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Original Article

Platelet concentrates in diabetic foot ulcers: A comparative review of PRP, PRF, and CGF with case insights

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ABSTRACT

Diabetic foot ulcers (DFUs) are severe complications of diabetes, often leading to chronic wounds, amputations, and increased mortality risk. Platelet concentrates (PCs)—natural biomaterials utilized in regenerative medicine—have garnered attention for their capacity to enhance tissue repair and wound healing. This study reviews the preparation methods, biological mechanisms, and clinical efficacy of three generations of PCs: platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factors (CGF). Comparative analysis reveals that PRP, the first generation, provides abundant growth factors but relies on anticoagulants, which may hinder fibrin formation and tissue adhesion. PRF, as the second generation, eliminates anticoagulants, forming a fibrin matrix that sustains growth factor release and enhances cell migration. CGF, the latest advancement, employs refined centrifugation to achieve higher growth factor concentrations and a denser fibrin matrix, accelerating tissue regeneration. Case series results demonstrated superior wound healing outcomes with CGF, including faster epithelialization and reduced healing time compared to PRP and PRF. These findings underscore CGF's potential as the most effective PC for managing DFUs, supporting its broader clinical adoption in advanced wound care.

1. Introduction

With advances in medical and industrial technologies, the development of regenerative medicine has accelerated. The field, which integrates engineering, life sciences, and medicine, aims to repair or replace damaged tissues [1], promote organ regeneration, restore physiological functions, and sustainably heal chronic injuries [2]. These developments bring both new hopes and challenges to medical progress. Among the serious complications of diabetes mellitus, diabetic foot ulcers (DFUs) are particularly concerning, as they are the leading cause of nontraumatic lower limb amputation [3]. Research indicates that the 5-year mortality rate

Abbreviations: A-PRF, Advanced Platelet-Rich Fibrin; CGF, Concentrated Growth Factors; DFUs, Diabetic-related foot ulcers; L-PRF, Leukocyte- and Platelet-Rich Fibrin; PCs, Platelet concentrates; PRP, Platelet-Rich Plasma; PRF, Platelet-Rich Fibrin; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor.

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for individuals with DFUs is approximately 30 %, and this rate exceeds 70 % for those requiring major amputations [4]. In addition, DFUs have a high recurrence rate, with approximately 30 % of patients recurring within one year and 70%–80 % within five years [5,6].

The standard of care for DFUs emphasizes early diagnosis, ulcer debridement, infection control, blood sugar management, and decompression therapy. Although these conventional treatments are widely available, the existing standard of care may not achieve the desired outcome in chronic, hard-to-heal DFU cases. Therefore, PC therapy has received increasing attention as a potential alternative therapy in recent years. The 2023 updated guidelines from the International Working Group on Diabetic Foot Disease (IWGDF) recommended platelets and their derivatives as adjunctive therapies to promote the healing of DFUs [7]. Exploring PCs as a supplement or alternative to traditional DFU therapy, especially in cases where conventional therapies have limited effectiveness, may offer improved treatment prospects for patients.

Platelet concentrates (PCs), a key natural biomaterial in regenerative medicine, have been widely used in wound healing and tissue regeneration. Based on their leukocyte, fibrin, and growth factor content, PCs are mainly classified into platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factors (CGF) [8].

PRP, the first-generation PC, is a platelet-rich substance that, when activated [9], rapidly releases various growth factors and cytokines to promote wound healing [10]. However, due to immune rejection associated with the anticoagulant used in PRP and its poor slow-release property, PRF, a second-generation platelet concentrate, was developed. PRF is an autologous leukocyte and platelet-rich fiber biomaterial without anticoagulants [11]. To further enhance the slow-release effect, CGF, the third-generation platelet concentrate, was developed. CGF is created using variable-speed centrifugation [12] with a scaffolding network structure which results in a more concentrated and long-lasting release of growth factors [13].

Therefore, this study discusses the roles of the three generations of PCs in the healing of DFUs, highlights the differences in their preparation techniques, and evaluates their therapeutic efficacy and future potential in diabetic wound management.

