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*Review Article*

# A systematic review and meta-analysis of treatment modalities and their impact on the healing progression of diabetic foot ulcers

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**Abstract:** Background: The diabetic foot ulcer (DFU) is a common and serious complication of diabetes mellitus, which occurs in 15-25% of diabetic patients at some point in their lives. However, most of the Diabetic foot ulcers (DFUs) do not heal with conventional methods of wound care and progress to become chronic, non-healing ulcers with high morbidity, mortality, and economic stakes. Some of the recent techniques in the management of ulcers include Systemic Hyperbaric Oxygen Therapy (s-HBOT), Platelet-Rich Plasma (PRP), Vacuum-Assisted Closure (VAC) Therapy, and Negative Pressure Wound Therapy (NPWT) that aim at improving the ulcer healing rate and minimize the risks of amputation. Objective: This work intends to conduct a comprehensive meta-analysis of the effectiveness, healing time and effect on amputation of these advanced treatment modalities on management of DFUs. Methods: The present study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for the reporting of systematic reviews and meta-analysis of randomized controlled trials. Information was obtained from 10 researches that considered different types of DFU treatment. The major end-points studied were rates of ulcer healing, time to heal and frequency of lower extremity amputations. The meta-analysis was conducted using R statistical software and the synthesis of results was done using forest and funnel plots. Results: The pooled analysis showed that NPWT significantly improved ulcer healing rates (OR = 2.07, 95% CI: 1.09-3.05) and reduced time to healing (Mean Diff = -22 days, 95% CI: -41.60 to -2.40). HBOT, particularly s-HBOT, demonstrated a substantial reduction in amputation rates (OR = 0.08, 95% CI: -0.11-0.28). PRP also showed promise, especially in reducing healing time (Mean Diff = -25 days, 95% CI: -34.80 to -15.20), though with more variability across studies. Conclusion: The results of NPWT were found to be significantly superior for ulcer closure and reduced healing time making it the treatment of choice for DFUs. Compared to controls, both HBOT and s-HBOT were strikingly effective in averting amputations. PRP had the possibility of being used as supplementary treatment especially in treatment with regard to the aspect of promotion of healing. Collectively, these results suggest that it is possible to use such advanced therapies to enhance the treatment of DFU; however, more effort is required to refine the protocols of such therapies and determine the sources of a differential response.

**Keywords:** Diabetic foot ulcers (DFU), negative pressure wound therapy (NPWT), hyperbaric oxygen therapy (HBOT), platelet-rich plasma (PRP), vacuum-assisted closure (VAC) therapy, meta-analysis, wound healing, amputation

## Introduction

Diabetic foot ulcers (DFUs) is one of the most chronic and disabling of the diabetes mellitus complications, with the prevalence of 15-25% of diabetic patients developing the ulcer during their lifetime [1, 2]. The non-healing ulcer commonly occurs due to neuropathy, peripheral vascular disease and impaired immunity, which makes even the slightest of the injuries to become a chronic non-healing ulcer [3]. DFUs are attended by substantial morbidity and mortality as well as presenting a substantial economic burden to healthcare systems globally [4]. These patients are more prone to infections, and if ulcers are left untreated or inadequately treated, then the patient is at risk for developing additional problems such as gangrene, osteomyelitis, and ultimately, amputation of the lower limbs [5]. About 85% of diabe-

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tes patients who end up losing their limbs have their ultra first, meaning that proper wound care is crucial [6].

In the past few decades, several modalities of treatment have been devised and applied to treat diabetic foot ulcers with a view to preventing the complications arising out of the same and the requirement of amputations [7]. Conventional practices of wound care including debridements, off loading, and infection control are still the fundamentals of DFU management [8]. However, due to high prevalence of non-healing ulcers even with the use of these measures, new therapies intended to augment the process of wound healing have been sought [9]. From among these therapies, Systemic Hyperbaric Oxygen Therapy (s-HBOT), Platelet-Rich Plasma (PRP), Vacuum-Assisted Closure (VAC) therapy, and Negative Pressure Wound Therapy (NPWT) have progressively turned out to be promising ones [9]. All these modalities provide a distinct mode of action that is targeted at managing the pathophysiologic burdens of DFUs, including ischemia, inflammation, and impaired granulation tissue formation [10].

