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Autologous platelet-rich plasma (APRP) in diabetes foot disease: a meta-analysis☆

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ABSTRACT

Introduction: This study will explore the effectiveness of autologous platelet-rich plasma in the treatment of diabetic foot disease compared to conventional treatments, based on the ulcer healing rate.
Methods: The electronic databases of PubMed, EMBASE, and WOS internet were searched. Evaluated outcome rate of complete ulcer healing. Statistical analysis was performed with RevMan 5.0 software and SPSS 25.0.
Results: Eleven RCTs with 828 patients were included in this study. The meta-analysis showed a higher complete ulcer healing rate (OR = 3.69, 95 % CI 2.62 to 5.20, $P < 0.01$, $I^2 = 0$ %) in growth factors based in autologous platelech-rich plasma (aPRP) group compared with control. Mixed evidence was seen for publication bias, but analyses by using the trim-and-fill method did not appreciably alter results.
Conclusion: Autologous platelet-rich plasma can improve the complete healing rate of the ulcer compared to current conventional treatments in diabetic foot ulcer patients.

1. Introduction

Diabetes mellitus (DM) has become a serious international health problem. Despite recent global efforts to address the DM pandemic, the diabetic population rate continues to rise, reaching 537 million in 2021. The projections are ambitious, but most countries are far from achieving the World Health Organisation's goal of a zero increase in prevalence by 2025.[1] By 2030, the International Diabetes Federation (IDF) estimates that one in every 9 adults will have DM, affecting a total population of 643 million.[2]

DM imposes a substantial economic burden on countries, health systems, people with DM and their families.[3] The global costs associated with DM have been increasing, rising from 232 billion dollars in 2007 to 966 billion dollars in 2021. This represents a 316 % increase in just 15 years. The IDF estimates that the total health expenditure related to DM will reach 1.03 trillion dollars by 2030 and 1.05 trillion dollars by 2045.[4–9]

Foot complications are one of the leading causes of hospitalisation in patients with DM, demanding prolonged stays.[10] Unfortunately, 15 % of the diabetic population will develop diabetic foot ulcers (DFU) during their disease,[11] with 25 % of them leading to lower limb amputation.[12,13] Lower limb amputations are performed at a frequency that is 15 times higher among diabetics compared to non-diabetic patients[14] and 83 % of lower limb amputations in diabetic patients are preceded by DFU.[15]

The current standard hospital treatments for patients with DFU include debridement, antibiotic administration, revascularisation and the use of offloading orthoses[16]. However, these treatments do not guarantee success in their closure.[17] Failure to achieve ulcer closure may be due to the lack of healing factors, such as platelet-derived growth factor (PDGF), or the absence or scarcity of vascular endothelial growth factor (VEGF), which is significantly diminished in DFU patients.[11]

Due to the decrease in growth factors, which are responsible for physiological healing processes, local therapies are being used to stimulate ulcer healing and closure. These include high-voltage pulsed current electrostimulation,[18] hyperbaric oxygen therapy,[19] vacuum-assisted closure[20] and treatments using specific growth factors such as granulocyte colony-stimulating factors, nerve growth factor, or the use

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of epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF).[11]

The process of ulcer healing in DFU patients is a complex mechanism that involves the integrated interface between molecular signals and different cells, such as platelets. In the presence of a diabetic wound, these platelets are activated by thrombin and platelet-rich plasma (aPRP) releases platelet-derived growth factors (PDGF), VEGF, EGF, insulin-like growth factor and transforming growth factor-beta (TGF-β).[21]

PRP is a blood derivative with a concentration of platelets that is four times higher than normal (1,000,000 platelets/μl). It is a highly efficient treatment considering its cost and effectiveness in the ability to stimulate cell proliferation and differentiation. Activated platelets regulate angiogenesis and cellular mitogenesis.[21] aPRP not only improves wound healing but also aids in skin tissue regeneration.[22]

Numerous clinical studies have demonstrated how growth factors based in aPRP acts in the healing of ulcers in DFU patients, but not many of them have been properly designed. Therefore, this review was conducted to address the hypothesis that "the use of aPRP growth factors as a treatment for ulcer closure in DFU patients leads to a higher success rate compared to conventional treatments".

2. Material and methods

This systematic review and meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard.[25] In addition, this systematic review and meta-analysis protocol was registered with the international prospective register of systematic reviews (PROSPERO) online database (PROSPERO Identifier: CRD42023423203).

2.1. Eligibility criteria

This meta-analysis was based on randomised controlled trials (RCTs) investigating the effect of growths factors based in aPRP versus conventional treatments for ulcer healing in DFU patients. Only human studies in English or Spanish were considered. Inclusion was not limited by the study size. Excluded publications included review articles, comments and studies that did not provide a measure of association. The results were reported following the guidelines of the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[25]

Articles were included in the meta-analysis if they met the following inclusion criteria: the study was an RCT; the target population was diagnosed with DFU; the intervention program was based on aPRP and control; and the study variable was the rate of DFU closure.

Exclusion criteria were as follows: studies that did not focus on comparing the effect of outcomes; language other than English or Spanish; and studies that did not provide quantitative results suitable for statistical analysis.