2. Preparation of PRP, PRF, and CGF

Currently, the preparation of PRP lacks standardization. Secondary centrifugation is commonly employed in clinical practice [14]. The procedure involves drawing whole blood into sterile test tubes containing anticoagulants, followed by the first centrifugation to separate the blood components. A second centrifugation is then performed to concentrate the platelets further. This process results in two layers: the upper layer contains platelet-poor plasma (PPP), while the lower layer is PRP [15]. In contrast, PRF has a simpler preparation technique and does not require the addition of anticoagulants or activators. Whole blood is drawn and subjected to a single centrifugation, which separates the blood into three layers: the upper layer consists of PPP, the middle layer is PRF, and the bottom layer contains erythrocytes. CGF is prepared using a modified centrifugation technique without anticoagulants. The process involves varying centrifugation speeds and durations to optimize growth factor concentration [16]. Whole blood is processed using a CGF variable speed centrifuge, which causes platelets to collide and fragment under different centrifugal forces, dividing the blood into three layers. The middle layer, containing CGF, also includes some uncleaved platelets. Here, we provide specific preparations for PRP and CGF in subsequent case reports. PRP: Blood is collected in a sterile tube containing anticoagulant solution and first centrifuged at 5600 rpm to form three layers. The upper layer is transferred to a new sterile tube. The lower layer is then centrifuged at 2500–3000 rpm and the PRP is obtained. CGF: Blood is collected in sterile tubes without anticoagulant solution and the blood sample is centrifuged at alternating speeds: 2 min at 2700 rpm; 4 min at 2400 rpm; 4 min at 2700 rpm; and 3 min at 3000 rpm. After this process, the sample is separated into three layers: the middle layer is the CGF. For the preparation of PRF, see: centrifugation at 3000 rpm for 8 min [17], at the end of the process, three different layers are obtained: the middle layer is PRF (Fig. 1).

3. PRP in diabetic wound management

Extensive research has supported the use of PRP in the management of DFU. Studies indicated that PRP treatment significantly reduced the size of the wound[18–21], accelerated healing [22,23], and alleviated pain [24]. The PRP injection group achieved a 95 % complete wound healing rate, which was significantly higher than that of the conventional treatment group [25]. Healing time and pain improvement were notably superior in the PRP-treated group compared to the control group [24] and were particularly effective in specific patient populations, such as women and individuals over 55 years of age [26]. Additionally, PRP combined with other therapies, such as negative pressure wound therapy [27,28] and herbal treatment [29], has been shown to enhance wound healing outcomes significantly.

The author's team compared both allogeneic and autologous PRP and found that both treatments significantly shortened wound healing time without adverse effects. This suggested that allogeneic PRP could be used as a viable alternative when autologous PRP was unavailable [30]. A study of 90 patients with DFUs indicated that PRP was effective in promoting DFU healing, regardless of patient factors such as age, gender, smoking status, or blood pressure. However, it did not significantly affect the rate of amputation or amputation site [31]. In contrast, a different view was held by a clinical study involving 182 patients with DFUs, which suggested that PRP effectively promoted wound healing and, for the first time, identified potential factors for failure of PRP therapy, including severe obesity (BMI$\geq$30 kg/m^2), smoking, diabetes mellitus duration of 20 years or more, and renal insufficiency (GFR <60 mL/min/1.73 m^2) [32]. Despite these challenges, PRP can still serve as an effective adjunctive therapy in patients with DFUs complicated by peripheral arterial disease [33]. Our previous clinical observational studies suggested that PRP when used in combination with treatments for DFUs complicated by necrotizing fasciitis, gas gangrene, and osteomyelitis, contributed to ulcer healing and successful limb preservation [28,34].

The following is a clinical case from our center, illustrating the use of PRP in the treatment of DFU complicated by osteomyelitis.

The patient is a 68-year-old female with a history of type 2 diabetes for 8 years, intermittently taking oral hypoglycemic agents, with poor glycemic control. She also has a 3-year history of hypertension and has not been regularly using antihypertensive medications. The ulcer developed without a clear cause over the past two months, presenting as an ulcer on the fifth toe and heel of the left foot, with erythema, edema, necrotic skin turning black, and associated pain (Fig. 2a). Upon admission, osteomyelitis was diagnosed. The patient received anti-infective, wound debridement, and negative pressure wound therapy, followed by PRP therapy, resulting in successful wound healing (Fig. 2b).

