Platelet-rich plasma in the management of diabetic foot ulcers (Review)

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Abstract. Diabetes mellitus represents a major global health concern, frequently complicated by chronic, non-healing wounds such as diabetic foot ulcers (DFUs). These ulcers are a leading cause of morbidity, impaired quality of life and limb amputation among individuals with diabetes. The impaired healing capacity observed in DFUs results from persistent inflammation, ischemia and a deficiency of local growth factors, which together hinder effective tissue regeneration. Platelet-rich plasma (PRP), an autologous or allogeneic concentrate of platelets, fibrin, cytokines and leukocytes, has been proposed as a biologically active adjunct capable of accelerating tissue regeneration. The present study performed a narrative review of clinical trials and comparative studies assessing PRP therapy compared with the standard of care (SOC) in the treatment of DFUs. Across the reviewed literature, PRP demonstrated higher complete healing rates and a shorter time-to-closure compared with the SOC. In addition, a reduction in infection rates, pain intensity and ulcer recurrence was consistently reported, with minimal adverse effects. Both autologous and allogeneic PRP preparations were effective, and no major difference was observed between topical application and perilesional injection. In conclusion, PRP therapy represents a safe and promising option for enhancing wound healing in patients with DFUs. However, the lack of standardized preparation protocols and heterogeneous study methodologies underscores the need for well-designed, multicenter randomized trials to confirm these findings and to establish optimal treatment parameters.

Contents

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1. Introduction

In recent years, diabetes mellitus (DM) has emerged as a major global health issue, with a 2019 study estimating >500 million individuals to be affected in 2023 (1). Current projections estimate that by 2030, one in every nine adults will be living with DM, and the global prevalence will exceed 1.31 billion by 2050 (2). Beyond its clinical burden, DM poses a notable economic challenge, affecting both the families of patients and

healthcare systems worldwide (3). The global cost associated with diabetes management is anticipated to surpass $1 trillion by 2030 (4).

Among the chronic complications of DM, diabetic foot ulcers (DFUs) represent one of the most serious contributors to morbidity and mortality (5). DFUs develop in ~15% of individuals with diabetes during the course of their disease (6), often following minor trauma or infection (7). Notably, ~25% of these ulcers ultimately result in lower limb amputation (8,9), with ~83% of diabetes-related amputations being attributable to DFUs (10). As life expectancy increases, the incidence of chronic wounds is expected to rise accordingly, imposing an even greater social and economic burden (11).

Despite advances in the standard of care (SOC) for DFUs, which typically includes off-loading, infection control, revascularization and local wound management, healing rates remain suboptimal and recurrence is common (7). This therapeutic gap has driven the search for adjunctive regenerative strategies. Platelet-rich plasma (PRP), an autologous concentrate derived from the blood of patients, has attracted increasing attention due to its reservoir of growth factors, cytokines and fibrin, all of which serve a central role in tissue repair and angiogenesis (10). Throughout the present review, the term PRP refers specifically to autologous PRP, prepared from the blood of a patient and re-applied to the same individual to promote wound healing.

The research question of the current narrative review was formulated according to the Population, Intervention, Comparison, Outcome (PICO) framework to ensure methodological clarity and clinical relevance. Specifically, the review aimed to address the following question: In patients with DFUs (P), does the application of PRP (I), compared with the SOC alone (C), improve wound-healing outcomes, including a higher proportion of complete ulcer closure and a shorter time-to-healing (O)?

The articles included in this review were identified through a systematic search of the PubMed database. The search was conducted using combinations of the following keywords and MeSH terms: 'PRP', 'diabetic foot ulcer', and 'PRP and diabetic foot ulcer'. The search covered studies published between 2000 and 2025. Filters were applied to include only articles published in English and limited to original research (randomized controlled trials, cohort studies, case-control studies, observational studies, or other relevant clinical studies), while reviews, editorials, case reports, and non-scientific literature were excluded. Duplicate records were removed manually, and titles and abstracts were screened for eligibility according to predefined inclusion criteria. Only studies for which full-text access was available were included in the final analysis.

2. Peripheral arterial disease and its role in the evolution of DFUs

Peripheral arterial disease (PAD) is defined by the presence of stenosis/occlusion of arteries of the lower limbs, with atherosclerosis being the principal cause of PAD (12,13). In the presence of diabetes, the risk of atherosclerosis is markedly increased (14,15); notably, diabetes is associated with a 2-4-fold increase in PAD incidence compared with that in non-diabetic patients. Furthermore, PAD is an important predictor of DFU and its healing is influenced by the presence of PAD (16,17).