The following Population, Intervention, Control and Outcome (PICO) framework was used: P: Adult patients diagnosed with DFU with chronic ulcers; I: aPRP treatment; C: Conventional ulcer treatment; and O: Primary outcome: Rate of ulcer closure.

The objective of this review was to focus on the effect of aPRP treatment on ulcer healing in DFU patients. To identify the evidence, searches were conducted in the WoS, EMBASE and PubMed databases. The last search was conducted in May 2023. The search was performed using the keywords "Diabetic foot ulcer," "DFU," "platelet-rich plasma," and "PRP," using the Boolean operators "AND" and "OR".

2.2. Selection process, data collection and data list

The bibliographic management software Zotero v.6.0.26 was used for article selection, where two main independent reviewers (F.M.B and A.M.R) conducted a double-blind assessment of titles and abstracts (Cohen's kappa: 0.81) to determine whether each item met the inclusion criteria. In cases of doubt, the full text of the article was evaluated (Cohen's kappa: 0.88). Any disagreements were resolved through discussion and if a consensus could not be reached, the opinion of a third reviewer (M.R.M) was sought. It was also planned, if necessary, to email the original authors for further information on study details, but this measure was not needed. The main reviewers independently created two tables where they extracted data from the eligible articles: first author, year of publication, country of origin and sample size, as well as the method, results and conclusions of each article. Data were sought for any outcome related to the dependent variable under investigation, ulcer closure rate in diabetic foot, in the experimental group and control group. The assessment of bias risk for each article was conducted separately by the main reviewers using the tool recommended by the Collaboration with Cochrane.[26] In addition, the main reviewers conducted a methodological evaluation of the articles using the Critical Appraisal Skills Program in Spanish (CASPe), excluding any article that scored below 8 out of a total of 11 points.[27]

The statistical analysis was based on the dichotomous method, assuming either a fixed-effects or random-effects model to calculate the odds ratio (OR) with a 95 % confidence interval (CI = 95 %). The heterogeneity of the studies was assessed using the statistical parameter of heterogeneity I2, with a value ranging from 0 % to 100 %, where 0 % indicates no heterogeneity, 25 % indicates low heterogeneity, 50 % indicates moderate heterogeneity and $\geq$ 75 % indicates high heterogeneity.[28] If I2 was equal to or >50 %, a random-effects model would be assumed, while for a heterogeneity percentage below 50 %, a fixed-effects model would be chosen. A p-value <0.05 was considered statistically significant.[29] A sensitivity analysis was conducted by replicating the results of the meta-analysis, excluding one study included in the review at each step, to check whether the results obtained were similar in direction, effect size and statistical significance, indicating robustness of the analysis.[30] Publication bias was initially analysed qualitatively through visual examination of a funnel plot and the Egger's test[31] was performed to assess possible publication bias more accurately. If there was any statistically significant bias ($p > 0.1$), a "trim and fill" analysis[32] would be conducted to estimate the number of additional studies needed to eliminate publication bias and the new effect size would be compared to the previous one to assess for significant differences. The SPSS v.28 and RevMan v.5.3 software packages were used for calculations and statistical analysis.

3. Results

3.1. Study selection

The study selection process was presented using the PRISMA flow diagram (Fig. 1). Initially, a total of $n = 542$ articles were identified, resulting in a total of $n = 56$ articles for full-text reading and eligibility assessment. Finally, $n = 11$ articles were included in this review (Fig. 1. Diagram flow) These articles were assessed for risk of bias, with satisfactory results. Additionally, critical appraisal was conducted using the CASPe tool, indicating high methodological quality (Table 2).

The studies included a total of $n = 418$ individuals in the experimental group and $n = 410$ individuals in the control group, resulting in a total of $n = 828$ participants (Table 1).

The quality of the studies was assessed using the CASPe tool for critical reading of scientific evidence in the 11 clinical trials included in this review.[33–43] All studies passed the evaluation, with scores ranging from 10 to 11 out of a total of 11 points (Table 2), indicating high quality. No articles were rejected.[27]

The risk of bias assessment was conducted using the tool recommended by the Cochrane Collaboration, which identifies five types of bias with their respective domains: selection bias with four domains, performance bias and detection bias with one domain each, attrition bias with two domains and reporting bias with one domain[26] (Figs. 2 and