Although PRP has demonstrated significant results in trauma management, its application presents several limitations. First, PRP exhibits limited efficacy at the wound site, which may be due to the short half-life of the growth factors it contains [35]. Second, the addition of anticoagulants and heterologous thrombin to PRP leads

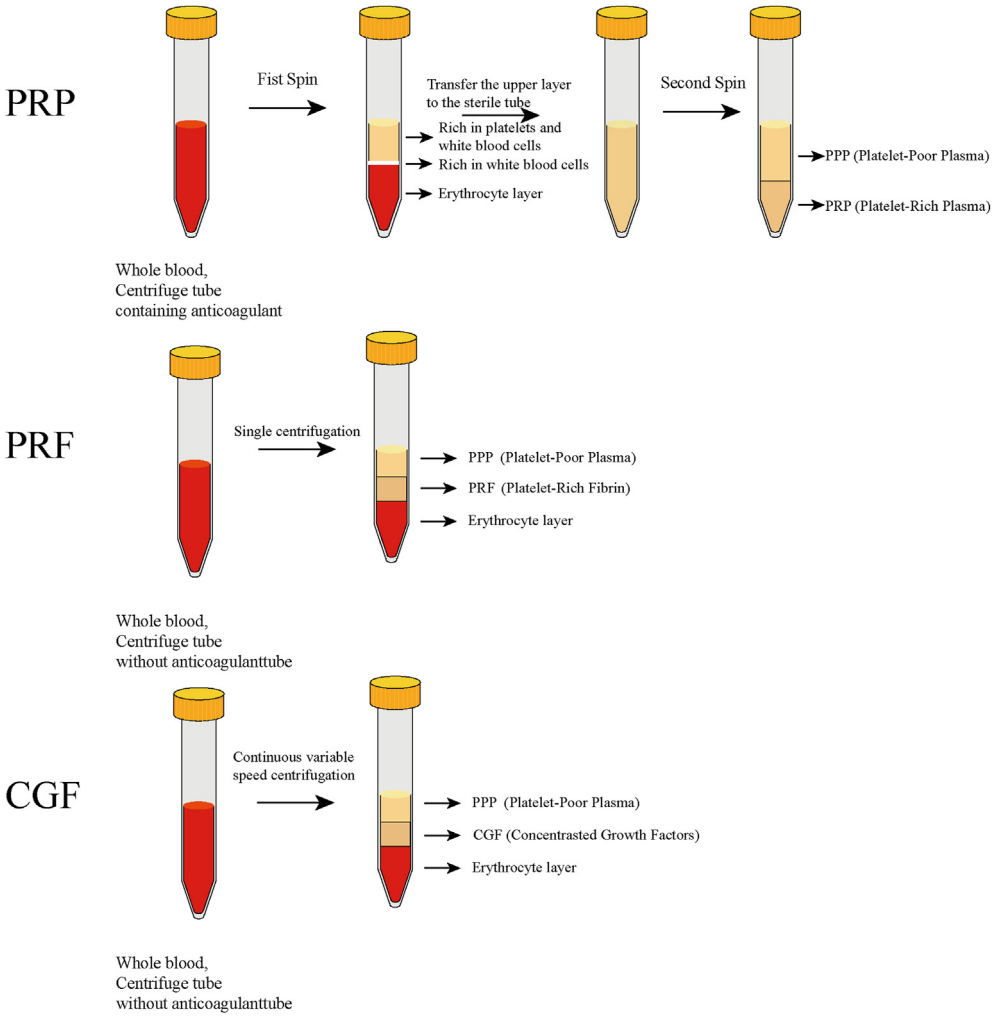

Fig. 1. PRP, PRF, and CGF preparation process.