s-HBOT is based on the treatment with hyperbaric oxygen providing a higher concentration of oxygen dissolved in the blood plasma that promotes tissue oxygenation, neoangiogenesis, and immunomodulation, for example, in case of ischemic ulcers [11]. It specifically involves autologous PRP where the growth factors and cytokines that are involved in tissue repair are utilised in order to enhance the healing process [12]. VAC Therapy and NPWT are two different techniques that involve the use of negative pressure on the wound site, which is helpful in contracting the wound, to help in removal of wound exudates, in reducing the number of bacteria present in the wound, and in promoting granulation tissue formation [13]. Although, these therapies have only been proved effective in clinical trials, there is dearth of information on comparative efficacy of these therapies for clinicians to effectively choose the best therapy for a given patient [14].

Since the diabetic foot ulcer is a pivotal determinant of the overall prognosis of diabetic patients and health system burden, this work is essential in its objective to provide a comprehensive and structured analysis and comparison of the effectiveness of innovative treatment approaches to DFUs. Through this approach of meta-analysis of the randomized controlled trials, this study aims at coming up with a clear picture of some of the best practices that should be adopted so as to enhance healing of ulcers and at the same time reducing the rate of complications like amputations. The outcomes of this study will provide useful recommendations for clinical practice and improve the quality of care given to patients with diabetic foot ulcers with a view of decreasing the prevalence of this devastating disease.

## Objectives

1. To systematically review and compare the efficacy of s-HBOT, PRP therapy, VAC Therapy, and NPWT in the treatment of diabetic foot ulcers. 2. To assess the impact of these treatment modalities on ulcer healing rates, time to healing, and the incidence of lower extremity amputations.

## Methodology

### *Search strategy*

The present systematic review and meta-analysis have been prepared following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. To this end, a systematic search approach was used to retrieve studies that assessed the treatment outcomes of various modalities of DFUs. Potentially relevant studies were identified using several electronic databases such as PubMed, MEDLINE, Embase, and the Cochrane Library. The search terms used included MeSH terms, including 'diabetic foot ulcer', 'Negative Pressure Wound Therapy', 'Platelet-Rich Plasma', 'Hyperbaric Oxygen Therapy', 'Vacuum-Assisted Closure Therapy' and 'randomized controlled trial', 'RCT'. The analysis is based on studies published in English only and includes articles from the beginning of recorded literature up to the present. To add further studies that might have been missed in the search, references of the included studies and other review articles were manually scanned.

### *Inclusion and exclusion criteria*

Inclusion criteria: 1. Studies evaluated the efficacy of treatment modalities for diabetic foot ulcers. 2. Randomized controlled trials (RCTs).

3. Studies published in English. 4. Studies involving adult patients (≥18 years) diagnosed diabetic foot ulcers. 5. Studies reporting clinical outcomes such as ulcer healing rates, time to healing, and amputation rates.

Exclusion criteria: 1. Non-randomized studies, observational studies, case reports, and reviews. 2. Studies involving non-diabetic foot ulcers or other types of wounds. 3. Studies not reporting clinical outcomes of interest. 4. Studies with incomplete or insufficient data for analysis. 5. Duplicates of previously published studies.

*Study screening*

The initial input for the searches was done in an electronic reference management software where the records were de-duplicated. The titles and abstracts of the studies that met the inclusion criteria were then independently reviewed by two investigators. A list of such studies was created and those that seemed to meet the criteria or those with insufficient information in the abstract were reviewed in full text. In case of any conflict of opinion between the two reviewers during the screening process, then the conflict was discussed and settled, or else a third reviewer was consulted. Based on the criteria of the systematic review and meta-analysis, the full-text articles of the potentially eligible studies were obtained and reviewed in order to determine their suitability for the review.

*Data extraction*

Data extraction was done manually by two researchers using a data extraction form that has been developed. Information extracted was on the study title, authors, year of publication, study type, number of participants, characteristics of participants, treatment regimes used, control interventions, clinical assessment (for example, ulcer healing rates, time to healing and amputation rates) and side effects reported. Where a study included more than one treatment arm, data from each of the arms were extracted separately. The extracted data were then verified for their credibility and inter-observer reliability, by discussion between the reviewers to sort out the differences.