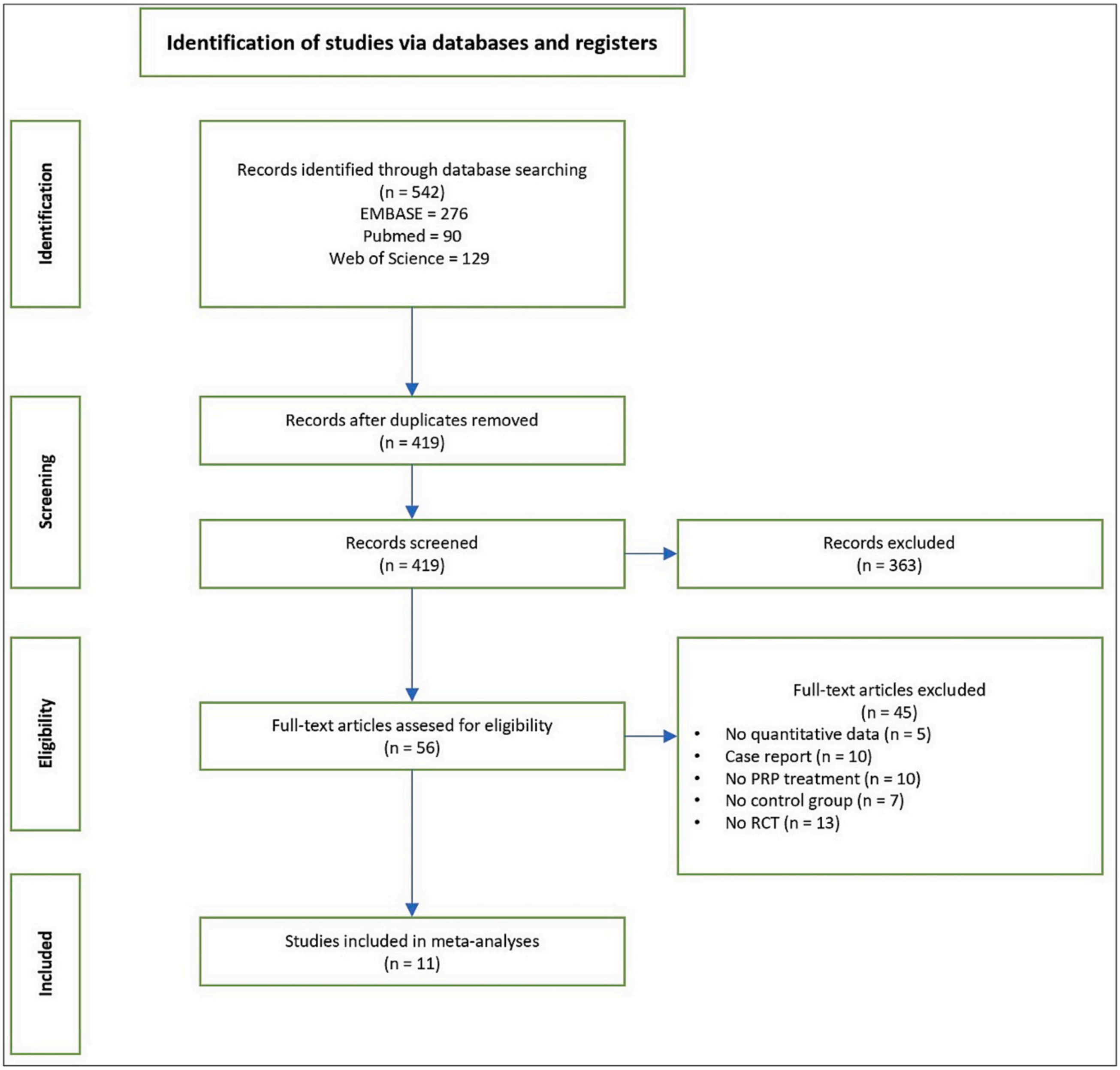


Fig. 1. PRISMA (2020) flowchart detailing information flow throughout the review process.

3).

The assessment of this tool allows analysis of the presence of a low risk of bias, high risk of bias, or unclear risk of bias in each domain. If there is incomplete information for analysis, it is considered an unclear risk of bias. In this study, an intervention was considered to have a low risk of bias when there was a low risk of bias in all key domains, an unclear risk of bias when there was a low risk of bias in one or more key domains and a high risk of bias when there was a high risk of bias in one or more key domains.

3.2. Results of individual studies

Among the 11 studies included,[33–43] Ullah[43] contributed the most to the analysis, with 23.9 % of the total weight, while the article by Elsaid[35] contributed the least, with 1.2 %. As it is an analysis of dichotomous data, the Odds Ratio was used to calculate the effect size, considering the number of cases with ulcer closure and the sample size in each group. The overall odds ratio was 3.69 [2.62, 5.20], favouring the experimental group. In other words, there is 3.69 times greater likelihood of ulcer healing in DFUs if the closure of the ulcer occurs randomly with conventional treatment. The heterogeneity test yielded an index where the I2 value was 0 %, indicating a lack of heterogeneity among the effects calculated from the 11 studies. Assuming a fixed-effects model, we can conclude that there are no differences between the effects estimated by these studies (Table 3). The sensitivity analysis confirmed the robustness of the study findings in terms of direction, statistical significance and effect size (Table 4).

The publication bias was visually assessed using a funnel plot (Fig. 4), which indicated a slight publication bias due to the absence of studies in the lower-left area of the effect size line (1.326, SE = 0.1729; $p < 0.001$; CI[0.987, 1.665]) (Table 5). To further investigate this bias, the Egger's test[31] was conducted, resulting in an intercept coefficient of 0.52 (which is close to zero) with a p-value >0.1 (Table 6). As the next step, a trim and fill analysis was performed to estimate the number of additional studies required (Table 6). The trim and fill analysis suggested the need for 4 additional studies and, after their inclusion, the adjusted

Table 1
Summary of individual trials, by intervention strategy.

