Efficacy of Autologous Platelet-Rich Gel for Diabetic Foot Wound Healing: A Meta-Analysis of 15 Randomized Controlled Trials

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Objectives: The meta-analysis was performed to summarize the available evidence and determine the healing effectiveness of autologous platelet-rich gel (APG) on diabetic foot (DF) wounds.

Approach: PubMed and The Cochrane Library and CNKI databases were searched to identify prior randomized controlled trials. Methodological qualities of included studies were assessed using Cochrane Handbook for Systematic Reviews of Intervention. Healing rate was considered the primary outcome; the secondary outcomes included healing time and adverse events.

Results: Fifteen studies involving a total of 827 subjects were analyzed in the meta-analysis. Considering the primary outcome, the average healing rate in APG group was 85.8% and ranged from 68.4% to 100%. Relatively, the control group was 57.4% and ranged from 18.2% to 75.0%. Eligible studies were compared with a fixed effects model ($I^2=0.0\%$, $p=0.496$), indicating a higher healing rate with APG (risk ratio [RR] 1.44, 95% confidence interval [CI]: 1.32–1.57, $z=8.50$, $p<0.001$). The leave-one-out sensitivity analysis is robust. Considering the secondary outcomes, APG therapy needed less time (weighted mean difference –10.75 days, 95% CI: –11.67 to 8.86 days, $z=14.34$, $p<0.001$) and had fewer adverse events (RR 0.44, 95% CI: 0.25–0.76, $z=2.94$, $p=0.003$).

Innovation: APG therapy is an innovative and effective approach to promote DF wound healing and reduce healing time and adverse events.

Conclusion: The meta-analysis demonstrates that APG therapy has a positive effect on the treatment of DF wounds. However, additional well-designed and high-quality studies are needed to reach a conclusion with more confidence.

Keywords: autologous platelet-rich gel, diabetic foot, wound healing, meta-analysis

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INTRODUCTION

DIABETIC FOOT (DF) IS a common and severe problem throughout the world, which is caused by a combination of sensory neuropathy, foot deformity, and inadequate arterial circulation.¹ DF has a high global prevalence ranging from 4% to 10%, and the lifetime incidence is 10–25% among patients with diabetes. Moreover, 15% of patients with diabetes have at least one foot wound in

their lifetime, approximately.^{2,3} DF wounds are the main reasons for hospitalization, it also makes up for 40–70% of all nontraumatic amputations of the lower limbs in diabetes.^{4,5} DF is related to high morbidity and mortality in patients with diabetes.^{4,5} In addition, DF wounds impose a profound burden on patient's health-related life, primarily reflected in the mobility and pain/discomfort domains, and the financial

burden on the patient's family and health care.⁶ A review found that the total cost for treating DF wounds and amputation is ~\$10.9 billion (\$9–\$13 billion) per year. In addition to the direct cost, indirect costs are associated with the loss of productivity and quality of life.⁷

At present, there are many treatment options for DF wounds consisting of adequate vascular supply, hyperbaric oxygen therapy (HBOT), offloading high pressure, debridement, and use of dressings. In regard to adequate vascular supply, Hinchliffe *et al.* reviewed 57 articles to evaluate the effectiveness of revascularization for DF wounds; the results showed the healing rate was 60% or more during the 12-month follow-up.⁸ A previous review regarding HBOT in DF wounds found that HBOT is an adjunctive therapy for DF wounds associated with a higher healing rate (odds ratio [OR] 14.25, 95% confidence interval [CI]: 7.08–28.68), potentially preventing amputation (OR 0.30; 95% CI: 0.10–0.89).⁹ A similar conclusion was obtained in a randomized controlled trial (RCT).¹⁰ As for offloading high pressure, a practice guidance on offloading interventions applied in DF wounds had reported that 92–100% of DF wounds healed in the mean of 21–40 days and could prevent recurrence.¹¹ A published meta-analysis about debridement for DF wounds indicated that autolytic debridement increased the healing rate (risk ratio [RR] 1.89; 95% CI: 1.35–2.64) and larval debridement reduced the amputation rate (RR 0.43; 95% CI: 0.21–0.88).¹² Xu *et al.* had reported honey dressings can stimulate healing of DF wounds (RR 1.05, 95% CI: 0.96–1.16).¹³ Application of hyaluronic acid dressings is also reported to be effective for DF wounds (84.6% vs. 41.6%) by Lee *et al.*¹⁴