*Data synthesis*

The data extracted were analyzed using R statistical software, which is preferred for the conduct of meta-analysis. The primary outcome measures such as the proportion of ulcers healed, time to healing and amputation rates were reported using simple statistics. For the studies reporting similar outcomes, meta-analysis was done to calculate the overall effect size. Heterogeneity across the studies was evaluated using the $I^2$ statistic which estimates the percentage of the total variability in effect estimates that is attributable to heterogeneity rather than sampling error. To control for the possible variation between the studies, a random effects model was used.

For the meta-analysis, odds ratios (ORs) and their 95% confidence intervals (CIs) were obtained for dichotomous outcomes including proportion of ulcers healed and amputation rates. Where outcomes were measured on a continuous scale, including time to healing, WMDs or SMDs were used if data were available. The forest plots were created to show the pooled effect size and the studies' estimates values. There was also a sensitivity analyses done to determine the validity of the results and a funnel plot used to determine presence or otherwise of publication bias.

## Results

The search process across different databases yielded a total of 350 studies, after the removel of duplicates and applying the inclusion and the exclusion criteria a total of 10 studies are included in this systematic review and meta analysis that evaluate the effectiveness of different treatment approaches in managing DFUs. **Figure 1** represents the PRISMA flow chart diagram of the selection process of included studies. These studies also differed in sample size, study type and design and the kind of treatments that were under consideration. The treatment modalities that were discussed in this review were s-HBOT, PRP, VAC Therapy, and NPWT. The studies compared were undertaken between 1996 and 2021 and involved 18-342 participants with a diagnosed DFU at different stages of severity. **Table 1** represents the detailed study characteristics of included studies.