First author, year of publication	Country	Total	Time treatment	Treatment strategy	Ulcer classification	PRP preparation	PRP application	Healing rate	Conclusions
A. El-Mabood,[33] 2018	Egypt	80	12 weeks	aPRP vs SOC	Nonhealing wounds on feet, persistent wound for 3–6 months, wound size of the foot ranging from 6.5 to 8.5 cm 2.	First whole blood centrifuge at ×300 *g* for 5 min at 18 °C.	Sprayed with PRP around the wound edges (subdermal) and the floor (if deep). Dressing was performed and lifted for 1 week until a follow-up session. Reinjection was performed after 2 weeks.	CG = 82.5 % EG = 97.5 %	aPRP is more effective with fewer complications, less infection, exudates, pain, and failed healing.
S. Essa,[34] 2023	Saudi Arabia	80	12 weeks	aPRP gel vs SOC	Wagner type I or II ulcers.	Whole blood is collected and anticoagulated with citrate dextrose solution. 60 ml of anticoagulated blood is centrifuged. Glass fibers and Ca2+ added in order to start clotting.	PRP was applied directly to the ulcer after cleaning with a surgical soap solution then covered with a conventional dressing. The frequency of dressing change was every 72 h. The dressing was done for up to 12 weeks or stopped if the ulcer healed.	CG = 75 % EG = 90 %	SilvrSTAT Gel a(PRP gel) is effective in the treatment of DFU.
A. Elsaid,[35] 2020	Egypt	24	20 weeks	aPRP gel vs SOC	Non-infected chronic foot ulcer confined to one anatomical site. Chronicity was defined as non-healing ulcer for 12 or more weeks.	20 ml venous blood. First centrifugation at 3600 rounds/min. Second at 2400 rounds/min. Total time 30 min.	PRP gel was applied and was covered with Vaseline gauze, few layers of sterile gauze, and non-compressible bandage. This was repeated twice weekly. The dressing protocol was applied for 20 weeks or until complete healing of the ulcer occurred.	CG = 0 % EG = 25 %.	aPRP gel resulted in a more significant reduction in the size of the ulcer.
L. Li,[36] 2015	China	103	12 weeks	aPRP vs SOC	Wagner type II or III ulcers.	20-100 ml venous blood. First centrifugation at 313 *g* (4 min). Second at 2400 rounds/min. Total time 30 min.	Suile dressing and bandages were changed every 3 days, wound area reduction rates did not reach 80 % or higher, or left wound areas were larger than 1 cm^2, 2 weeks after APG application.	CG = 67.3 % EG = 69.0 %	aPRP gel application plus standard treatment, compared with standard treatment.
A. Goda,[37] 2018	Egypt	50	12 weeks	aPRP vs SOC	Texas Diabetic Foot Classification: grade IA or grade IC.	20 ml of venous blood. First centrifugation at 1000 rpm (7–10 min). Second centrifugated at 1252 g (6 min).	PRP was applied to the ulcer followed by Vaseline gauze and then sterile dressing. The frequency of change of dressing was twice weekly. The dressing protocol was performed for up to 12 weeks or stopped whenever healing occurred.	CG = 49 % EG = 66 %	Autologous PRP is effective and safe for treatment of diabetic foot ulcer
G. Saldalamacchia,[38] 2004	Italy	14	5 weeks	aPRP vs SOC	Wagner type II or III ulcers.	NC	Weekly topical application of PRP gel with covered with standard dressing changed weekly.	CG = 29 % EG = 71 %	The effectiveness of aPRP is unequivocally established.
M. Ahmed,[39] 2017	Egypt	56	12 weeks	aPRP gel vs SOC	Texas Diabetic Foot Classification: IA, IIA, IC, IIC	20 ml of venous blood. First centrifugation at 1500 rpm (5 min). Second centrifugation at 3500 rpm (5 min).	PRP gel applied on the wound after being washed with 0.9 % normal saline solution and covered with sterile non-absorbing dressing.	CG = 68 % EG = 86 %	aPRP gel is more effective than the local antiseptic dressing in terms of healing rate and prevention of infection in clean diabetic ulcers.
A. Ullah,[43] 2022	Pakistan	160	12 weeks	aPRP vs SOC	Wagner classification.	5 ml venous blood. First centrifugation at high velocity. Second centrifugation at high velocity.	EG received three injections (1 ml/1 cm^2) around the edges of the wound and the base of the ulcer. Each being two weeks apart.	CG = 46.35 % EG = 80.00 %	aPRP was significantly better than conventional dressing in the management of diabetic foot ulcer.
X. Liao,[42] 2019	China	60	3 weeks	aPRP vs SOC	Refractory foot ulcers had been treated for >6 months.	60 ml venous blood. First centrifugated at 400 g (10 min). Second centrifugated at 1200 g (20 min).	PRP injected into the wound surface. Was wet coated with a wet gauze and dressed. Wound healing was observed every other day, and the wound dressing was changed.	CG = 44.0 % EG = 92.9 %	aPRP is an effective, safe adjuvant treatment for chronic wounds.
W. Gude,[40] 2019	Mexico	129	12 weeks	aPRP gel vs SOC	Wagner type II or III ulcers.	5–20 ml venous blood. First centrifugation (1 min). Second centrifugation inverted (15-30sg).	Two Aurix applications in each of the first 2 weeks of treatment followed by one application every week thereafter for 12 weeks.	CG = 30.2 % EG = 48.5 %	The effectiveness of Aurix (aPRP gel) is unequivocally established.
N. Kontopodis,[41] 2016	Greece	72	24 months	aPRP vs SOC	Texas Diabetic Foot Classification: IC.	Venous blood. First centrifugation at 3000 rpm (8 min). Second centrifugation at 3000 rpm (3–5 min).	PRP placed on the bed of the ulcer using a sterile syringe, 2/weeks for 16 weeks. Area was covered with a moist saline gauze dressing.	CG = 56 % EG = 83 %	aPRP useful adjunct during management of DFU.