Autologous platelet-rich gel (APG) as a biological therapy has been applied to DF as well. In 1986, the first clinical study conducted by Knighton *et al.*, mentioned APG was prepared from each patients' blood and removed by centrifugation, which revealed the positive effects of APG for the healing of chronic refractory wounds.¹⁵ All patients achieved a healing rate of 100% at the average of 10.6 weeks.¹⁵ Furthermore, Krupski *et al.* conducted the first randomized, prospective, double-blind, placebo-controlled study in 1991 and showed the ability of APG to facilitate the healing of chronic wounds (33% vs. 24%).¹⁶ Based on the apparent efficacy on chronic wounds, the studies of APG used for DF date from 2004. Saldalamacchia *et al.* conducted the first prospective controlled trial¹⁷ on the effectiveness and safety of APG for the treatment of DF wounds, demonstrating that

applying APG promotes healing of diabetic cutaneous wounds (71% vs. 29%, OR 6.2). A prospective randomized clinical trial conducted by Li proved APG is superior to standard therapy in healing rate (84.8% vs. 69.0%), healing time (36 days vs. 45 days), and safety (8.5% vs. 13.8%). Ahmed *et al.* published a study¹⁸ comparing the effect of local antiseptic dressing with APG on the DF wounds; the outcomes of study indicated that APG is more effective than antiseptic dressing in terms of healing rate (85.7% vs. 65.9%) and prevention of infection (4% vs. 21%). Because the application of APG for chronic wounds has been widely recognized, there are published systematic reviews and meta-analyses of APG therapy in maxillofacial surgery¹⁹ and surgical wounds¹⁷ in PubMed. However, concerning the application of APG in DF, there are still some problems: a few available studies have different conclusions regarding the usefulness of APG,^{20–22} the sample sizes of published clinical studies are small, and we have not found published meta-analysis evaluating the effectiveness of APG for the healing of DF to date. In such situation, a meta-analysis is a useful tool to reach a specific conclusion.

The purpose of this study was to determine the efficacy of APG with control treatment. To that end, (1) we thoroughly and systematically collected scientific evidences and performed a meta-analysis that compared the differences in healing rate, healing time, and adverse events between APG and control treatments. (2) The meta-analysis used an evaluation of the homogeneity of the healing rate in each trial and an estimate of the 95% CIs of the combined data, an estimation of the effects of treatment duration and total healing rate on the percentage healed as endpoints, and an assessment of the weighted mean difference (WMD) healing time by the trial endpoint.

CLINICAL PROBLEM ADDRESSED

The mobility and pain/discomfort domains of DF wounds impose a profound burden on patient's health-related life, and the financial burden on the patient's family and health care. Some human trials show the growth factors contained in the APG can stimulate DF wound healing. Consistent with this, our study is conducted to compare the efficacy between the APG and control treatment; the primary outcome is healing rate, while the secondary outcomes are healing time and adverse events. The findings from the study indicate the better efficacy of APG than control treatments; APG therefore can be a clinical treatment.

MATERIALS AND METHODS

Literature search strategy

To identify related studies, PubMed, The Cochrane Library, and CNKI databases were searched with no restrictions placed on publication date or languages, using combinations of the keywords based on Medical Subject Headings (MeSH). The search was performed using the following search strategy: (“diabetic foot” [MeSH Terms] OR “diabetic foot” [Title/Abstract] OR “diabetes foot” [Title/Abstract] OR “DF” [Title/Abstract] OR “diabetes feet” [Title/Abstract] OR “diabetic foot” [Title/Abstract] OR “diabetic patients with DF” [Title/Abstract]) AND (“ulcer” [Title/Abstract] OR “wound” [Title/Abstract] OR “hole” [Title/Abstract] OR “canker” [Title/Abstract] OR “anabrosis” [Title/Abstract]) AND (“blood platelets” [MeSH Terms] OR “platelet*” [Title/Abstract] OR “PRG” [Title/Abstract] OR “autologous platelet-rich gel” [Title/Abstract] OR “APG” [Title/Abstract] OR “PRP*” [Title/Abstract]). This search was adapted for each database, duplicates were removed after confirming identical publication information, and references of screened articles were hand-searched for identification of other potentially relevant studies.

