https://doi.org/10.46389/rjd-2025-1665
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2025; volume 32, issue 4, pages 527–532

Review

Role of platelet-rich fibrin in wound healing

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Received: 22 August 2025 / Accepted: 12 November 2025

Abstract

Platelet-rich fibrin (PRF) is a fibrin matrix that can function as a resorbable membrane and trap platelet cytokines, growth factors, and cells. These particles may be discharged from the matrix within a predetermined time frame. Research has demonstrated the use of autologous platelet-rich fibrin in various fields, and it is considered a therapeutic biomaterial. The goal is to review and debate the various approaches to using platelet-rich fibrin as a healing aid in extraoral wound sites. A literature search of review articles, systematic reviews, and studies on platelet-rich fibrin was conducted using PubMed and Google Scholar search engines, focusing on the mesh terms wound healing, growth factors, and regeneration. Hemostasis, graft stabilization, wound sealing, bone regeneration, and wound healing can all be aided by PRF. The fibrin matrix can guide stem cell migration and the healing program more effectively due to its improved organization. Even though PRF is a member of a relatively novel class of platelet concentrates, its considerable cicatricial capacity can be explained by the fibrin molecule's biologic activity alone. It has recently been demonstrated that there is an excellent opportunity for the PRF to be used as a healing aid in various extraoral treatment contexts, based on encouraging results. Although there was much debate regarding the advantages of first-generation platelet concentrates, second-generation platelet concentrate (L-PRF) appeared to yield better and more consistent outcomes. L-PRF has several benefits, including being autologous, easy to collect, chair-side preparation, and straightforward clinical application, thereby avoiding the risks associated with allogeneic products. As such, it appears appropriate for application in both general and specialist practice.

Keywords: growth factors, platelet-rich fibrin, wound healing, regeneration

Introduction

In the realms of dentistry and other medicine, wound healing has been and continues to be a crucial subject. Wound healing has been shown to benefit from the use of biomaterials. They can be produced in the lab utilizing a range of chemical techniques, or they can be obtained from nature [1].

Numerous attempts have been undertaken to identify novel and targeted bioactive additions that enhance regeneration, control inflammation, and promote and expedite healing. Sports medicine and orthopaedics have investigated the potential benefits of platelet concentrates in achieving these objectives [2].

Platelet concentrates undoubtedly promote wound healing by facilitating the recruitment, growth, and maturation of cells involved in regeneration [3]. The first tissue adhesives, or fibrin glues, were platelet concentrates. Following that, various types of platelet concentrates were developed. Platelet concentrates are classified into four primary groups based on their leukocyte content and fibrin structure [4]. One of them is Leukocyte Platelet-Rich Fibrin.

PRF is a platelet and immunological concentration that gathers on a single fibrin membrane. It includes every component of a blood sample that is beneficial to immunity and healing [5]. This novel biomaterial resembles an autologous cicatrical matrix; it is neither

a platelet concentrate per se nor similar to fibrin glue. It is just blood that has been centrifuged; nothing more [6]. A fibrin matrix polymerized in a tetramolecular structure, together with circulating stem cells, leucocytes, platelets, and cytokines, makes up PRF [1].

Based on clinical tests, this biomaterial is a suitable matrix for establishing a cohesive healing process that does not involve excessive inflammation. When implemented in combination with bone grafts, PRF in the form of a platelet gel offers various benefits, including enhanced wound healing, bone development, maturation, wound sealing, and hemostasis, as well as improved handling qualities of graft materials [3]. It is also applicable as a membrane. To increase bone density, several clinical studies recommend using PRF in conjunction with bone grafts [7]. Because PRF processing does not need chemicals and the autologous blood's inherent ability to create fibrin is included, PRF is more biocompatible than PRP. When growth factor release rates are examined, PRF exhibits prolonged release owing in part to its composition, which inhibits early growth factor proteolysis, as well as its larger concentration of growth factors. In contrast, PRP exhibits quick and instantaneous growth factor activation [8].

General characteristics of L-PRF membranes

Platelets in L-PRF

A minimum of 90% of the platelets from the blood sample are still inside the fibrin clot following centrifugation. The lower part of the clot, where the clot and red blood cells meet, is where the platelets are mostly found [9].