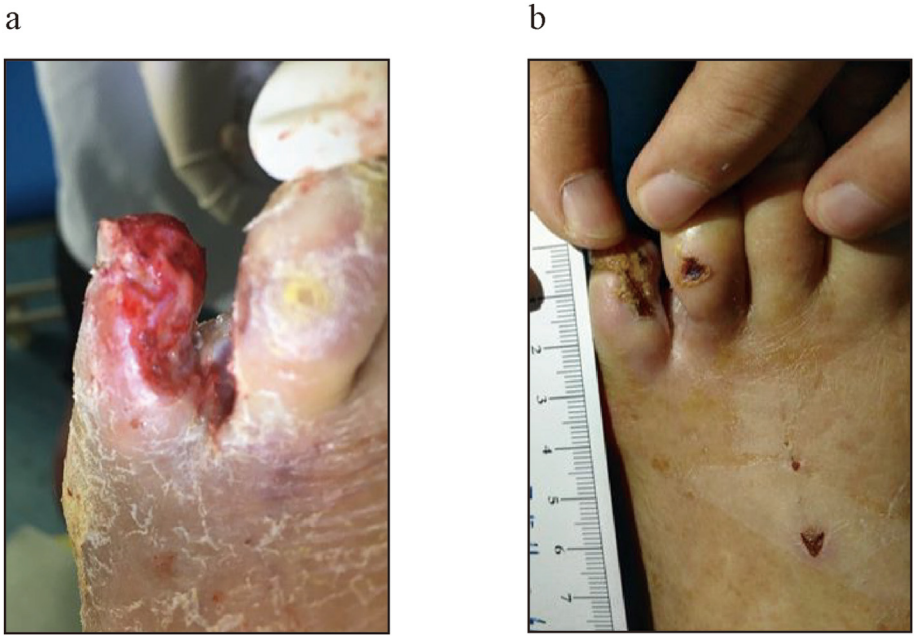

Fig. 2. PRP treatment for DFU patient with osteomyelitis. a) Ulceration, redness, and swelling with pain in the fifth toe of the left foot. b) after PRP treatment, the wound healed well.

to the instantaneous activation of platelets and the immediate release of high concentrations of cytokines; however, the subsequent release of cytokines is lower and of shorter duration, which does not sustain long-term therapeutic effects. In addition, the use of anticoagulants and heterologous thrombin may increase the risk of immune rejection [36,37] and contribute to the polymerization of fibrinogen, resulting in a structurally rigid and inelastic fibrin network that is not conducive to cytokine storage or cellular activity [38].

In response to these limitations, researchers have developed PRF, a second-generation platelet concentrate, to improve efficacy and address the shortcomings of PRP.

4. PRF in diabetic wound management

In 2001, Choukroun introduced the concept of PRF [8]. Unlike PRP, PRF is prepared without any additives, such as anticoagulants, and requires only a single centrifugation step. It is considered a second-generation platelet concentrate due to its ease of preparation and safety.

The application of PRF in trauma management, particularly in DFUs, has garnered widespread attention. Studies have shown that Leukocyte- and Platelet-Rich Fibrin (L-PRF) significantly enhances DFU healing [39,40]. Patients treated with L-PRF exhibited higher overall healing rates compared to control groups. A retrospective study demonstrated that patients with DFUs treated with L-PRP were able to undergo skin grafting earlier and had a significantly lower incidence of skin necrosis, postoperative infection, ulcer recurrence, and amputation, indicating the positive impact of L-PRF in the treatment of critically ill DFU patients [41]. In addition, advanced platelet-rich fibrin (A-PRF), which was rich in leukocytes and platelets, has shown comparable healing-promoting potential in DFU patients with osteomyelitis [42]. L-PRF has also been shown to be highly effective in treating difficult-to-heal wounds, such as refractory venous ulcers, pressure ulcers, and complex wounds [43].

In combination therapy, PRF combined with oral vitamins E and C have been shown to significantly enhance wound healing, reduce oxidative stress, and lower erythrocyte sedimentation rates and high-sensitivity C-reactive protein levels in patients with DFUs [44]. Furthermore, the application of PRF alongside hyaluronic acid application has been shown to promote angiogenesis and reduce the inflammatory response, thereby accelerating wound healing [45]. Due to the shortcomings of PRF in terms of insufficient concentration of growth factors and short duration of maintenance of bioactivity, CGF was developed to provide higher concentrations and a sustained release of growth factors for enhanced tissue repair.

5. CGF in diabetic wound management

In 2006, Sacco introduced the concept of concentrated growth factor (CGF) based on PRF [46]. CGF is prepared through uninterrupted, variable-speed centrifugation without the use of additives. Compared with PRF, CGF exhibits higher tensile strength, increased growth factor content, and greater viscosity and adhesion [47,48], making it recognized as a third-generation platelet concentrate. Depending on the clinical requirements, CGF can be formulated into gel CGF, liquid CGF, or loose gel CGF [49].

While CGF is primarily employed in the field of oral and maxillofacial surgery, clinical studies have demonstrated its efficacy in the management of DFUs. A study involving 18 patients with chronic ulcers, including 6 patients with DFUs, showed significant effects of CGF treatment [50]. Furthermore, a randomized controlled trial involving 100 patients with chronic mixed leg ulcers randomized participants into two groups: Group A, which received standard treatment plus CGF dressings, and Group B, which received standard treatment alone. After 12 weeks of treatment, the results showed that the healing rate was 100 % in Group A compared to 68 % in Group B, with Group A showing significant improvement in pain relief, suggesting that CGF accelerated leg ulcer healing and provided substantial pain reduction [51]. These findings suggested that CGF can accelerate the healing of leg ulcers and offer substantial pain relief. In addition, a clinical case report described a 37-year-old male patient with a 2.0 cm $\times$ 3.5 cm co-infected chronic ulcerative wound on the deep fascial layer of his right calf, which healed successfully following three sessions of CGF treatment alongside anti-infection measures and debridement [52].