Inclusion and exclusion criteria

Inclusion/exclusion criteria were defined according to a structured approach type PICO_S (population, intervention, comparison, outcomes, study design): (1) P = population. Wagner grade 1–4 patients (≥18 years of age) presenting with foot wounds were included in study. (2) I = intervention. Eligible studies for inclusion in meta-analysis had to use APG as a topical application. (3) C = comparison. Studies compared the use of APG (not platelet-derived growth factor [PDGF]) with placebo or other biomaterials that were eligible for meta-analysis. (4) O = outcomes. The primary outcome variable to the eligible studies was represented by healing rate. The healing referred to completely healed. When DF wounds heal completely, the reduction rate was calculated as [initial area (cm²) – final area (cm²)]/initial area (cm²) reaches 100% and complete epithelial cover in the absence of discharge.²³ The secondary outcomes considered were healing time and adverse events. The adverse events were defined as advanced infection, formication, or prickling sensation. Infection was defined as the results of microbial culture on the DF wound surfaces being not consistent with the results before APG treatment. The definition of formication was patients describing an itchy feeling of ants crawling on the ulcers, and prickling sensation was defined as patients describing a feeling of piercing pain on the ulcers. (5) S = study design. Only

RCT studies were included. The exclusion criteria were case series, case reports, retrospective studies, animal studies, technical studies, and reviews.

Study selection and data extraction

Based on the predefined inclusion/exclusion criteria, one reviewer first screened all articles and removed the obviously irrelevant ones. Then, two reviewers independently screened the titles and abstracts of studies. In a secondary screening, the full text of the remaining studies was evaluated for eligibility. Any discrepancy among the reviewers in the study selection was resolved by consensus. Two reviewers used a standardized data extraction form to collect all relevant information regarding study characteristics (name, type, and country) and patient characteristics (age, sex, and sample sizes). Moreover, characteristics of wounds (Wagner grade and duration of treatment), treatment protocols (the number of treatment and control group, and randomization), and the results of studies were also recorded. Finally, if the results of two reviewers reached an agreement, we reached the final conclusion directly. If there were discrepancies between two reviewers, the senior author acted as a referee to arbitrate differences between two reviewers in interpretation of data. If the advice of the senior author was in accordance with one of two reviewers, we adopted this advice as the final conclusion. Moreover, if neither of conclusions of two reviewers was consistent with the advice of the senior author, the two reviewers should conduct the process again.

Quality assessment

The risk-of-bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions to assess the quality of each included RCTs²⁴ and the results of assessment is shown in Fig. 2. The following six domains were evaluated: random sequence generation, allocation concealment, blinding of patients and practitioner, blinding of outcome assessor, incomplete outcome data, and selective reporting risk. Qualities of the studies are defined as follows: if all previously mentioned key domains were met, the risk of bias was estimated to be low; if only one key domain was missing, the risk of bias was estimated to be unclear; and when two or more key domains were not met, the risk of bias was estimated to be high. Two reviewers independently assessed the eligible studies; the final conclusion was concluded directly if the results of two reviewers reach the same conclusion. The senior author acted as a referee to arbitrate differences in interpretation of data when there were discrepancies between two reviewers. If the senior author agreed with one of two reviewers, we adopted the results of this

reviewer as the final conclusion. Moreover, if neither of results of two reviewers was consistent with the advice of the senior author, the two reviewers should repeat the process.

Statistical analysis

To calculate efficiency, the software STATA 12.0 (STATA Corp., College Station, TX) was used to perform the statistical analysis. A p -value of less than 0.05 was regarded to be significant. The healing rate was used to estimate the efficiency of APG in treating DF wounds. Mantel-Haenszel method was used to calculate the dichotomous outcome when considering healing rate and adverse events, and was recorded as the RR with 95% CI and the weight contribution of each study. In addition, healing time was evaluated as continuous outcome variables by inverse variance method; it was performed on the basis of WMD with 95% CI. Statistical heterogeneity between the studies was assessed using Cochran's Q test and I^2 .²⁵ The extent of heterogeneity was classified as either low ($I^2 < 25\%$) or high ($I^2 > 75\%$). A fixed-effects model of analysis was used where I^2 index is less than 50% and p -value > 0.05 . Otherwise, random-effects model was used.²⁶ Moreover, risk of publication

bias was checked by a funnel plot, as well as using Egger's test and Begg's test. A symmetrical, inverted, funnel-shaped scatter plot suggested an absence of bias.²⁷ Meta-regression was conducted to examine the relationship between the duration of treatment and healing rate.²⁸ The effect of each study quality on the ultimate result was demonstrated by a leave-one-out sensitivity analysis. Finally, subgroup analysis was done when the number of available studies is more than 10; it was employed for variables of different Wagner stages of DF and different countries (China or non-China).