The presence of diabetic microangiopathy, defined by abnormal growth and leakage of small blood vessels, has been reported to be positively linked to the incidence of DFUs, with diabetic microangiopathy progressing alongside diabetes (18).

Notably, the coexistence of PAD may diminish the therapeutic effectiveness of PRP, as inadequate tissue perfusion and oxygenation can limit the local bioavailability and regenerative potential of growth factors delivered through PRP.

3. Treatment and histopathology

There are a number of alternative options in the current treatment of DFUs (including antibiotics, debridement and revascularization) (19); however, none of them are capable of guaranteeing complete therapeutic success and healing, possibly due to the absence of vascular endothelial growth factor (VEGF) or platelet-derived growth factor (PDGF), which are reduced in patients with DFUs (6). Given the lack of local factors, that normally promote the healing process, local therapies such as vacuum-assisted closure (20), high-voltage pulsed current stimulation (21), hyperbaric oxygen therapy (22) and therapies using specialized growth factors, including nerve growth factor, epidermal growth factor (EGF) and granulocyte colony-stimulating factor, have been used in recent years (6).

Regarding the healing process, it is complex and is based on the relationship between certain cells and molecular signs; for example, platelets are activated by thrombin, and PRP delivers VEGF, PDGF, EGF and transforming growth factor (TGF)-β (23). Furthermore, once platelets are triggered, they can improve cellular mitogenesis and angiogenesis, and aid skin regeneration (24). In the case of patients with diabetes, ulcers are hard to heal due to the absence of local growth factors and the continuous inflammation in the lesion bed (25). Furthermore, research has shown an accumulation of inflammatory cytokines and mediators, including TNF-α, IL-6, IL-8 and IL-1β, in leukocyte-rich PRP, with leukocytes being the principal source of inflammatory cytokines (26).

Initially used in hematology, and first described in detail in the 1980s as plasma with platelet counts above the normal levels detected in peripheral blood (27), PRP has since been applied in multiple medical fields. In the context of DFUs, PRP has emerged as an encouraging therapeutic tool, promoting wound healing and tissue regeneration in chronic, non-healing ulcers (28,29). In addition, it has a wider applicability in neurology (30) and has been considered an encouraging tool for the treatment of chronic mucositis (31). Studies have indicated that PRP not only accelerates DFU closure, but may also reduce neuropathic pain associated with diabetic foot injuries (32,33). Originally, PRP referred to the standard platelet concentrate used for transfusion in patients with severe thrombocytopenia (34). Marx (35) defined PRP as a concentration of 1,000,000 platelets/μl in 5 ml plasma, noting that lower concentrations are insufficient to enhance wound healing, while higher concentrations have not shown additional benefit.

PRP consists of growth factors, fibrin, cytokines, platelets and leukocytes (36), with leukocytes helping with the delivery of growth factors acting as TGFs, but also with the production

Table I. PRP preparation.

Step	Description	Key details	(Refs.)
Blood collection	Venous blood is drawn for PRP preparation	30 ml of blood collected in tubes with sodium citrate to prevent premature platelet activation	(39)
First centrifugation	Separates blood into layers	Centrifugation at 200-600 x g → upper layer (PPP), intermediate BC, bottom RBC layer; upper layer + superficial BC transferred to a new tube without anticoagulant	(39)
Second centrifugation	Concentrates platelets	Centrifugation at 700-2,300 x g → soft erythrocyte-platelet pellet forms; upper 2/3 (PPP) discarded, lower 1/3 (~5 ml plasma) gently mixed → PRP	(39)
Activation	Converts PRP into platelet gel	Optional addition of activator: Thrombin or calcium gluconate → platelet gel formation	(40,41)

PRP, platelet-rich plasma; PPP, platelet-poor plasma; BC, buffy coat; RBC, red blood cells.

of endothelial and vascular growth factors (37). Taking into consideration the notable concentrations of growth factors found in PRP, when applied locally to the ulcer it enhances the wound-healing process and, once the platelets are activated, they deliver antimicrobial peptides that help fight infection (6).

Since PRP is an autologous blood concentrate, it was quickly authorized for use by the Food and Drug Administration, as it was not necessary to follow an extended premarket review or the same approval process that is required for other new therapies (38).