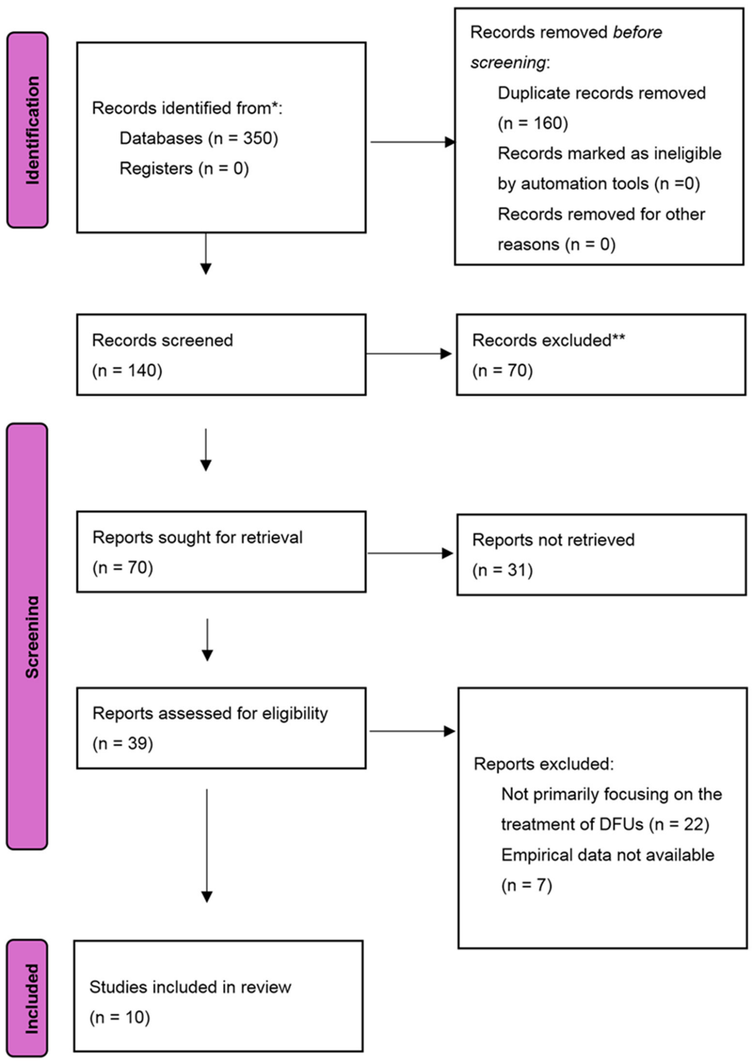


**Figure 1.** PRISMA Flow diagram of included studies.

*Systemic Hyperbaric Oxygen Therapy (s-HBOT)*

There were two major works on the s-HBOT. The first one was performed by Faglia et al. in 1996 [15] with 70 patients with type 2 diabetes and with severe, mainly ischemic, foot ulcers. Major amputation rates were significantly lower in the s-HBOT group compared to the control group. In particular, the frequency of major amputations was significantly lower in the s-HBOT group and constituted only 9% in contrast to the control group with 33%. In addition, patients in the s-HBOT group had better TcPo2 since this is an important factor in affecting the ulcerated tissue and promoting wound healing. Consequently, the outcomes of the study showed lower odds of major amputation in the s-HBOT group with an OR of 0. 084 (P = 0. 033) which shows that s-HBOT is very effective in severe DFU cases.

The second study by Abidia et al. [16] included 18 diabetic patients with ischemic lower extremity ulcers in which s-HBOT was compared to pressurized air as a control. The results were quite dramatic; 100 percent of the patients in the s-HBOT group was completely ulcer-free at six weeks compared with only 37 percent of the patients in the control group. Also, the reduction in wound size was as follows; s-HBOT 100% and control 52% with *P* value <0. 05. These outcomes highlighted the existing prospects of s-HBOT for the improvement of healing in ischemic pathologies with critical diminishments of blood flow and oxygen supply.

*Platelet-Rich Plasma (PRP) therapy*

Another modality that was investigated in many of the included studies was the PRP. Driver et al. [17] conducted an RCT in the year 2006 in which 72 patients with non healing diabetic foot ulcers participated. This study was based on autologous PRP gel and compared it with a saline gel which was taken as a control. The findings were encouraging; the patients in the PRP group had a much higher healing rate with 68 percent of the patients, displaying complete ulcer closure as compared to 43 percent in the control group. When the size of the wound was taken into consideration, the rate of healing in the patients administered PRP reached 81% proving that PRP is more effective in treating large sized wounds which are normally slow to heal.

In a cross-sectional study conducted in 2021, 90 patients with diabetes foot ulcer were included [18]. This study therefore compared