RESULTS

Literature search

In total, 156 articles were qualified in database search after duplicates were removed. Of those, 89 articles were excluded because they were not related to the topic or incomplete. A total of 67 articles went forward for inclusion/exclusion criteria review. Fifty-two articles were excluded due to the exclusion criteria. Finally, the remaining 15 articles^{17,18,30-41} met the inclusion criteria and were enrolled in the meta-analysis. The study selection process was illustrated in a flow diagram (Fig. 1).

Figure 1. Flow diagram of selection of studies for inclusion. RCT, randomized controlled trial.

Table 1. Characteristics of included studies

First Author (Year)	Study Type	Country	Age (Years)	Sample Size	Gender (M/F)	Wagner Grade	Duration of Treatment (Weeks)	Healing Rate (%)		Healing Time (Days)		Adverse Events (%)	
								APG Group	Control Group	Number	Mean ± SD	APG Group	Control Group
Liu (2016)	RCT	China	38–71	60	34/26	2–3	8	93.3% (28/30)	63.3% (19/30)	30	32.6 ± 2.4	NA	NA
Zhang (2016)	RCT	China	45–80	52	NA	1–3	8	72% (18/25)	22.2% (6/27)	25	36.4 ± 2.3	NA	NA
Ahmed (2016)	RCT	Egypt	18–80	56	38/18	NA	12	85.7% (24/28)	67.9% (19/28)	28	NA	7.1% (2/28)	21.4% (6/28)
Zhou (2015)	RCT	China	35–79	48	31/27	1–4	6	91.7% (22/24)	75% (18/24)	24	NA	NA	NA
Ma (2014)	RCT	China	18–85	62	43/19	1–4	6	93.6% (29/31)	71.0% (22/31)	31	20.8 ± 10.1	NA	NA
Qi (2014)	RCT	China	45–78	72	47/25	1–3	NA	94.4% (34/36)	69.4% (25/36)	36	28.5 ± 10.1	NA	NA
Serra (2013)	RCT	Italy	41–85	58	26/12	NA	NA	96.2% (25/26)	59.4% (19/32)	26	NA	NA	NA
Li (2015)	RCT	China	NA	117	75/42	1–3	12	84.8% (50/59)	69.0% (40/58)	59	36 ± 10.2	8.5% (5/59)	13.8% (8/58)
Saad (2011)	RCT	Egypt	40–60	24	NA	1 or 2	20	100% (12/12)	75% (9/12)	12	NA	NA	NA
Wang (2009)	RCT	China	47–76	46	46/20	2–3	12	95.7% (22/23)	56.5% (13/23)	23	31.6 ± 24.2	0	0
Chen (2008)	RCT	China	43–83	108	69/39	1–3	NA	78.2% (43/55)	52.8% (28/53)	55	29.3 ± 10.8	NA	NA
Wei (2008)	RCT	China	48–64	22	16/6	NA	12	81.8% (9/11)	18.2% (2/11)	11	NA	2	NA
Yan (2008)	RCT	China	38–72	48	27/21	1–2	NA	73.9% (17/23)	36% (9/25)	23	18.9 ± 2.7	0	NA
Driver 2006	RCT	US	18–95	40	32/8	1 or 2	12	68.4% (13/19)	42.9% (9/21)	19	42.9 ± 18.3	31.6% (6/19)	81.0% (17/21)
Saldamacchia (2004)	RCT	Italy	50–70	14	6/8	2 or 3	5	71.4% (5/7)	28.6% (2/7)	7	NA	0	NA

Adverse events include infection, formication, or pricking sensation.

APG, autologous platelet-rich gel; F, female; M, male; NA, not available; RCT, randomized controlled trial; SD, standard deviation.