Consequently, the face, or the bottom part of the clot, is thought to be the most physiologically active. There are various granules in the cytoplasm of platelets. At the moment of activation, the content becomes available. Numerous cytokines and active compounds, including osteonectin, von Willebrand factor, factor V, serotonin, and antimicrobial proteins, are present in these granules [10].

Platelets activate themselves when they come into contact with the collagen in the injured blood vessel. Hemostasis is initiated and maintained by platelet aggregation, which is dependent on this activation. Degranulation, followed by the successive production of different cytokines, is a step in the stimulation of platelets. They promote the proliferation and migration of cells into the fibrin matrix [11].

Although maintaining homeostasis is the primary function of platelets, they can also bind, aggregate, and internalize microbes to aid in the removal of pathogens from the bloodstream. To destroy protozoal infections and release a variety of strong antimicrobial peptides, platelets participate in antibody-dependent cell cytotoxicity activities [12].

Leukocytes in L-PRF

Dohan and associates analyzed the cellular content of L-PRF membranes and concluded that more than 50% of the leukocytes are concentrated in the fibrin matrix. A cell count performed at the shows that more than 75% of the leukocytes remain within the L-PRF membrane, whereas the concentration in the L-PRF exudate is very low. The latter, however, contains a high concentration of growth factors [13].

Leukocytes play a crucial role in maintaining platelet concentrations. Leukocytes can regulate cell division and multiplication, in addition to their potential antibacterial properties. They are also the first cells to initiate neoangiogenesis and are fundamental to the wound-healing process [3]. Vascular endothelial growth factors, which function as a powerful vascular growth factor, are actually present in them. The above-mentioned growth factors are also produced by the leukocytes [8].

As a sign of acute inflammation, neutrophils are drawn to the area of injury within minutes of impact. They go in the direction of the wounded area and become entangled in the fibrin web, creating a strong defense from infections and viruses. Their primary job is to produce growth factors as well as inflammatory cytokines [14].

The most common type of leukocyte, monocytes, can develop into macrophages and play a crucial role in the healing process. As phagocytes and antigen-presenting cells, they perform immunologic tasks [15].

Inflammatory conditions have been linked to macrophages. However, they are also vital to the healing of broken bones. There is growing awareness of the function of monocytes and macrophages in bone healing. During *in vitro* experiments, macrophages appear to control signals from osteogenic cells and encourage mineralization [16].

In the event of bone damage, mesenchymal stem cells are stimulated to undergo osteogenesis by monocytes and macrophages, which also release growth factors like PDGF-BB and bone morphogenetic protein 2 (BMP-2). Collagenase, which is secreted by macrophages,

https://doi.org/10.46389/rjd-2025-1665

aids in wound cleansing [9]. Furthermore, they provide growth factors such as platelet-derived growth factor, which is crucial for angiogenesis, and tumour growth factor, which activates keratinocytes [14].

These substances also affect blood vessel endothelial cells, promoting the adhesion and migration of neutrophils and lymphocytes out of blood vessels. Leukocytes included in blood derivatives, such as L-PRF, may be advantageous even if they emit free radicals known as activated oxygen species during phagocytosis activity and the ischemia-reperfusion process [15].

Growth factors in L-PRF

The ejection of growth factors is an essential function of platelets. By drawing and activating macrophages, fibroblasts, and endothelial cells, the alpha-granules in platelets contain PDGF, insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), vascular endothelial growth factor, as well as tumor growth factor, which initiates the healing process of wounds [16].

L-PRF membranes constantly produce a significant amount of growth factors for seven days. The platelets generate a considerable quantity of them. PRP gel also contains these growth factors [17].

However, due to the chemical activation of the platelet composition, they are released only during the initial hours and disintegrate entirely in the solution within three days. The variations in fibrin architecture between the PRF families account for this discrepancy. While PRP gel families undergo artificially induced polymerization with extrinsic growth factor involvement, resulting in their instant release and usage or destruction, PRF exhibits natural polymerization with intrinsic growth factor integration [18].