Preliminary clinical observation from our team indicates that CGF is effective in treating patients with DFU complicated by osteomyelitis, resulting in a high rate of limb preservation. The following classic case of DFU treated with CGF at our center highlights the remarkable efficacy of CGF in clinical practice.

The patient is an 80-year-old female with a 30-year history of type 2 diabetes, controlled with oral hypoglycemic agents and well-managed blood glucose levels. She has a past medical history of coronary artery disease and lumbar disc herniation. Two years ago, she discontinued aspirin therapy on her own after initial treatment. Currently, she experiences occasional palpitations. Two months ago, the patient was wearing shoes improperly, resulting in a rupture on the right plantar foot about the size of a soybean, due to sensory numbness did not find the wound in time, and the right foot forefoot gradually appeared to be black and purple skin. One month ago, the patient underwent debridement exploration of the right foot and necrotic tissue enucleation followed by prolonged nonhealing of the foot wound with oozing and pus flow (Fig. 3a). After the patient was transferred to our hospital, she underwent ultrasonic debridement and wound-sealing negative pressure suction with CGF (Fig. 3b), and the wound healed well and was successfully preserved (Fig. 3c).

A synthesis of literature and clinical case reports indicates that CGF therapy is effective in promoting wound healing in DFUs. When combined with anti-infective therapy, strict glycemic control, and comprehensive wound management, CGF significantly enhances wound healing and improves limb preservation rate in DFU patients. This approach represents a novel and effective therapeutic option for the management of DFUs.

Further studies have demonstrated that CGF has shown significant efficacy in treating bone defects [53], arthritis [54], and nerve damage repair [16], and could promote tissue regeneration [55]. Compared to PRP and PRF, CGF not only contains higher concentrations of growth factors but also has a prolonged slow-release profile, which theoretically provides greater benefits for tissue repair and regeneration. Therefore, CGF exhibits superior clinical and biotechnological potential, positioning it for broader application in wound repair therapies. Despite the many advantages of CGF, its extraction process remains complex and costly, requiring specialized equipment, techniques, and individualized processing. Variations in procedural methods and technical expertise may affect the quality and concentration of CGF, which in turn could impact treatment outcomes. Additionally, the high costs associated with the equipment, consumables, and skilled personnel required for CGF extraction and application may place a financial burden on patients, especially in resource-limited settings. Therefore, to enhance the clinical value and broader applicability of CGF, it is essential to standardize operational procedures and strengthen clinical validation.

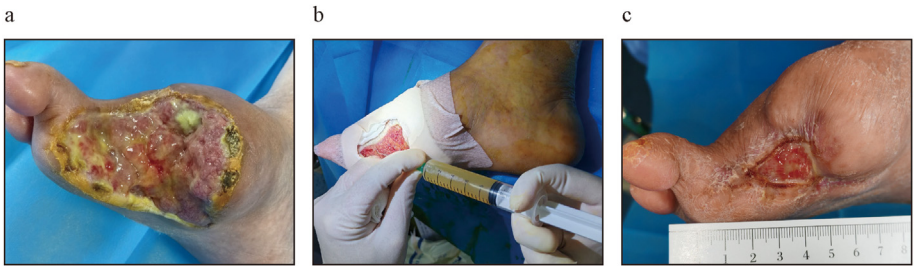

Fig. 3. CGF treatment for elderly DFU patient with severe infection. a) Long-term non-healing of the foot wound after enucleation of necrotic tissue, accompanied by oozing and pus flow. b) treatment with CGF. c) the wound healed well and the limb was successfully preserved.

Table 1
Differences in mechanisms between PRP, PRF, and CGF.