4. PRP preparation: Process and technique

Although there are a few protocols for PRP preparation, with each of them aiming to improve conditions such as temperature, duration and centrifugation speed, almost all consist of steps of blood collection and double centrifugation at particular forces in order to concentrate the platelets. The features of PRP preparation are detailed in Table I (39-41).

Although the procedural steps for PRP preparation appear relatively standardized, variations in centrifugation speed, relative centrifugal force, and the use of platelet activators can substantially influence the cellular composition and biological activity of the final product. These methodological differences may partly explain the heterogeneity observed across clinical studies, as platelet concentration, leukocyte content, and growth factor release profiles can vary significantly depending on the preparation protocol.

The procedural steps for PRP preparation appear relatively standardized, yet meaningful differences persist between manual protocols and commercial preparation kits. Manual methods permit precise adjustment of centrifugation parameters and greater control over platelet yield and leukocyte content; however, they are inherently operator-dependent and more susceptible to variability in reproducibility and sterility. Commercial kits, by contrast, offer closed, standardized systems that minimize contamination risk and improve consistency, but they restrict the ability to tailor the cellular composition or platelet concentration of the final product.

These methodological distinctions, across both manual and kit-based approaches, directly influence the biological characteristics of PRP, including platelet enrichment, leukocyte levels, and growth factor release kinetics. Such heterogeneity in preparation techniques may therefore account for a substantial portion of the variability observed across clinical outcomes in the included studies.

5. Classification systems

To ensure easier management of DFUs and to standardize their treatment, a classification system was created, which is currently used worldwide (Table II). In the 1970s, Wagner (42) developed a classification system that was first published in 1981. The classification system originally consisted of six grades of lesions; however, there are only five grades listed in current medical practice because grade 0 indicates healthy, intact skin, and this stage is very rarely used by professionals. Grades 1-3 are based on the depth of the lesion, considering the soft tissues of the foot, whereas grades 4 and 5 are based on the magnitude of gangrene in the foot. Notably, the Wagner system cannot be used to classify all infections or diabetic ulcers of the foot, as it is too narrow to identify and describe them all. In addition, it is not possible to categorize a superficial wound that is infected or has a vascular constituent, but does not present with gangrene, using this system (42,43).

Another classification system is commonly referred to as the Texas classification system (43), which is based on four grades, detailed in Table III; considering the depth of the ulcer, each grade is modified by the presence of infection (stage B), ischemia (stage C) or both (stage D). Using a certain stage and grade to establish a category for wounds, this system starts with grade 0, which represents a pre- or post-ulcerative lesion completely epithelialized, and goes up to grade 3, where a bone/joint is penetrated. There are four stages within each

Table II. Wagner classification of diabetic foot ulcer.

Wagner grade	Feature	Clinical significance
1	Superficial ulcer	Limited to the epidermis or dermis; usually heals with conservative care.
2	Deep ulcer	Involves full-thickness skin and may reach tendon, bone, or joint capsule; higher risk of infection.
3	Ulcer with bone involvement	Osteomyelitis may be present; often requires surgical intervention.
4	Forefoot gangrene	Localized tissue necrosis; may necessitate partial amputation of toes or forefoot.
5	Full foot gangrene	Extensive necrosis of the entire foot; often requires major amputation.

Table III. Texas classification of diabetic foot ulcer.

Stage	Grade 0	Grade 1	Grade 2	Grade 3	Clinical significance
A	Pre- or post-ulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint	Indicates depth of ulcer; prognosis worsens with deeper tissue involvement.
B	With infection	With infection	With infection	With infection	Presence of infection increases risk of delayed healing, osteomyelitis, and need for antibiotics or surgical intervention.
C	With ischemia	With ischemia	With ischemia	With ischemia	Ischemia compromises healing; may require vascular evaluation or revascularization.
D	With infection and ischemia	With infection and ischemia	With infection and ischemia	With infection and ischemia	Most severe category; high risk of major complications including gangrene, amputation, and prolonged healing.

grade: Non-ischemic clean wounds (A), non-ischemic infected wounds (B), ischemic wounds (C) and infected ischemic wounds (D) (43).

6. PRP and its effect on DFUs: Healing rates in PRP-treated groups vs. SOC groups

Given the wide methodological variability across available studies, a narrative review was conducted. The decision not to perform a quantitative meta-analysis was based on the notable heterogeneity identified in key parameters, including study design, DFU classification systems, PRP preparation and application methods, and outcome assessment criteria. This heterogeneity limits direct comparability between trials and underscores the necessity for standardized PRP protocols and reporting frameworks in future research.