Fibrin in L-PRF

An essential component of platelet aggregation during hemostasis and wound healing is the insoluble clotting protein fibrin. Thrombin transforms fibrinogen, the precursor of fibrin, into fibrin, which attaches to platelets to create long, nonsoluble strands [19].

When thrombin is found in physiological concentrations, it facilitates the slow and physiological development of a fibrin matrix. According to [20], fibrin wires tend to become polymerized and develop a biochemical structure with trimolecular or equilateral connections. This results in a thin and flexible fibrin network that promotes the trapping of cytokines and cell motility.

As a matrix, this three-dimensional network plays a crucial role in promoting the growth of various types of inflammatory, endothelial, and other cells. Moreover, this matrix has the capacity to absorb glycosaminoglycans, which come from blood platelets. According to [20], these glycosaminoglycans have an excellent affinity for flowing peptides (such as cytokines) and a significant capacity to stimulate cell migration along with healing processes.

Stem cells in L-PRF

Dohan and associates demonstrated that exposure to L-PRF significantly stimulated human bone mesenchymal stem cells. Throughout the first few weeks of the experiment under normal settings and the entire duration under differentiated conditions, this impact was dose-dependent [21]. Up until the 14th and 28th day, accordingly, the cultures lacking L-PRF in differentiation circumstances did not differentiate to a higher degree than the colonies with L-PRF in regular circumstances [21].

The scanning electron microscopy (SEM) culture analysis at day 14 revealed that the groups with L-PRF had more numerous and more structured mineralization nodules compared to the control groups [21].

Extraoral applications of L-PRF

L-PRF is utilized in several countries for the management of non-healing skin ulcers, including venous leg ulcers (VLUs), pressure ulcers (PUs), diabetic foot ulcers (DFUs), and acute surgical wounds [8].

Individuals' standard of living is significantly impacted by these wounds, particularly if they are resistant to healing despite receiving proper care [9].

They are a major source of morbidity and are linked to expensive treatment expenses. Debridement of necrotic tissues, revascularization surgery, infection control, hyperbaric therapy, mechanical unloading, blood glucose management, foot care education, mechanical compression, or limb elevation are some of the common treatments for persistent ulcers [10].

For some individuals, complete wound closure following routine therapy for venous leg ulcers may take months or even years. Wound closure fails in up to half of these patients. Comparable wound closure rates (24.2% and 30.9% at 12 and 20 weeks, respectively) have been observed for diabetic foot ulcers [11]. There is insufficient data to recommend any specific wound washing method or treatment for pressure ulcers.

Moreover, wound closure is still quite challenging. Advanced wound care is advised if such treatment is unsuccessful [14].

Over the past decade, a wide range of cutting-edge treatments have been proposed. Their effectiveness, relative effectiveness, and potential drawbacks, however, are not fully proven. The majority of these cutting-edge treatments are expensive, and it is not always clear that they are superior to the best wound care practices [16].

In a continuing clinical study, the administration of L-PRF was able to treat at least 10 of the 15 major wounds, resulting in 100% wound closure for venous leg ulcers measuring 10 cm^2. Again, L-PRF appears to be more effective for deep foot ulcers, closing wounds 100% in cases where conventional wound treatment was ineffective [22].

The continuous diffusion of growth factors and the substantial amount of platelets and leukocytes in L-PRF membranes account for their favourable effects in the wound repair of chronic leg ulcers [23]. In particular, it appears critical that pro-inflammatory cytokines (interleukin-1 (IL-1), IL-6, tumor necrosis factor-(TNF-), and an anti-inflammatory cytokine (IL-4) be released gradually over a period of up to seven days, along with matrix glycoproteins (trombospondin-1, fibronectin, and vitronectin) [18]. This may also clarify why, when administered as a surgical adjunct, L-PRF may serve as an immune regulation node with inflammatory capabilities, thereby reducing postoperative infections [16].