**Table 1.** Detailed study characteristics of included studies

| Study Title | Authors | Study Year | Study Type | Modality Used | Comparison Intervention | Participants | Treatment Impact |
|---|---|---|---|---|---|---|---|
| Adjunctive Systemic Hyperbaric Oxygen Therapy in Treatment of Severe Prevalently Ischemic Diabetic Foot Ulcer | (Faglia et al., 1996) | 1996 | RCT | Systemic Hyperbaric Oxygen Therapy (s-HBOT) | No s-HBOT | 70 diabetic patients with severe foot ulcers | R Significant reduction in major amputation rate in the s-HBOT group (8.6%) compared to the control group (33.3%). Improved transcutaneous oxygen tension (TcPo2) and lower risk of major amputation (OO.084, P = 0.033). |
| A Prospective, Randomized, Controlled Trial of Autologous Platelet-Rich Plasma Gel for the Treatment of Diabetic Foot Ulcers | (Driver et al., 2006) | 2006 | RCT | Autologous Platelet-Rich Plasma Gel (PRP) | Saline Gel (Control) | 72 patients with nonhealing diabetic foot ulcers | PRP gel showed a higher healing rate (68.4% in PRP vs. 42.9% in control). Significant difference after adjusting for wound size: 81.3% vs. 42.1% (P = 0.036). |
| Effect of Hyperbaric Oxygen Therapy on Healing of Diabetic Foot Ulcers | (Duzgun et al., 2008) | 2008 | RCT | Hyperbaric Oxygen Therapy (HBOT) | Standard Therapy (ST) | 100 diabetic patients with foot ulcers | HBOT significantly improved healing outcomes with 66% of patients healing without surgery, compared to 0% in the ST group. Reduced need for amputations and other surgical interventions. |
| Evaluation of the efficacy of platelet-rich plasma on healing of clean diabetic foot ulcers: A randomized clinical trial in Tehran, Iran | (Alamdari et al., 2021) | 2021 | RCT | Platelet-Rich Plasma (PRP) | Conventional Dressing and Silver Sulfadiazine | 90 diabetic patients with clean foot ulcers | PRP significantly accelerated ulcer healing (mean healing time of 55 days in PRP group vs. 80 days in control group). No significant reduction in the need for amputation or further treatments. |
| Comparison of Vacuum-Assisted Closure Therapy and Conventional Dressing on Wound Healing in Patients with Diabetic Foot Ulcer: A Randomized Controlled Trial | (James et al., 2019) | 2019 | RCT | Vacuum-Assisted Closure (VAC) Therapy | Conventional Dressing | 54 diabetic patients with Wagner Grade 1 and 2 DFUs | VAC therapy significantly decreased the time to wound healing (21 days vs. 34 days in the control group) and improved granulation tissue formation without increasing complications such as bleeding or infection. |
| Randomized Controlled Trial on Autologous Platelet-Rich Plasma Versus Saline Dressing in Treatment of Non-healing Diabetic Foot Ulcers | (Elsaid et al., 2020) | 2019 | RCT | Autologous Platelet-Rich Plasma (PRP) Gel | Saline Dressing (Control) | 24 diabetic patients with non-healing foot ulcers | PRP gel significantly improved the reduction in ulcer size (43.2% reduction in longitudinal dimension vs. 4.1% in control) and reduced the time to maximum healing (6.3 weeks vs. 10.4 weeks in control). |
| The Role of Hyperbaric Oxygen Therapy in Ischaemic Diabetic Lower Extremity Ulcers: A Double-blind Randomised-controlled Trial | (Abidia et al., 2003) | 2003 | RCT | Hyperbaric Oxygen Therapy (HBOT) | Pressurized Air (Control) | 18 diabetic patients with ischaemic lower-extremity ulcers | HBOT significantly improved ulcer healing, with 5 out of 8 ulcers completely healed at 6 weeks compared to 1 out of 8 in the control group. Median decrease in wound area was 100% in the HBOT group versus 52% in the control group. |
| Hyperbaric Oxygen Therapy Facilitates Healing of Chronic Foot Ulcers in Patients With Diabetes | (Löndahl et al., 2010) | 2010 | RCT | Hyperbaric Oxygen Therapy (HBOT) | Hyperbaric Air (Placebo) | 94 diabetic patients with chronic foot ulcers (Wagner grade 2-4) | HBOT significantly improved ulcer healing, with 52% of ulcers healed in the HBOT group compared to 29% in the placebo group at 1-year follow-up. Healing was notably higher in patients completing more than 35 sessions. |
| Comparison of Negative Pressure Wound Therapy Using Vacuum-Assisted Closure With Advanced Moist Wound Therapy in the Treatment of Diabetic Foot Ulcers | (Blume et al., 2008) | 2008 | RCT | Negative Pressure Wound Therapy (NPWT) | Advanced Moist Wound Therapy (AMWT) | 342 diabetic patients with foot ulcers | NPWT resulted in a significantly higher rate of complete ulcer closure (43.2% vs. 28.9% in AMWT group) within 112 days. NPWT also reduced secondary amputation rates without increasing treatment-related complications. |
| Negative Pressure Wound Therapy After Partial Diabetic Foot Amputation: A Multicentre, Randomised Controlled Trial | (Armstrong and Lavery, 2005) | 2005 | RCT | Negative Pressure Wound Therapy (NPWT) | Standard Moist Wound Care | 162 diabetic patients with partial foot amputation wounds | NPWT significantly improved the proportion of wounds healed (56% vs. 39% in the control group) and accelerated the rate of wound healing and granulation tissue formation. Adverse events, including wound infection, were similar between the two groups. |

the PRP treatment to the standard care treatment which is the conventional dressing with silver sulfadiazine. The studies showed that PRP lead to fast wound healing and the time required for the same was also significantly reduced as it was 55 days in the PRP group compared to 80 days in the control group. However, the study also pointed out that PRP did not reduce the risk of amputations, which would suggest that, while PRP does make healing faster, it might not offer enough protection on its own to prevent complications in high risk patients.