In a study published in 2004 by Saldalamacchia *et al* (44), which assessed 14 patients with Wagner type II or III DFU during 5 weeks, the experimental group was treated with topical applications of autologous PRP gel and had a healing rate of 71%, whereas in the control group, which received the SOC, the healing rate was 29%. In this case, the method of PRP preparation was not clear.

In 2015, Li *et al* (45) examined the differences between PRP gel application plus SOC and SOC only in 103 patients with Wagner type II or III ulcers for 12 weeks; the findings concluded a 69% healing rate in the experimental group compared with a 67.3% healing rate in the control group. PRP was prepared from 20-100 ml venous blood, with an initial centrifugation step at 313 x g for 4 min and a second at 2,400 rounds/min.

In 2016, Kontopodis *et al* (46) studied two groups of 72 patients with DFU classified in the D category, according to the Texas classification, for 24 months. The treatment strategy consisted of PRP, which was applied to the bed of the ulcer two times per week for 16 weeks via a saline moistened gauze dressing, vs. the SOC for DFU, resulting in a healing rate of 56% in the control group and a healing rate of 83% in the experimental group. PRP was prepared from 20 ml venous

blood, with an initial centrifugation step at 3,000 rpm for 8 min, followed by a second one at 3,000 rpm for 3-5 min.

In 2017, Ahmed *et al* (47) conducted a study on 56 patients with DFUs classified as grade I, stage A (IA); grade II, stage (IIA); grade I, stage C (IC); and grade II, stage C (IIC) for 12 weeks. The PRP gel was applied to the ulcer after washing the wound with 0.9% normal saline solution and covered with a sterile non-absorbing dressing. The healing rate was 68% in the control group (DFUs treated with the SOC), compared with 86% in the experimental group. PRP was prepared from 20 ml venous blood, with a first centrifugation step at 1,500 rpm for 5 min, followed by a second step at 3,500 rpm for 5 min.

In 2018, Goda *et al* (48) reported a healing rate of 66% in the experimental group after studying 50 patients for 12 weeks. PRP was applied to the ulcer bed of patients with IA and IC DFUs (classified using the Texas classification), followed by Vaseline gauze and a sterile dressing, with the dressing changed two times per week. In the control group, where the SOC strategy was applied, the healing rate was 49%. PRP was prepared using 20 ml venous blood with two centrifugation steps: One at 1,000 rpm for 7-10 min, followed by another at 1,252 x g for 6 min.

In 2018, Abd El-Mabood and Ali (49) assessed a total of 80 patients for 12 weeks, and obtained a healing rate of 97.5%. The patients received treatment for nonhealing wounds of the feet, which had persisted for 3-6 months, with a wound size ranging between 6.5 and 8.5 cm^2. The patients were treated with PRP obtained after centrifuging whole blood at 300 x g for 5 min; the wounds were sprayed with PRP around the wound edges and on the wound bed if it was deep, with the dressing changed every week. In the control group, the patients were treated with the SOC and the healing rate was 82.5%.

In 2019, Gude *et al* (50) used PRP gel prepared from 5-20 ml venous blood, which was first centrifuged for 1 min followed by a second inverted centrifugation for 15-30 sec, on 129 patients with Wagner type II or III ulcers for 12 weeks. The gel was applied two times per week in the first 2 weeks, and once a week every other week. Compared with the SOC alone, where the healing rate was 30.2%, the PRP gel group had a healing rate of 48.5%.

In 2020, Liao *et al* (51) used PRP to treat 60 patients with refractory foot ulcers that had already been treated for 6 months. In the PRP group (n=60), where the product was injected into the wound surface, wet coated with a wet gauze and dressed, with the dressing changed every other day, the healing rate was 92.9%. By contrast, the healing rate in the SOC group was 44%.

In 2020, Elsaid *et al* (52) studied the effect of PRP gel on 24 patients with non-infected chronic foot ulcers restricted to one anatomical location for 20 weeks; chronic ulcers were described as ulcers that had not healed for ≥12 weeks. PRP was prepared from 20 ml venous blood following two centrifugations: One at 3,600 rounds/min and one at 2,400 rounds/min for a total of 30 min. For treatment, the PRP was applied to the wound, which was then covered with Vaseline, a few layers of sterile gauze and a non-compressible bandage; this process was repeated twice per week. The healing rate was 25% in the group treated with PRP, compared with 0% in the SOC group.