Functionality	PRP	PRF	CGF
Proliferative	Releases a variety of growth factors, the major ones including VEGF, fibroblast growth factor(FGF), TGF-β, platelet-derived growth factor(PDGF), epidermal growth factor(EGF), epidermal growth factor (EGF) and insulin-like growth factor (IGF), among others [59,66]. Stimulates the proliferation and migration of fibroblasts [67], decreases Bax gene expression, and reduces apoptosis in fibroblast [68]	Release of various growth factors, such as VEGF, EGF, TGF -β, PDGF, FGF, and insulin-like growth factor(IL-GF), promotes wound healing [69,70]and PRF releases more TGF-β than PRP [71]	Release of various growth factors, such as PDGF, TGF-β, IGF, VEGF, EGF, and FGF, etc., and CGF has a higher concentration of TGF-β1 and PDGF-BB [47] synergistically promoting tissue regeneration and repair than PRP
Anticancer	Aggregating macrophages, decreasing Interleukin-6(IL-6), increasing Interleukin-10(IL-10), decreasing pro-inflammatory factor expression, and increasing anti-inflammatory factor levels through the microRNA-21/programmed cell death factor 4 (PDCD4)/nuclear factor-κB(NF-κB) signaling pathway [72,73]	High concentrations of leukocytes release Interleukin-1β(IL-1β), IL-6, TNF-α, and healing factors (e.g., Interleukin-4(IL-4), VEGF) to fight infection and modulate inflammation	Three-dimensional mesh fibrin is rich in a large number of white blood cells, effectively preventing infection and regulating inflammation
Antibacterial	Contains high concentrations of platelets, leukocytes, and a variety of antimicrobial peptides [74–76], inhibits biofilm production [77], enhances antibiotic effects, and possesses strong antimicrobial properties against bacteria such as Methicillin-resistant Staphylococcus aureus (MRSA) and Methicillin-sensitive Staphylococcus aureus (MSSA) [78,79]	Contains a high concentration of leukocytes with antimicrobial properties	Contains a high concentration of leukocytes, continuous release of growth factors, inhibits bacterial reproduction, and enhances the antimicrobial effect
Slow-release		With a fibronectin backbone that retains growth factors, sustained release is achieved [11]. IGF-1 and PDGF-AB are released in PRP up to the first day, whereas in PRF sustained release occurs in the first three days [71]	Releases growth factors for 8–10 days and provides an excellent biological scaffold to promote tissue regeneration and wound healing [54,80]
Clinical findings	PRP is applied to diabetic wounds, providing some acceleration in healing, but the cure rate and healing time are relatively longer.	PRF has good results in diabetic wound treatment promotes healing and accelerates wound closure better than PRP.	CGF has more prominent efficacy and a higher healing rate with the shortest healing time, which is suitable for the treatment of long-term chronic diabetic wounds. Additionally, CGF has also shown potential positive effects in the treatment of osteomyelitis.

6. Differences in mechanisms between PRP, PRF, and CGF

The growth factors contained in PRP are the primary components responsible for promoting wound repair, and the leukocytes, fibronectin, inhibitory peptides, and immunoglobulins in it also play a supportive role in wound healing [56–58]. These elements participate in multiple stages of wound healing, including hemostasis, coagulation, inflammation mediation, neovascularization, and tissue remodeling [59]. PRP facilitates wound healing through four mechanisms: promoting hemostasis and coagulation, modulating the local inflammatory response, stimulating neovascularization, and enhancing tissue remodeling.

During the centrifugation process, both PRF and CGF form gels, with the centrifugal force stretching and aligning fibrin, thereby entrapping a higher number of platelets and leukocytes within their three-dimensional fibrin structures. The loose, mesh-like three-dimensional structure of PRF enables the efficient storage and sustained activity of cells and growth factors. Through the regulation of inflammatory cells, PRF exerts a potent anti-infective effect. Activated platelets in PRF secrete significant quantities of growth factors that facilitate tissue repair, making PRF valuable for the treatment of chronic hard-to-heal wounds [60].

CGF contains essentially the same types of growth factors as PRF. However, CGF is more elastic and easy to shape, with its three-

dimensional mesh structure consisting of a dense network of interwoven fibrous proteins. The structure of the CGF fibrin network is relatively loose, and a large number of platelets and platelet clusters are located in the upper part of it. With the slow degradation of the fibrin network, the platelet clusters gradually break down, so that a large number of growth factors are slowly released, prolonging the time of action of the growth factors [61]. Studies have shown that the three-dimensional reticulofibrillar proteins in CGF are enriched with a large number of leukocytes [10], which play a critical role in preventing infection and modulating the inflammatory response. Additionally, the presence of transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and a large number of $CD34^+$ cells in CGF contributes to vascular maintenance [62], neovascularization [63], vascular regeneration [64], and immunomodulation.