CG = control group, EG = experimental group, PRP = platelech-rich plasma, DFU = diabetic foot ulcer, HR = Healing rate, SOC = Standard of care. min = minutes. G = grams, rpm = revolutions per minute, ml = millilitres, cm = centimetres, NC = Not Clear. sg = seconds

CG = control group, EG = experimental group, aPRP = autologous platelech-rich plasma, DFU = diabetic foot ulcer, HR = Healing rate, SOC = Standard of care, min = minutes. G = grams. RPM = revolutions per minute, ml = millilitres, cm = centimetres, NC = Not Clear. sg = seconds.

Table 2
Points table by CASPe tool for critical reading of scientific evidence.

Ref	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	T
E. Elsaid[35]	YES	YES	YES	–	YES	YES	YES	YES	YES	YES	YES	10/11
A.Goda[37]	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	11/11
A. Ulahh[43]	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	10/11
El-Mabood[33]	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	10/11
G. Saldalamacchia[38]	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	10/11
L. Li[36]	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	10/11
M. Ahmed[39]	YES	YES	YES	–	YES	YES	YES	YES	YES	YES	YES	10/11
N. Kontopodis[41]	YES	YES	YES	–	YES	YES	YES	YES	YES	YES	YES	10/11
S. Essa[34]	YES	YES	YES	–	YES	YES	YES	YES	YES	YES	YES	10/11
W. Gude[40]	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	10/11
X. Liao[42]	YES	YES	YES	–	YES	YES	YES	YES	YES	YES	YES	10/11

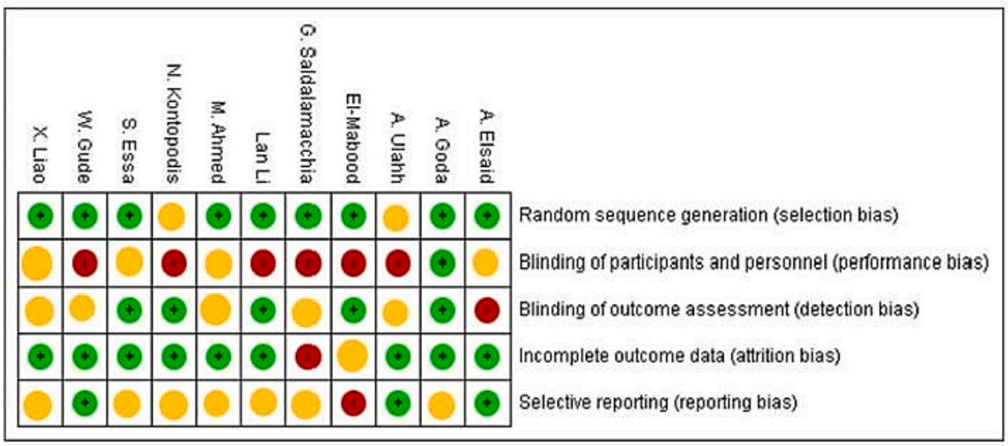


Fig. 2. Risk assessment.

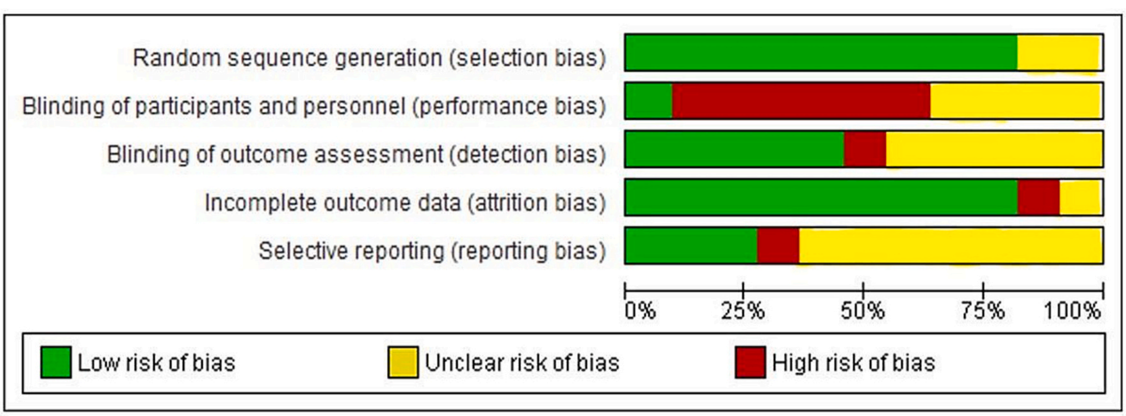


Fig. 3. Risk assessment (cont.).