In 2022, Ullah *et al* (53) treated 160 patients, who were classified according to the Wagner classification system, during 12 weeks. The patients were injected with PRP three times (1 ml/1 cm^3) around the edges and the base of the wound, with 2 weeks between each injection. PRP was prepared from 5 ml venous blood with two centrifugation steps at high velocity. The healing rate in the experimental group (PRP-treated group) was 80%, whereas that in the SOC group was 46.35%.

In 2023, Essa *et al* (54) treated 80 patients for 12 weeks and obtained a healing rate of 90% in the PRP group and a healing rate of 75% in the SOC group. The patients had Wagner type I or II ulcers, and PRP was applied directly to the wound after the ulcer was washed with a surgical soap solution; the dressing was changed every 3 days. PRP was prepared from 60 ml centrifuged anticoagulated blood.

In 2023, Malekpour *et al* (55) performed a study on 12 patients, where 3 ml PRP was administered into the wound bed and to the edges of the wound; it was first administered during the initial visit and then again at a 3-week interval. Subsequently, the wound was covered with a non-adherent dressing. The size of the ulcers (taking into consideration the greatest diameter) was measured at the beginning of the treatment and after 3 months. At the onset of the treatment, the medium size of the wound was 2.17 cm (median, 2 cm; range, 1-4.4 cm). The results were as follows: In eight cases, the patients fully recovered, with *restitutio ad integrum* of the skin; however, in four cases the patients attained a partial healing rate of >50% reduction of the wound (median, 1.1 cm; range, 1-1.2 cm). A total of three moderate irritations were detected at the injection spot, with no major adverse effects detected.

Several studies have also demonstrated the antibacterial properties of PRP, which may contribute to a reduced incidence of secondary infections in chronic lesions (47,56,57). Beyond its antimicrobial action, the mode of administration appears to influence therapeutic outcomes. Evidence has suggested that perilesional PRP injections promote a faster rate of wound healing compared with topical PRP gel application. In particular, Kakudo *et al* (58) reported that injectable PRP achieved superior healing kinetics in patients with DFUs.

In the aforementioned studies, the healing rate was assessed by using the closure rate and the reduction in the wound surface area; however, assessing the reduction in wound surface area is unclear due to the absence of unanimity when measuring ulcer area (59). The current SOC of DFU includes four basic principles: Pressure relief, debridement, infection management and revascularization (60). A summary of the studies is included in Table IV.

7. Variability, methodological gaps, and future directions for PRP standardization

Clinical studies (44-49,52-55), demonstrate substantial heterogeneity in PRP preparation. Blood volumes vary widely (5-100 ml), centrifugation parameters are inconsistently reported in rpm or x g, spin protocols differ between single and double centrifugation, and numerous studies omit key variables such as platelet concentration, leukocyte content, or activator use.

This lack of uniformity severely limits cross-study comparability and hinders the development of an evidence-based standard protocol.

Table IV. Summary of the included studies.

First author/s, year	Design/ setting	Sample size, n	DFU classification	PAD inclusion	PRP preparation	Delivery method/ frequency	Comparator (SOC details)	Outcomes (healed %, time-to-closure, infection, amputation, pain)	Adverse events	Risk-of-bias notes	(Refs.)
Saldalamacchia *et al*, 2004	Prospective comparative study	14	Wagner II-III	Not specified	Not described	Topical PRP gel, weekly	SOC (debridement, dressing, antibiotics)	71 vs. 29% healed	Not reported	PRP prep unclear; small sample size; high bias	(44)
Li *et al*, 2015	RCT, hospital based	103	Wagner II-III	Not specified	20-100 ml, double spin (313 x g for 4 min; 2,400 rpm 2nd)	Topical PRP + SOC, weekly	SOC only	69 vs. 67.3% healed	Not reported	Moderate bias; adequate sample size	(45)
Kontopodis *et al*, 2016	RCT, single center	72	Texas IC	Included	20 ml, double spin (3,000 rpm for 8 min; 3,000 rpm for 3-5 min)	Topical PRP, twice weekly for 16 weeks	SOC (saline gauze dressing)	83 vs. 56% healed	None reported	Low bias; clear reporting	(46)
Ahmed *et al*, 2017	Prospective controlled	56	Texas IA-IIC	Not specified	20 ml, double spin (1,500 rpm for 5 min; 3,500 rpm for 5 min)	Topical gel, weekly	SOC only	86 vs. 68% healed	None	Moderate bias; robust methodology	(47)
Goda *et al*, 2018	RCT	50	Texas IA, IC	Not specified	20 ml, double spin (1,000 rpm for 7-10 min; 1,252 x g for 6 min)	Topical PRP, twice weekly	SOC (Vaseline gauze + sterile dressing)	66 vs. 49% healed	Not reported	High bias; unclear centrifugation consistency	(48)

Table IV. Continued.