Compared with the constant-speed centrifugation protocol used for PRF, the uninterrupted variable-speed centrifugation method for CGF better facilitates the stretching of fibronectin and the formation of a three-dimensional fibronectin network structure. This centrifugation process improves the tensile strength and stability of fibrin. The three-dimensional network not only facilitates the proliferation and migration of endothelial cells and fibroblasts but also serves as a storage matrix and scaffold for various cells and growth factors and consequently, CGF exhibits stronger tissue regeneration capabilities and holds broader potential for reparative applications [65] (Table 1).

7. Conclusion and prospects

In the treatment of DFUs, PCs are natural biomaterials of interest due to their slow-release growth factor properties. PRP, PRF, and CGF are the three main types of PCs, each with distinct advantages and disadvantages, while CGF shows particular potential.

PRP separates platelets from the blood by centrifugation and prepares a highly concentrated platelet suspension, enriched with a variety of growth factors, which helps promote cell proliferation, angiogenesis, and tissue repair. Research has demonstrated that PRP significantly accelerates DFU healing and reduces the risk of infection. However, PRP presents some limitations. First, the preparation of PRP often necessitates the use of additives, such as thrombin, which can trigger immune rejection and increase the risk of cross-infection. Second, the preparation of PRP is relatively complex, typically requiring two centrifugation steps. In addition, the fibrin mesh structure in PRP is less developed than that of PRF or CGF, leading to a shorter duration of growth factor release.

PRF, on the other hand, is obtained via low-speed centrifugation without the use of anticoagulants and is capable of slowly releasing growth factors, promoting wound healing over a longer period of time. The preparation of PRF is simple and safe. However, the healing efficacy of PRF may be inferior to PRP due to its lower concentration of growth factors, and clinical studies investigating PRF remain limited.

In comparison, CGF shows unique advantages in DFU treatment. CGF is extracted by continuous variable-speed centrifugation, which further concentrates its platelet and growth factor content, giving it an advantageous performance in promoting tissue repair and regeneration. CGF not only contains a higher concentration of growth factors but also exhibits slow-release properties comparable to PRF, allowing it to deliver pro-healing factors over an extended period, thereby accelerating the healing of chronic DFU ulcers. Furthermore, the preparation process of CGF is simpler and does not require the addition of anticoagulants, which reduces the complexity and potential risks involved in the preparation process.

Despite its potential, the application of CGF in the treatment of DFU still faces some challenges. At present, most of the clinical studies of CGF are small-scale studies, and there is a lack of large-scale, multicenter validation, which limits its widespread clinical application. Meanwhile, individual variability in CGF preparation can result in inconsistencies in composition and concentration between batches, necessitating the development of standardized procedures and quality control measures. In addition, the long-term efficacy of CGF and its role in preventing recurrence remain unclear, warranting further long-term follow-up studies to evaluate its durability and stability.

In summary, CGF, as a novel material of natural slow-release high-concentration growth factors, shows a promising application in DFU treatment. Conducting large-scale, multi-center clinical trials is crucial for establishing a robust evidence base. As more data accumulate, it may become possible to better refine the clinical indications, preparation protocols, and dosage regimens for CGF, thereby providing more personalized treatment plans for individual patients. Moreover, studies with longer follow-up periods will be essential for assessing the durability of CGF treatment and its role in reducing complications and improving the quality of life of patients. Additionally, exploring the synergistic effects of CGF in combination with other adjunctive therapies, such as advanced wound dressings or stem cell treatments, could further enhance its healing potential. Despite current challenges, CGF has the potential to improve limb preservation and reduce mortality and disability rates in DFU patients as further research is conducted. We are optimistic about the future role of CGF in diabetic wound healing and believe that, with advancements in research and technology, CGF is poised to become a cornerstone of DFU treatment.

Data availability

The article and the additional information include all data generated or analyzed during this study.

Contribution statement

W.-Q. D. and H.-Y.W. conceptualized this article; X.-Y.J. and Y.C. searched and summarized the literature; M.-L.Y., B.D., and H.W. wrote the article; W.-Q. D., H.-Y.W., and L.G. revised the manuscript; W.-Q. D., H.-Y.W., and L.G. have primary responsibility for the final content. All authors read and approved the final manuscript.

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Declaration of competing interest

The authors have declared no conflict of interest.

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