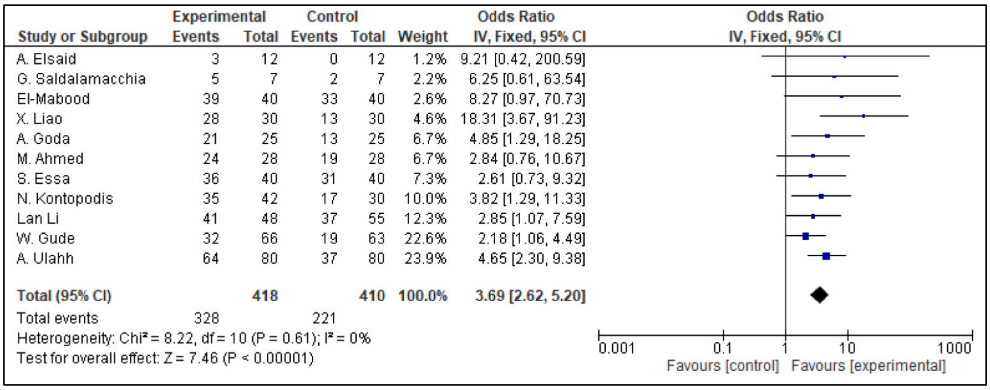
effect size became 1.152 (SE = 1.611; $p > 0.001$; CI[0.386, 1.468]). This new effect size is very similar to the previous one (1.326 ± 0.1729 to 1.152 ± 0.1611) and remains statistically significant ($p > 0.001$) (Table 5).

4. Discussion

The aim of this meta-analysis was to compare the ulcer healing rates in patients with DFUs between aPRP and current conventional treatments. DFUs are one of the most common risk factors for morbidity and mortality worldwide, leading to complex and long-term treatments, which also result in significant healthcare costs.[44] Ulcers in this population often develop due to minor trauma or infection.[45] The problem of non-healing ulcers is attributed to the lack of growth factors that promote physiological wound healing and the inflammatory imbalance occurring in the wound bed.[46] Currently, novel treatments are being developed to reverse and regulate the mechanisms of ulcer and wound healing.[47]

Researchers have found that platelets, in addition to their haemostatic properties, can release numerous growth factors and cytokines, thus playing a key role in tissue regeneration and wound healing. aPRP-based treatments, derived from platelets, are easy to obtain and prepare and have demonstrated efficacy in the healing of chronic wounds. This plasma primarily contains platelets, fibrin, growth factors, cytokines and leukocytes, possessing anti-infective properties and immunomodulatory agents.[48] Furthermore, leukocytes contribute to the release of growth

Table 3
Results of individual studies.



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
A. Elsaid	3	12	0	12	1.2%	9.21 [0.42, 200.59]
G. Saldalamacchia	5	7	2	7	2.2%	6.25 [0.61, 63.54]
El-Mabood	39	40	33	40	2.6%	8.27 [0.97, 70.73]
X. Liao	28	30	13	30	4.6%	18.31 [3.67, 91.23]
A. Goda	21	25	13	25	6.7%	4.85 [1.29, 18.25]
M. Ahmed	24	28	19	28	6.7%	2.84 [0.76, 10.67]
S. Essa	36	40	31	40	7.3%	2.61 [0.73, 9.32]
N. Kontopodis	35	42	17	30	10.0%	3.82 [1.29, 11.33]
Lan Li	41	48	37	55	12.3%	2.85 [1.07, 7.59]
W. Gude	32	66	19	63	22.6%	2.18 [1.06, 4.49]
A. Ulahh	64	80	37	80	23.9%	4.65 [2.30, 9.38]
Total (95% CI)		**418**		**410**	**100.0%**	**3.69 [2.62, 5.20]**
Total events	328		221			

Heterogeneity: Chi² = 8.22, df = 10 (P = 0.61); I² = 0%
Test for overall effect: Z = 7.46 (P < 0.00001)

Table 4
Sensitivity analysis.