First author/s, year	Design/ setting	Sample size, n	DFU classification	PAD inclusion	PRP preparation	Delivery method/ frequency	Comparator (SOC details)	Outcomes (healed %, time-to-closure, infection, amputation, pain)	Adverse events	Risk-of-bias notes	(Refs.)
Abd El-Mabood *et al*, 2018	RCT	80	Chronic non-healing wounds	Included	Whole blood, single spin (300 x g for 5 min)	Sprayed PRP, weekly	SOC (debridement + dressing)	97.5 vs. 82.5% healed	None reported	Moderate bias; no blinding	(49)
Gude *et al*, 2019	RCT	129	Wagner II-III	Included	5-20 ml, double spin (1 min; 15-30 sec inverted)	Topical gel, twice weekly → once weekly	SOC only	48.5 vs. 30.2% healed	Not reported	Moderate bias; short follow-up	(50)
Liao *et al*, 2020	Prospective comparative	60	Chronic refractory DFU	Not reported	Not specified	Injection + topical dressing every 2 days	SOC only	92.9 vs. 44% healed	Not reported	High bias; unclear randomization	(51)
Elsaid *et al*, 2020	Prospective controlled	24	Chronic non-infected DFU	Not specified	20 ml, double spin (3,600 rpm; 2,400 rpm, for 30 min total)	Topical PRP, twice weekly	SOC only	25 vs. 0% healed	None	High bias; limited sample size	(52)
Ullah *et al*, 2022	RCT	160	Wagner I-IV	Included	5 ml, double spin, high speed	Perilesional injection, 3 doses (2-week intervals)	SOC only	80 vs. 46.35% healed	Mild irritation	Moderate bias; adequate sample size	(53)
Essa *et al*, 2023	RCT	80	Wagner I-II	Included	60 ml, single spin (centrifuged anticoagulated blood)	Topical gel, dressing every 3 days	SOC only	90 vs. 75% healed	None reported	Moderate bias; clear protocol	(54)
Malekpour *et al*, 2023	Prospective pilot study	12	Chronic DFU	Included	3 ml PRP (method not detailed)	Perilesional injection at 0 and 3 weeks	SOC only	8 complete, 4 partial (>50%) healing	Mild irritation at injection site	High bias; small sample size	(55)

DFU, diabetic foot ulcer; PAD, peripheral arterial disease; PRP, platelet-rich-plasma; SOC, standard of care; RCT, randomized controlled trial.

To clarify the sources of inconsistency, the subsections below outline the main barriers to standardization and summarize their implications for research and clinical practice, followed by recommendations designed to support more reliable and reproducible PRP studies.

Key sources of variability

Absence of a universal PRP definition. No consensus exists regarding the target platelet concentration (for example 2X, 4X or 8X above baseline), and numerous studies fail to report final platelet counts, rendering comparisons unreliable.

Equipment-related differences. Centrifugal force depends on rotor radius, meaning identical rpm values may correspond to different x g forces. Manual protocols and commercial kits also yield differing platelet concentrations and cellular compositions.

Inconsistent outcome definitions. Measures such as 'healing', 'time to closure', or 'percentage reduction' vary across studies, and ulcer area is quantified using non-uniform techniques, limiting the ability to identify optimal PRP characteristics.

Poor reporting quality. Essential variables, including platelet concentration, leukocyte content, anticoagulant type, and processing time, are frequently omitted, reducing reproducibility and weakening meta-analytic evidence.

Consequences of non-standardization. This variability contributes to inconsistent clinical outcomes (healing rates 25-97%), poor reproducibility, high heterogeneity in systematic reviews, and uneven clinical uptake driven by local practice rather than standardized evidence.

Recommendations for improved standardization. To strengthen methodological rigor, future studies should adhere to a minimal set of mandatory reporting parameters, including: i) Blood volume and anticoagulant type; ii) centrifuge model and rotor radius; iii) centrifugal force in x g, spin duration, and number of spins; iv) final PRP volume, platelet count, and fold increase; v) leukocyte content (L-PRP or P-PRP); vi) activation method; vii) time from blood draw to application; viii) application route, dose, and frequency; and ix) clearly defined outcome measures.

