue regeneration by enhancing angiogenesis, reducing inflammation, and increasing gingival stability.(Table 2)

5. Platelet-rich fibrin for osteoradionecrosis (ORN) and medication-related osteoradionecrosis of jaw (MRONJ)

The use of PRF as an adjunct in the management of ORN and MRONJ has gained increasing attention due to its regenerative and immunomodulatory properties.(Table 2) Several clinical studies suggest that adjunctive PRF or L-PRF during MRONJ surgery may improve mucosal healing, reduce postoperative pain, and support short-term clinical resolution, although the evidence remains limited by small sample sizes and heterogeneous protocols[117,118]. Although earlier pilot and observational studies suggested that PRF may improve mucosal healing after MRONJ surgery, a recent randomized controlled trial found no statistically significant additional benefit of L-PRF over surgery alone, despite numerically higher 6-month complete resolution rates (92% [11/12] vs. 83% [15/18])[117,119]. In ORN, PRF has also shown promising outcomes. Case series report that PRF used in combination with sequestrectomy facilitates faster mucosal coverage and reduces wound dehiscence[120-122]. Experimental studies suggest that PRF-derived growth factors, including VEGF and TGF-β, stimulate angiogenesis in irradiated tissues where

vascular compromise is a key factor[123]. Moreover, leukocytes present in PRF may modulate chronic inflammation, creating a favorable microenvironment for healing[74]. Systematic reviews support the potential adjunctive role of autologous platelet concentrates, including PRF/L-PRF, in MRONJ management; however, high-level evidence remains insufficient, and data for ORN are still largely limited to small observational studies[118,123,124].

6. Platelet-rich fibrin for temporomandibular disorders (TMD)

Intra-articular administration of injectable platelet-rich fibrin (i-PRF), particularly as an adjunct to arthrocentesis (Table 2), has been investigated for intracapsular TMD such as temporomandibular joint (TMJ) osteoarthritis and disc displacement. Randomized and prospective clinical studies suggest that i-PRF may reduce pain and improve mandibular function, including maximal mouth opening, when compared with arthrocentesis alone in selected patients[125,126]. In patients with disc displacement with reduction, arthrocentesis combined with i-PRF was reported to be a safe and effective approach, with improvements in pain and joint function[127]. Preliminary clinical evidence also suggests that i-PRF may reduce articular clicking in internal derangement cases[128]. When compared with hyaluronic acid and PRP, i-PRF appears to provide similar clinical improvement in pain reduction, although superiority over other injectables remains uncertain[129]. Overall, current reviews suggest that i-PRF may provide additional pain relief and functional improvement after TMJ lavage or arthrocentesis, but the evidence is still limited by small sample sizes, heterogeneous protocols, and the lack of long-term multicenter randomized trials[130,131].

VI. Future Directions for Modification and Application of Platelet-Rich Fibrin

Despite the substantial advances in PRF research and its expanding clinical use in oral and maxillofacial surgery, several biological and technical challenges remain unresolved. First, the preparation parameters of PRF—including centrifugal force, rotor angle, centrifugation radius, and tube composition—can significantly influence fibrin architecture, cellular composition, and growth factor release kinetics[27,132]. However, preparation methods remain highly heterogeneous across studies[133-135]. In particular, revolutions per minute (RPM) alone is insufficient to describe PRF protocols because the actual relative centrifugal force (RCF) depends on the rotor radius, rotor design, tube angulation, and the position at which RCF is calculated[55,136]. This lack of standardized reporting limits reproducibility and complicates direct comparison of clinical outcomes[27]. Therefore, future clinical trials should adopt standardized and easy-to-remember reporting frameworks that capture the key technical determinants of PRF preparation. In this context, the AR2T3 acronym proposed by Herrera-Vizcaino[136] provides a practical reporting framework for both vertical and H-PRF centrifugation protocols. Broader adoption of such standardized reporting systems would reduce inter-study variability, facilitate reproducibility and meta-analysis, and allow clinicians to translate PRF protocols more reliably across different centrifuges, devices, and clinical settings.

Second, the precise biological role of leukocytes and erythrocyte-derived components within PRF requires further clarification. Leukocytes may enhance wound healing and tissue regeneration through immunomodulatory effects and secondary growth factor stimulation. Conversely, excessive leukocyte-associated inflammatory cytokine release has been suggested to impair collagen type I synthesis and alkaline phosphatase activity in osteoblasts, potentially affecting bone regeneration negatively[137]. In addition, emerging *in vitro* evidence suggests that erythrocyte-derived components, including hemoglobin-rich red clot lysates, may not be merely contaminants but could modulate osteoclastogenesis and inflammatory responses; however, their controlled incorporation into PRF remains experimental and requires further validation before clinical translation[58,79].

Third, overcoming the rapid degradation and limited mechanical stiffness of conventional PRF membranes represents another key priority for future research. These limitations restrict the use of PRF as a stand-alone barrier membrane in GBR or as a volume-stable material in ARP. Recent approaches include thermal manipulation or heat-compression techniques designed to increase fibrin density and extend degradation time[138]. Albumin gel–PRF mixtures, such as Alb-PRF, combine heated serum albumin with liquid PRF to create a more stable autologous fibrin-albumin matrix with prolonged resorption and sustained biological activity[139,140]. In parallel, cross-linking strategies using biomaterials or chemical cross-linkers have been explored to reduce enzymatic degradation and modulate growth factors release kinetics[141]. However, because excessive cross-linking or thermal modification may alter cellular compatibility, growth factor bioactivity, and natural fibrin architecture, further *in vivo* and

clinical studies are required before these modified PRF formulations can be recommended as predictable substitutes for conventional barrier membranes.

Another important future direction involves the development of advanced drug-loading and biofunctionalization strategies. The timing and method of incorporating therapeutic agents into PRF are critical determinants of fibrin stability and biological activity. Pre-centrifugation drug loading may interfere with clot formation and fibrin polymerization, whereas post-centrifugation incorporation appears to better preserve fibrin architecture and the physiologic coagulation cascade[22]. Future biomaterial engineering approaches should therefore aim to optimize sustained drug release systems while maintaining the conformational stability and bioactivity of embedded growth factors and cytokines.

Overall, future translational research integrating PRF with stem cells, peripheral nerve regeneration, exosomes, biomimetic scaffolds, and three-dimensional biofabrication technologies may further expand its role from a simple autologous biomaterial toward a customizable immune-regulatory regenerative platform in oral and maxillofacial surgery.

ORCID

Dong Ho Cho, *https://orcid.org/0009-0006-1639-910*X
Yong Seung Kim, *https://orcid.org/0009-0002-0928-572*X
Jun Lee, *https://orcid.org/0009-0002-9139-6751*
Joo-Young Park, *https://orcid.org/0000-0002-0333-6349*

Authors' Contributions

D.H.C. participated in data collection, study design, and writing the manuscript. J.Y.P. designed the study, coordinated, and revised the manuscript. Y.S.K. and J.L. helped to revise the manuscript. All authors read and approved of the final manuscript.

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Conflict of Interest

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