Discarded study	OR (M-H, Fixed, 95 % CI)	Chi2	df	I2	Z
A. Elsaid, 2020	3.77 [2.69, 5.29]	7.91	9 (*P* = 0.54)	0 %	7.67 (*P* < 0.00001)
G. Saldalamacchia, 2004	3.79 [2.69, 5.32]	8.06	9 (*P* = 0.053)	0 %	7.66 (*P* < 0.00001)
A. El-Mabood, 2018	3.72 [2.64, 5.24]	7.69	9 (*P* = 0.57)	0 %	7.54 (*P* < 0.00001)
X. Liao, 2019	3.47 [2.45, 4.92]	4.23	9 (*p* = 0.90)	0 %	7.00 (P < 0.00001)
A. Goda, 2018	3.76 [2.66, 5.33]	8.09	9 (*P* = 0.52)	0 %	7.46 (P < 0.00001)
M. Ahmed, 2017	3.90 [2.76, 5.53]	8.10	9 (p = 0.52)	0 %	7.66 (P < 0.00001)
S. Essa, 2023	3.94 [2.78, 5.58]	7.96	9 (p = 0.54)	0 %	7.69 (P < 0.00001)
N. Kontopodis, 2016	3.82 [2.68, 5.45]	8.26	9 (*p* = 0.51)	0 %	7.42 (*P* < 0.00001)
L. Li, 2015	3.98 [2.78, 5.70]	7.96	9 (P = 0.54)	0 %	7.55 (P < 0.00001)
A. Ullah, 2022	3.61 [2.46, 5.30]	7.74	9 (*P* = 0.56)	0 %	6.56 (P < 0.00001)
W. Gude, 2019	4.45 [3.03, 6.54]	5.61	9 (*P* = 0.78)	0 %	7.62 (P < 0.00001)

factors acting as transforming growth factors, as well as the production of vascular and endothelial growth factors.[49] When aPRP is uniformly applied to a wound or ulcer, the high concentrations of growth factors help to regulate the wound healing process. Through their activation, platelets release active antimicrobial peptides to combat infection.[11]

The 11 studies included in this meta-analysis[33–43] recruited a total of 828 patients diagnosed with DFU, with 418 patients treated with aPRP and 410 patients treated with conventional treatments. The use of aPRP resulted in significantly higher rates of complete wound healing compared to conventional treatments (3.69 times higher odds of healing in the experimental group). However, caution should be exercised when interpreting the results due to the limited sample size in some of the studies. It is recommended to update this study as more research becomes available to further confirm these findings. A slight publication bias was observed, but its influence on effect size and confidence intervals was minimal. The *p*-values remained statistically significant both in the initial analysis and when including additional studies. Previous meta-analyses have also demonstrated the efficacy of aPRP treatments for DFU ulcers. Dai[50] included 10 randomised clinical trials with a total of 456 participants, showing positive results for aPRP compared to conventional treatments. Del Pino-Sedeño[51] conducted a review and meta-analysis, including 8 randomised clinical trials and 2 prospective longitudinal observational studies, concluding that aPRP treatment should be considered for DFU. Yan[52] performed a meta-analysis with 11 randomised clinical trials involving 829 participants, comparing aPRP with conventional topical treatments, and similarly concluded that aPRP is safe and more effective than conventional treatments for diabetic ulcers. Regarding assessment of the risk of bias, the blinding of participants and personnel domain was compromised with a high risk of bias due to the absence of blinding in 6 out of the 11 trials.[33,36,38,40,41,43] Blinding is a condition imposed on a specific procedure to preserve the knowledge of the assigned treatment, the course of the treatment, or previous observations.[53] This should be considered in future studies as the number of clinical trials increases and it could be an inclusion criterion for future meta-analyses and reviews. The lack of blinding in participants in clinical trials can introduce biases in physiological responses (depending on the intervention group), including treatment adherence, as well as potential loss to follow-up.[54] On the other hand, the lack of blinding of the research personnel could impact the differential administration of co-interventions, the possibility of adjusting doses, or even the potential to encourage or discourage differential adherence to the study.[55]

In this meta-analysis, the selected outcome variable was the ulcer closure rate, as it is currently the most reliable variable for evaluation. Closure rate, along with the reduction in ulcer surface area, are two commonly used variables for reporting the outcomes of aPRP treatments in ulcer closure.[56] However, the assessment based on ulcer surface measurement is highly controversial due to the absence of depth and the lack of consensus on the technique to be used for surface measurement.[57]

The treatment duration in the included studies ranged from several weeks, except for the 24-month study, indicating that the results can be observed between 3 weeks and 20 weeks of treatment. However, further studies are needed to investigate the progression of these healed ulcers over time and to assess potential adverse effects that may occur outside the treatment and observation periods of the included studies.

Regarding the classification of diabetic foot lesions 5 studies[34,36,38,40,43] classified ulcers based on the Wagner Scale.[58] One of them was based on patients with type I and/or II ulcers. The remaining studies used patients with type II and/or III ulcers for treatment. The University of Texas Staging System for Diabetic Foot Ulcers[59] was used in three studies,[37,39,41] ranging from type 1 A to 2C ulcers, the largest sample being patients with type 1 A and/or 1C ulcers. Three articles[33,35,42] do not show which classification system they use.