Platelet-rich fibrin for intraoral wound

Choukroun *et al*. initially created PRF in France with a focus on oral and maxillofacial surgery. PRF is a naturally occurring biomaterial based on fibrin that promotes the growth of microvascularization and can direct the migration of epithelial cells to its surface. It is clear that there is interest in such a membrane, mostly to shield exposed wounds and hasten healing [14]. The use of this matrix is highly sought after in situations involving infected wounds, as it contains leukocytes and facilitates their movement. By modifying a cluster of differentiation receptors, including CD11/CD18 receptors, among others, fibrin and its degradation products contribute to the body's natural defense against infection. In light of this, PRF is frequently utilized with good outcomes in a variety of surgical procedures, such as the excision of large periapical lesions following enucleation, the surgical extraction of impacted canines as well as third molars, preprosthetic surgeries, graft stabilization in a variety of operations, implant placement in borderline cases etc. In contrast to the time required for physiologic healing, cavities containing PRF demonstrated full recovery in half the time [24].

Role of platelet-rich fibrin in adolescent wound healing

By initiating hemostasis to halt bleeding, releasing growth factors and chemokines to coordinate inflammation and tissue repair during the proliferation phase, and facilitating wound contraction and remodeling to restore skin continuity, platelets play a critical, multi-stage role in the healing of adolescent wounds. Due to their enhanced regenerative ability and more active cellular turnover, adolescents typically heal wounds faster and more effectively than adults [18]. Even if the biological processes are the same, adolescents have several benefits that help them heal more quickly and effectively, leaving fewer scars. Increased cell turnover: A younger body naturally produces new tissues and cells more quickly. Enhanced collagen synthesis: Collagen is a crucial structural protein for wound healing, and adolescents make more of it. Reduced comorbidities: They typically have fewer underlying medical disorders, such as diabetes or vascular disease, which can impede or make healing more difficult for adults. Reduced comorbidities: They typically have fewer underlying medical disorders, such as diabetes or vascular disease, which can impede or complicate healing for adults [20].

Although their role is comparable to that of other age groups, further research is needed to fully understand any potential age-specific variations in adolescent wound healing and platelet activity [20].

Discussion

PRF is a newer type of platelet concentrate that was initially employed in France by Choukroun *et al*. It is superior to PRP due to its streamlined processing method, which eliminates the need for biological blood treatment. PRF can help with hemostasis, graft stabilization, wound sealing, bone development, and wound healing. The improved organization of the fibrin matrix allows it to more effectively control stem cell movement and the healing process [17]. A plan to maximize the clinical use of PRF has now been presented based on the *in vitro* release of growth factors from

https://doi.org/10.46389/rjd-2025-1665

PRF and the outcomes of *in vivo* investigations. Studies conducted *in vitro* have demonstrated that PRF outperforms PRP. Wiltfang *et al.*'s analysis of several clinical studies produced positive outcomes. Dohan *et al.* found that PRF had superior healing qualities compared to PRP and exhibited a delayed release of growth factors, suggesting that PRF may also serve as a matrix that supports bone morphogenetic protein [12]. The ability of the cells to spread from the fibrin scaffold was noted in a work by Wu AC *et al.*, which showed that PRF may also function as a supporting matrix for bone morphogenetic protein [25].

Conclusions

Although there was much debate regarding the advantages of first-generation platelet concentrates, second-generation platelet concentrate (L-PRF) appeared to yield more reliable and consistent outcomes. L-PRF has several benefits, including being autologous, easy to collect, chairside preparation, and straightforward clinical application, all without the risks associated with allogeneic products. As such, it appears appropriate for application in both general and specialist practice. Due to its unique texture, L-PRF can be utilized in therapeutic settings in both its membranous (obtained after moderate compression) and amorphous (clot) forms. Similar to a tissue graft, the membranes can be utilized to cover and shield wounds. The biologic qualities of L-PRF unmistakably demonstrate intriguing surgical adaptability, along with all the attributes necessary to promote faster tissue regeneration and superior clinical results. In addition to promoting angiogenesis, L-PRF can also promote osteogenesis by acting as a scaffold for cellular motility. These are unquestionably the essential elements of the bone healing process. The conclusion that L-PRF can be employed for extraoral wound healing is supported by all of these characteristics.

Conflict of interest

The authors declare no conflict of interest.

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