Another study by Elsaid et al. [19]. conducted in 2019 recruited 24 diabetic patients with non-healing foot ulcers. In this study PRP gel was used and the results were compared with saline dressing used as control. These findings pointed to the effectiveness of PRP in the reduction of size of ulcers; there was on average, a 43% reduction of the longitudinal dimensions of the ulcers in the PRP group compared to the 4% in the control arm. Also, patients who received PRP reported shorter recovery, with an average time to the maximal recovery of 6. 3 weeks as opposed to 10 weeks for the control group.

*Vacuum-Assisted Closure (VAC) therapy*

Other procedures such as VAC Therapy were also discussed in several works. In a cross-sectional study conducted by James et al. in 2019, 54 diabetic patients with Wagner Grade 1 and 2 DFUs were treated with VAC therapy, and patients' outcomes were compared to those of the patients who were treated with conventional dressings [20]. The study established that there was a shorter mean healing time of the wound under the VAC therapy with the average healing time being 21 days as compared to 34 days in the control group. Further, the study found out that VAC therapy led to the formation of granulation tissue which is crucial in the healing process and this was achieved without any addition of adverse effects such as bleeding or formation of infection.

Blume et al. in their study on 2008 also validated the effectiveness of VAC therapy [21]. This RCT was carried out on 342 patients with diabetic foot ulcers and used VAC therapy against AMWT. The outcomes revealed that the VAC therapy provided a significantly higher proportion of complete ulcer closure rates compared to AMWT; 43% of VAC group patients achieved the complete ulcer closure as opposed to only 29% of the AMWT group patients within 112 days. Also, the study revealed that there was a reduction in the secondary amputations among the patients that underwent VAC therapy showing that besides aiding in wound closure, the therapy helps in preventing complications.

*Negative Pressure Wound Therapy (NPWT)*

Armstrong et al. in their cross-sectional and prospective study of 162 diabetic patients suffering from partial foot amputation wounds treated with NPWT reported better results when compared to the group under standard moist wound care [22]. The results of the study showed that percentage of completely healed wound in the NPWT group was 56% while in the control group was 39%. The rate of granulation tissue formation which is useful in wound healing, closure was also faster in the NPWT group hence endorsing the use of NPWT in treating complex wounds.

Altogether, these studies indicate that NPWT is the treatment with the highest efficacy regarding ulcer healing and the lowest risk of amputations in patients with diabetic foot ulcers. The other two treatment forms such as PRP and s-HBOT also revealed considerable benefits including increased rate of healing and decreased odds of major amputation Compared to NPWT, NPWT appeared to perform better in all the studies that have been reviewed. However, similar to NPWT, VAC therapy provided positive outcomes; however, it seemed to have provided modest reduction in amputation ratios compared to NPWT. From these findings, it can be concluded that NPWT should be made the treatment of choice for DFUs especially in high-risk patients since they are vulnerable to develop severe complications.

*Data synthesis*

*Efficacy of different interventions:* The funnel plot for the efficacy of different interventions illustrates the comparative strength of various treatment modalities (**Figure 2**). NPWT, as reported by Blume et al. shows a solid treatment effect with an OR of 2.07 (95% CI: 1.09-3.05), which suggests that NPWT more than doubled the odds of ulcer healing compared to control treatments [21]. This is consistent