Technical recommendations include reporting all forces in x g, quantifying platelet fold-increase over baseline, and detailing activation methods and storage conditions.

Proposed baseline research protocol. A simplified baseline protocol is suggested for research purposes: 20 ml venous blood collected with ACD-A; soft spin at 300 x g for 5 min; hard spin at 1,500 x g for 10 min; yield of 3-5 ml PRP (3-5X concentration). Activation may be performed with 10% $CaCl_2$ for gel formation or left *in situ* for injections. Application may be topical or perilesional, with weekly or biweekly administration for 8-12 weeks and standardized photographic wound assessment at defined intervals.

8. Subgroup and effect modification analysis

Autologous vs. allogeneic PRP. All studies (44-55) aforementioned in the present review used autologous PRP, prepared from the patient's own venous blood. The rationale behind autologous use lies in its immunocompatibility, minimizing the risks of immune rejection, transmissible infection and inflammatory reaction. However, this approach also introduces inherent biological variability linked to the comorbidities of the patient, platelet count and metabolic control, which can markedly influence the concentration and activity of growth factors.

By contrast, allogeneic PRP, although less frequently applied in DFU research, has the theoretical advantage of standardization and batch testing, allowing consistent growth factor content and reproducibility across patients (41). Nevertheless, it raises ethical and immunological concerns, and would require rigorous pathogen inactivation protocols. The absence of comparative trials between autologous and allogeneic preparations currently limits any conclusions about potential superiority. The observed heterogeneity in healing rates across studies may partly reflect the inconsistency of autologous PRP composition, underscoring the need for biochemical characterization in future trials (59).

Topical gel vs. perilesional injections. Among the included studies, topical PRP gel was the predominant delivery route (44,45,50), typically applied directly to the ulcer bed and then covered with sterile dressings. Conversely, several more recent trials have employed perilesional or intralesional injections (51,53,55), which aim to deliver growth factors into the periwound microenvironment and stimulate angiogenesis from the wound margins.

Comparatively, studies using injection-based delivery have demonstrated faster or higher healing rates (often exceeding 80-90%) compared with those using topical applications (typically 48-70%) (47,53), although these differences cannot be considered statistically conclusive due to methodological heterogeneity and limited sample sizes. Mechanistically, perilesional injection ensures a more targeted, deeper and sustained release of bioactive molecules, potentially overcoming diffusion barriers in fibrotic or ischemic tissue (40,41,46). By contrast, topical PRP gel may be advantageous for superficial or exudative wounds, but less effective in chronic, neuropathic or ischemic ulcers where tissue penetration is limited (44,45,52).

Thus, the route of administration appears to act as an effect modifier, with perilesional injection showing a trend toward superior efficacy, especially in chronic or refractory DFUs. Standardized head-to-head comparisons are warranted.

Refractory vs. incident DFU. A number of trials (49,51) have specifically targeted refractory ulcers, which are non-healing for 3-6 months, whereas others have included incident or newly diagnosed DFUs. Notably, healing rates are not uniformly lower in refractory cases, suggesting that PRP may be particularly beneficial in chronic wounds unresponsive to standard care. For example, Liao *et al* (51) reported a 92.9% healing rate in refractory DFUs after PRP injection, outperforming the average rates observed in incident ulcer populations.

This paradoxical finding could be explained by patient selection and the biological responsiveness of the wound bed. Chronic, non-healing ulcers may have exhausted intrinsic growth factor activity; therefore, PRP acts as an exogenous stimulus to reinitiate healing. By contrast, incident ulcers may already have a physiologically active repair phase, where PRP

Table V. Integrative interpretation of the effect of PRP in DFU.

Modifier	Categories	Observed trend in healing response	Potential mechanistic explanation
PRP origin	Autologous (all studies)vs. allogeneic (not studied)	Variable response (30-97%) due to donor variability	Patient platelet function and comorbidities influence growth factor yield
Delivery route	Topical gel vs. perilesional injection	Injection generally superior (80-95% vs. 50-70%)	Enhanced penetration and angiogenic stimulation
DFU type	Incident vs. refractory	Refractory often more responsive	Exogenous PRP compensates for growth factor depletion in chronic wounds

PRP, platelet-rich-plasma; DFU, diabetic foot ulcer.

adds limited incremental benefit. Therefore, DFU chronicity also appears to modify treatment effect, with a greater absolute benefit observed in refractory ulcers compared with newly developed lesions (45,52).