Considering that for ulcers type I, II and/or III (Wagner scale), or 1 A and/or 1C (Texas staging system) aPRP was superior in complete healing rates, it could be stated that it hypothetically works in: Grade 1 (Wagner scale): Superficial ulceration, but without penetration to

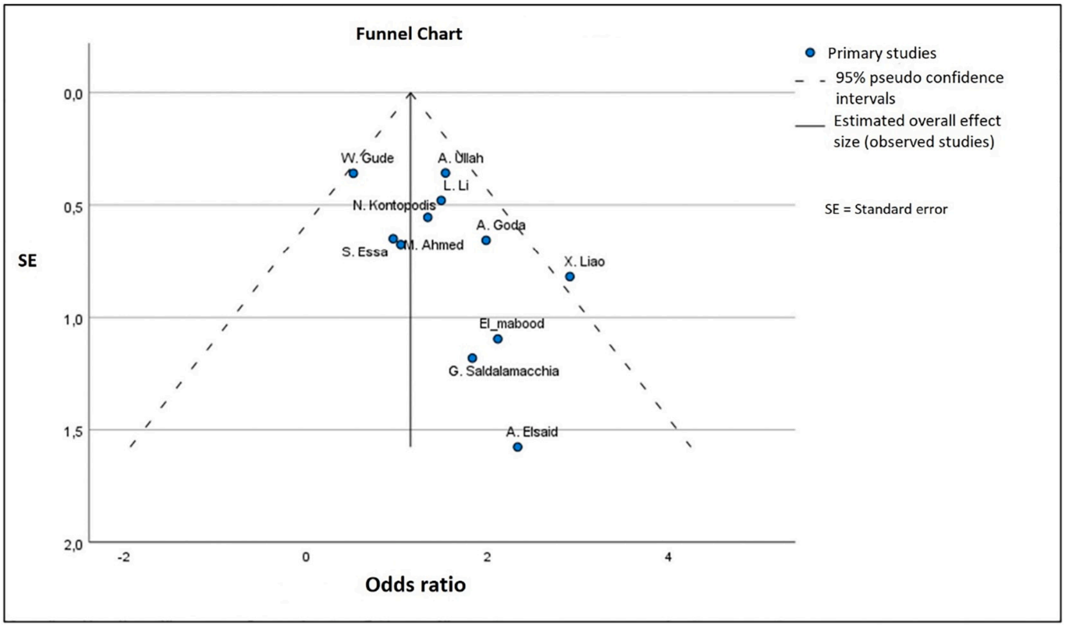


Fig. 4. Publication bias analysis.

Table 5
Size-effect calculation for trim and fill analysis.

	N°	Effect size	SE	Z	Sig.	C.I. 95 %	
						Lower	Upper
Observed	11	1.326	0.1729	7.670	<0.001	0,987	1.665
Observed + Imputed[a]	15	1.152	0.1611	7.148	<0.001	0,836	1.468

[a] Total imputated studies: 4; SE = Standard error.

deeper tissue. Grade 2 (Wagner scale): Deeper extension into tendon, bones, or joint capsule, which may be exposed. Grade 3 (Wagner scale): Presence of tendonitis, osteomyelitis, cellulitis, or deeper tissue abscess. 1 A (Texas staging system): Superficial wound, no penetration. 1C (Texas staging system): With ischemia.

Due to the absence of information on diabetic foot ulcers with signs of gangrene, we cannot state that aPRP is effective in higher levels of diabetic ulcer classification, beyond grade 3 (Wagner scale) or 1C (Texas staging system).

None of the selected articles show results on recurrence rate. A review and meta-analysis on recurrence rate could be a complementary opportunity to our study.

5. Conclusions

The findings of this study, incorporating more recent studies, align with previous meta-analyses and reviews, supporting the conclusion that current growth factors based in aPRP treatments can be considered the first choice for addressing ulcer closure and healing in patients with DFU. These treatments significantly increase the ulcer healing rate compared to existing conventional treatments. In conclusion, the use of this type of growth factors (aPRP) as a treatment for ulcer closure in patients with DFU demonstrates a higher success rate compared to conventional treatments.

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Table 6
Egger's regression-based test[a].

Parameter	Coefficient	Standard error	Z	Sig. (bilateral)	95 % confidence interval	
					Lower	Upper
(Intersection)	0.521	0.3596	1.450	0.147	−0.184	1226
SE[c]	0.000	.	.	.	.	.
A. Elsaid	1.810	1.6164	1.120	0.263	−1.358	4.978
G. Saldalamacchia	1.311	1.2367	1.060	0.289	−1.113	3.735
El_mabood	1.592	1.1524	1.381	0.167	−0.667	3.850
X. Liao	2.386	0.8949	2.666	0.008	0.632	4.140
A. Goda	1.462	0.7480	1.955	0.051	−0.004	2.928
M. Ahmed	0.523	0.7647	0.684	0.494	−0.976	2.022
S. Essa	0.439	0.7419	0.592	0.554	−1.015	1893
N. Kontopodis	0.820	0.6607	1.241	0.215	−0.475	2.115
L. Li	0.968	0.5994	1.614	0.106	−0.207	2.143
A. Ullah	1.015	0.5077	2.000	0.046	0.020	2.010
W. Gude	0[b]	.	.	.	.	.

[a] Meta-regression of fixed effects.
[b] This parameter is set to zero because it is redundant.
[c] Standard error of effect size.

CRediT authorship contribution statement

Maria Ruiz-Muñoz: Validation, Supervision, Methodology. **Francisco-Javier Martinez-Barrios:** Software, Project administration, Methodology, Formal analysis, Conceptualization. **Raul Fernandez-Torres:** Methodology. **Eva Lopezosa-Reca:** Supervision, Methodology. **Ana Marchena-Rodriguez:** Supervision, Methodology.

Declaration of competing interest

None.

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