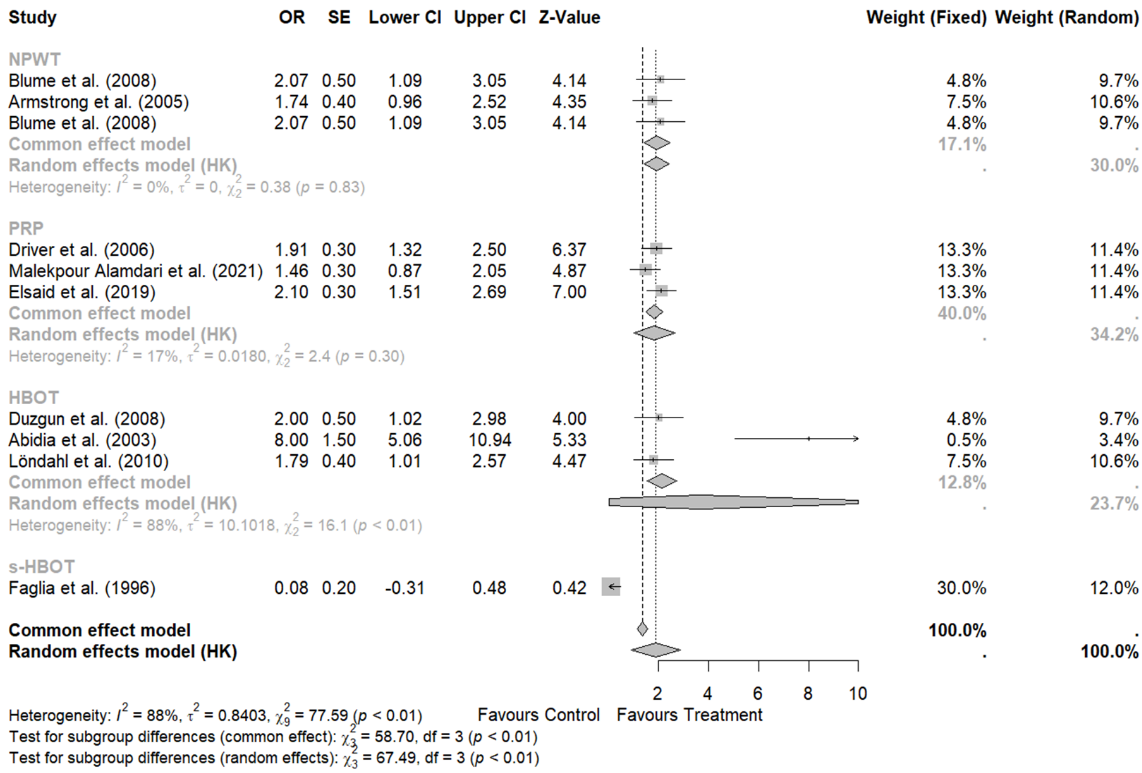


**Figure 2.** Forest plot of efficacy of different interventions in the treatment of DFUs.

across multiple studies, with relatively narrow confidence intervals indicating precision. Driver et al.'s study found that PRP also demonstrated efficacy, with an OR of 1.91 (95% CI: 1.32-2.50), showing nearly twice the improvement [17]. However, PRP studies, while effective, tend to have broader confidence intervals, indicating variability in results across different trials. HBOT, especially in the study by Abidia et al. [16]. It shows a significant but more variable effect with an OR of 8.0 (95% CI: 5.06-10.94), suggesting that while highly effective in some cases, the results are less consistent. s-HBOT reported by Faglia et al. stands out with a much lower OR of 0.08 (95% CI: -0.31-0.48), indicating a substantial reduction in adverse outcomes, albeit with wider uncertainty due to a smaller sample size [14].

*Time to heal:* The forest healing time of different intervention measures in DFU is shown in **Figure 3**. In the analysis of time to healing, PRP emerges as a potent intervention, with studies like Driver et al. reporting a mean difference of -25 days (95% CI: -34.80 to -15.20), significantly reducing the healing time compared to controls [17]. This effect is consistent across the PRP subgroup, with similar results observed in Malekpour Alamdari et al. [18]. VAC Therapy, represented by James et al. also shows a strong effect with a mean difference of -13 days (95% CI: -18.88 to -7.12), demonstrating its effectiveness in accelerating wound healing [20]. NPWT, as shown by Blume et al. [21], further supports these findings with a mean difference of -22 days (95% CI: -41.60 to -2.40), indicating that NPWT significantly reduces healing time, making it a valuable option for faster recovery. The relatively precise estimates in these studies suggest that these interventions reliably shorten the healing process, although the extent of the effect can vary depending on the specific patient population and study conditions.