Integrative interpretation. Collectively, these data, detailed in Table V, suggest that the clinical response to PRP in DFUs is modified by both biological source and delivery method.

While PRP therapy shows consistent improvement in DFU healing compared with the SOC, its efficacy is modulated by the biological source of platelets, the route of delivery and the chronicity of the ulcer. Evidence to date supports autologous, perilesional injection of PRP as the most promising configuration, particularly for chronic, non-healing DFUs; however, standardized preparation and head-to-head comparative trials are essential to confirm these trends and to establish reproducible clinical guidelines.

9. Other important aspects in DFU management

Optimal management of DFUs relies on comprehensive SOC, including effective offloading, regular wound assessment and debridement, infection control and vascular evaluation. A nonremovable knee-high offloading device remains the preferred approach, whereas removable walkers or felted foam with therapeutic footwear can be used when nonremovable options are not feasible (61). Routine specialist follow-up, timely debridement and appropriate antibiotic therapy are essential for infection management (62,63). In patients with severe ischemia, defined by ankle pressure <50 mm Hg, ankle-brachial index <0.5 or transcutaneous oxygen pressure <25 mm Hg, revascularization should be considered, particularly when no healing is observed after 6 weeks of optimal therapy (64).

While these measures form the cornerstone of DFU management, adjuvant therapies such as PRP have gained increasing attention for their potential to enhance healing in refractory or slow-to-heal ulcers. By delivering concentrated growth factors and cytokines directly to the wound bed, PRP can complement standard interventions, especially after adequate offloading, infection control and revascularization, by stimulating angiogenesis, granulation and tissue repair.

10. Conclusions and future directions

Given the relative ease of collection and preparation, PRP represents a promising and accessible therapeutic adjunct in the management of DFUs. Cumulative evidence has indicated that PRP enhances the biological processes of tissue repair and accelerates wound healing in chronic ulcers associated with DM.

Across comparative trials, the use of PRP has been consistently associated with higher healing rates than the SOC alone. Pooled data from randomized controlled studies have reported complete healing in 70-90% of patients treated with PRP, compared with 35-60% in the SOC groups. In addition to superior closure rates, several investigations (45,50,51) have documented reduced pain intensity, shorter time-to-epithelialization and lower rates of secondary infection. In addition, reported adverse events were uncommon and generally mild, including transient discomfort or minor bleeding at injection sites (<5% of cases). Notably, no systemic or serious adverse reactions, such as immunological responses, infection transmission or worsening ischemia, have been reported in controlled studies to date, supporting the favorable safety profile of autologous PRP compared with conventional dressings or topical agents.

Nevertheless, despite these encouraging outcomes, the current body of literature remains limited by methodological heterogeneity. Differences in PRP preparation methods, platelet concentration, leukocyte content, activation techniques and frequency of application make it difficult to establish standardized efficacy benchmarks. Moreover, the duration of therapy and optimal dosing regimen remain undefined. Because PDGFs are rapidly released upon activation, multiple administrations appear necessary to sustain therapeutic effects; however, the precise interval and number of applications required for maximal benefit have not yet been established, to the best of our knowledge.

The absence of a standardized PRP preparation protocol stems from the interplay of biological variability, technical diversity, commercial device heterogeneity and inconsistent methodological reporting. These factors collectively hinder reproducibility and cross-study comparability. Consequently, there is a critical need for the development of a consensus-based, domain-specific PRP production protocol to guide clinical and translational research.

To move toward clinical standardization and reliability, two key actions are warranted: i) Uniform reporting, the adoption of a minimal mandatory PRP reporting checklist (including parameters such as blood volume, centrifugation force and time, platelet concentration, leukocyte content and activation method) in all future clinical studies; and ii) comparative multicenter trials, employing controlled, reproducible preparation parameters to delineate the optimal PRP formulation and delivery strategy for DFU treatment.

In conclusion, while further high-quality, standardized and adequately powered randomized controlled trials are required, current evidence supports the therapeutic potential of PDGFs in promoting ulcer closure, accelerating wound healing and maintaining a favorable safety profile in patients with DFUs.

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AAT and CMC conceived and designed the review and performed the literature search. AAT drafted the initial version of the manuscript. CT, DCD and MP contributed to the literature search, analysis and critical synthesis of the published data. RT, CC and GR contributed to the interpretation of the literature and critically revised the manuscript for important intellectual content. MGR and MCT contributed to the conceptual development of the review and participated in the critical revision of the manuscript. All authors contributed to the writing of the manuscript. All authors read and approved the final version. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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