Characteristics of included studies

The included studies were conducted from 2004 to 2016. Within the eligible study, 827 subjects were enrolled in the studies (409 patients in APG group and 418 in control group). The age and gender distributions were similar between APG group and control group. The Wagner grades of DF wounds in included studies ranged from 1 to 4. Also, duration of treatment ranged between 5 and 20 weeks. The features of the included studies are summarized in Table 1.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ahmed M 2016	?	?	?	+	+	+	?
Chen H 2008	?	?	?	?	+	+	?
Driver VR 2006	+	+	+	+	+	+	?
Li L 2012	+	+	+	+	+	+	?
Liu G 2016	?	+	?	?	+	+	?
Ma L 2014	?	?	?	?	+	+	?
Qi K 2014	?	+	?	?	+	+	?
Saad Setta H 2011	+	+	?	?	+	+	?
Saldamacchia G 2004	?	?	?	+	+	+	?
Serra R 2013	?	+	?	+	+	+	?
Wang Y 2009	+	+	?	?	+	+	?
Wei C 2008	?	?	?	?	+	+	?
Yan H 2007	?	?	?	?	+	+	?
Zhang L 2016	?	?	?	?	+	+	?
Zhou X 2015	?	+	?	?	+	+	?

Figure 2. The quality assessment of 15 RCTs.

Figure 3. Forest plot with the comparison of healing rate between APG therapy and control therapy. APG, autologous platelet-rich gel.

Quality assessment

Four of included studies applied adequate random sequence generation. The rest of included studies had unclear risk. The allocation was concealed in four trials. In this meta-analysis, suc-

cessful blinding of patient and practitioner was reported in two trials, while the rest is unclear. Blinding of assessor is successful in four trials, while one is unsuccessful, and the rest are unclear. Attrition bias was low, except one study. Reporting

Figure 4. Funnel plot showing the publication bias.

bias was low with all included data coming from trials with low risks. Other bias was not mentioned in all included studies; so the included studies had unclear risk. The results are shown in Fig. 2.

Primary outcome: healing rate

The average of healing rate in the APG group was 85.8% compared with 57.4% in the control

group, respectively; the overall healing rate ranged from 68.4% to 100% and 18.2% to 75.0%. Fixed-effects model was used to evaluate APG group versus control group for the differences in healing rate with no heterogeneity ($I^2 = 0\%$, $p = 0.57$). The result was statistically significant in favor of APG therapy (RR 1.44, 95% CI: 1.32–1.57, $z = 8.50$, $p < 0.001$). Forest plot with the comparison of healing

Figure 5. (A) Meta regression showing the relationship of the duration of treatment and wound healing. (B) Meta regression showing the healing rate does not influence the wound healing.

Figure 6. Sensitivity analysis indicating obvious robustness of the results.

rate between APG therapy and control therapy is presented in Fig. 3.

Publication bias by funnel plot revealed an apparent asymmetry. Visual examination suggested the presence of a potential bias (Fig. 4). Furthermore, the publication bias also existed in Begg's test ($Z=3.22$, $p=0.001$) and Egger's test ($Z=3.22$, $p=0.001$).

Meta-regression demonstrated that effect size had no statistically significant association with the duration of treatment ($t=0.03$, $p=0.98$) (Fig. 5A) or healing rate ($t=-1.24$, $p=0.24$) (Fig. 5B). The results indicated that either duration of treatment or healing rate did not influence DF wound healing.

The leave-one-out sensitivity analysis was performed to analyze the repercussion of deleting the studies one by one in the meta-analysis. Details in Fig. 6 showed that the combined effect size of APG efficiency in DF wounds was not altered after omission (1.38; 95% CI: 1.26–1.54), indicating obvious robustness of the results.

Subgroup analysis by Wagner grade revealed APG was effective in the DF wounds in Wagner 1 (RR 1.10, 95% CI: 0.92–1.32), Wagner 2 (RR 1.36, 95% CI: 1.12–1.66), and Wagner 3 (RR 2.37, 95% CI: 1.45–3.88), respectively (Fig. 7A). Moreover, 14 studies were included in subgroup analysis for different countries (China or non-China). Ten were classified into the China group, and had an RR of 1.43 (95% CI: 1.30–1.57, $z=7.38$, $p<0.001$), and

four were classified into non-China group, and had an RR of 1.48 (95% CI: 1.23–1.77, $z=4.22$, $p<0.001$). The analysis of two subgroups demonstrated a statistically significant difference. The result is shown in Fig. 7B.

Secondary outcomes

Seven RCTs were identified to assess healing time. There was no significant statistical heterogeneity among the included studies; so a random-effects model was applied to estimate the APG group versus the control group ($I^2 = 51.5\%$, $p=0.036$). The result in Fig. 8 (WMD -10.75 days, 95% CI: -11.67 to 8.86 days, $z=14.34$, $p<0.001$) demonstrated a significant reduction in healing time with APG.

A total of four RCTs were included to evaluate adverse event rates. Fixed-effects model was used since the significant statistical heterogeneity was not indicated in the analysis ($I^2 = 0\%$, $p=0.731$). Compared with control therapy, APG therapy had fewer adverse events (RR 0.44, 95% CI: 0.25–0.76, $z=2.94$, $p=0.003$) (Fig. 9). However, the available data for adverse events were limited; more clinical trials are required to determine if there are adverse events related to treatment.

DISCUSSION

Our meta-analysis revealed the apparent conclusion that APG therapy has a positive efficacy on

Figure 7. (A1) Forest plot of the comparison between APG group and control for DF in Wagner 1 tends to support APG has a positive effect on DF wound healing. (A2) Forest plot of the comparison between APG and control groups for DF in Wagner 2 indicates APG has a positive effect on DF wound healing. (A3) Forest plot of the comparison between APG and control groups for DF in Wagner 3 supports APG has a positive effect on DF wound healing. (B1) Forest plot of the comparison between APG and control groups for DF in China indicates APG has a positive effect on DF wound healing. (B2) Forest plot of comparison between APG and control groups for DF in non-China indicates APG has a positive effect on DF wound healing. DF, diabetic foot; RR, risk ratio.

DF wounds; healing rate in APG group was higher than control group (85.8% vs. 57.4%). A review based on 6 studies had evaluated the use of platelet-rich plasma (PRP) on DF wounds by Picard *et al.*; 87.5% of included studies showed a significant benefit for the PRP to treat chronic DF wounds⁴²; however, they only performed a qualitative analysis on effectiveness of APG. Our studies systematically searched and included 15 RCTs to

conduct a quantitative analysis relatively. In addition, APG is a concentration of platelets in plasma and containing many platelet-released growth factors. A review regarding growth factors for DF wounds demonstrated that growth factors are associated with a higher healing rate (52.5% vs. 34.6%).⁴³ Martí-Carvajal *et al.* had reported that growth factors such as fibroblast growth factor (56.6% vs. 45.8%), epidermal growth factor (EGF)

Figure 8. Forest plot with the comparison of healing time between APG therapy and control therapy. Note: weights are from random effects analysis. WMD, weighted mean difference.

(86.3% vs. 50%), vascular endothelial growth factor (VEGF) (51.7% vs. 34.6%), and platelet-derived growth factors (64.3% vs. 25.9%) are beneficial for the healing of DF wounds.⁴³ Nevertheless, we consider APG to be a better option due to the fact that preparation of APG is more conventional and economical compared with growth factors.

APG can promote the healing of DF wounds, the probable mechanism as follows: the deficiency of

growth factors due to hyperglycemia and diabetic vascular and neural complications is considered a major factor for poor healing of DF wounds.⁴ (1) APG, which is derived from a patient's own blood contains cytokines, growth factors, chemokines, and fibrin scaffold.⁴⁴ (2) The mechanism of APG is beginning with α -granules degradation; various related growth factors, including PDGF, VEGF, transforming growth factor β (TGF- β), EGF, and

Figure 9. Forest plot with the comparison of adverse events between APG therapy and control therapy. Adverse events include infection, formication, or prickling sensation.

insulin-like growth factor (IGF), are considered essential for tissue repair.⁴⁵ (3) These growth factors are activated and released to stimulate wound healing. One of the possible pathways to promote healing is angiogenesis induction.⁴⁶ VEGF plays an important role in the induction of angiogenesis, inducing migration of endothelial cells.^{47,48} Other factors such as PDGF, TGF- β , and IGF have a significant effect on the angiogenesis as well.⁴⁹ (4) The process of healing can be accelerated due to new blood vessels maintaining blood supply and providing nutrition and oxygenation.⁵⁰ Moreover, it also can recruit macrophages and prevent infections.⁵¹

Healing rate increased as a whole; we also considered healing rate at different Wagner stages of DF wounds, we cannot extract data regarding healing rate at Wagner 4. Nagoba *et al.* had applied citric acid to different Wagner grades of DF; the results indicated that citric acid can promote healing of DF wounds in Wagner 1 (94.12%), Wagner 2 (94.23%), and Wagner 3 (86.21%). The results were consistent with our conclusion to some extent.⁵² However, too small sample sizes may lead to no statistical significance of APG in Wagner 1; in consideration of an RR of 1.10 (95% CI: 0.92–1.32), the result tends to support that APG is beneficial for DF wounds in Wagner 1. So, we concluded APG is beneficial for DF in Wagner 1–3 ultimately.

As the healing rate increased, the healing time decreased, our meta-analysis demonstrated (WMD –10.75 days, 95% CI: –11.67 to 8.86 days], $z = 14.34$, $p < 0.001$). Carter *et al.* had reported that PRP required fewer days compared with hyaluronic acid to complete wound healing (WMD –4.50, 95% CI: –17.0 to 8.0).⁵³ This conclusion is consistent with ours. It is generally acknowledged that the velocity of healing after 4 weeks of treatment determines the final velocity⁵⁴; DF wounds that cannot be controlled after 2–4 weeks of treatment are referred to refractory ulcer, and refractory ulcer will lead to amputation.⁵ In our meta-analysis, APG improved wounds in 4 weeks, and control therapy needed more time. Thus, we think APG can reduce the incidence of refractory ulcer or amputation.

In addition to higher healing rate and shorter healing time, APG therapy also had less adverse events (10.1% vs. 23.8%) in our meta-analysis. Carter *et al.* had performed a meta-analysis of 21 studies regarding use of APG on wound healing; they found APG is safer to wound healing by comparing APG with hyaluronic acid in four trials.⁵³ DF wounds also belong to wounds; based on this, our conclusion is certified to some extent. In many

other studies evaluating PRP or APG, there are no or few adverse events mentioned.^{55–57}

This meta-analysis has several limitations. First, based on the quality assessment, some included studies were of low quality, which could affect the results of meta-analysis, although they were not excluded. Second, the funnel plot revealed the significant publication bias. Since the studies we included were only English and Chinese literature, this may cause the bias. Third, compared with the primary outcome, there were relatively small studies for the secondary outcomes (seven studies for healing time and three for adverse events); this may make the conclusion lack data support and lead to potential bias. Fourth, the lack of long-term follow-up existed in some studies. In the process of follow-up, gradual decreasing differences in healing rates between APG group and control group may be detected. The increasing possibility of secondary hospitalization can also attribute to the deficiency of follow-up. Future studies should include more high-quality studies with comprehensive data.

The results of our meta-analysis indicate that application of APG can improve the healing rate, shorten the healing time, and decrease adverse events; APG therapy has a positive effect on DF wounds. The preparation of APG appears to be easy and safe; together with biological characteristics, APG is beneficial for clinical treatment. Furthermore, well-designed and high-quality studies are required to provide firmer evidence.

INNOVATION

In the treatment of DF wounds, APG can provide the necessary growth factors to facilitate wound healing. APG should be safe for topical administration as it is derived from a patient's own blood. Our meta-analysis indicates that application of APG can obviously improve the healing rate, shorten the healing time, and decrease the incidence of adverse events; APG therapy has a positive effect on DF wounds. The preparation of APG appears to be easy and safe; together with biological characteristics, APG is beneficial for clinical treatment.

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KEY FINDINGS

- APG can increase the healing rate of DF, and reduce the healing time and adverse events.
- APG has a positive effect on DF at different Wangers (1–3).
- APG can provide the necessary growth factors for DF wounds to improve healing.

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Abbreviations and Acronyms

APG	=	autologous platelet-rich gel
CI	=	confidence interval
DF	=	diabetic foot
EGF	=	epidermal growth factor
HBOT	=	hyperbaric oxygen therapy
IGF	=	insulin-like growth factor
MeSH	=	Medical Subject Headings
OR	=	odds ratio
PDGF	=	platelet-derived growth factor
PRP	=	platelet-rich plasma
RCTs	=	randomized controlled trials
RR	=	risk ratio
TGF- β	=	transforming growth factor β
VEGF	=	vascular endothelial growth factor
WMD	=	weighted mean difference