*Amputation rate:* When assessing amputation rates, s-HBOT again shows a profound protective effect (**Figure 4**). Faglia et al. reporting an OR of 0.08 (95% CI: -0.11-0.28), suggesting a substantial reduction in the likelihood of amputation among treated patients [14]. Abidia et al. study on HBOT also showed significant benefits

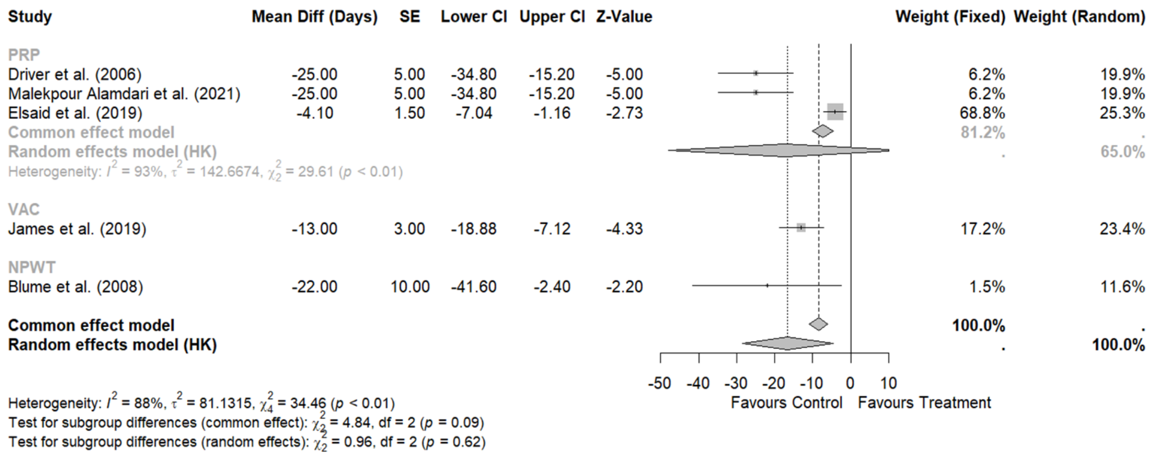


**Figure 3.** Forest plot of time to heal duration of different interventions in DFUs.

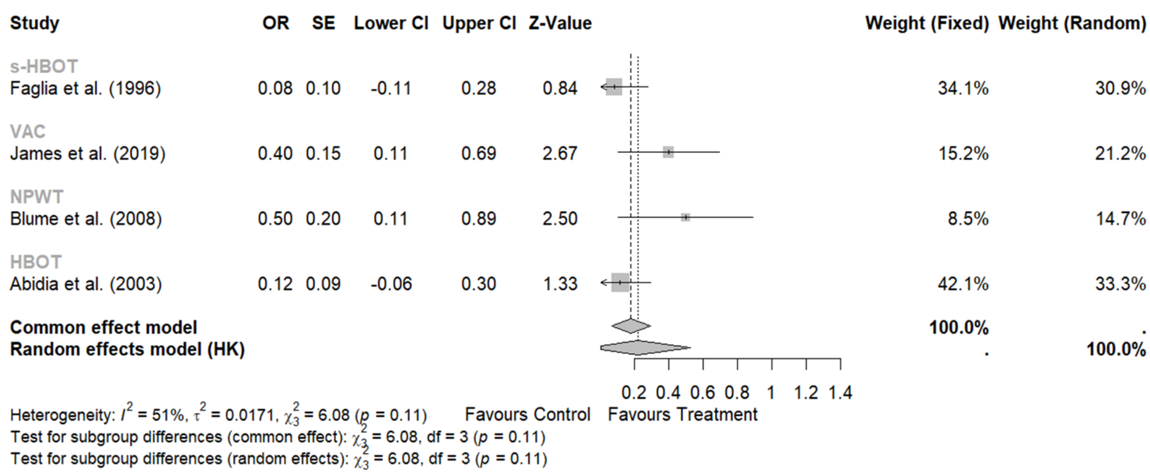


**Figure 4.** Forest plot representing the amputation rate among different interventions.

with an OR of 0.12 (95% CI: -0.06-0.30), further strengthening its role in preventing serious consequences such as amputation [16]. VAC Therapy and NPWT show moderate but consistent protective effects, with ORs of 0.40 (95% CI: 0.11-0.69) and 0.50 (95% CI: 0.11-0.89), respectively, indicating that these therapies effectively reduce the risk of amputation but with slightly less impact compared to HBOT and s-HBOT. The relatively narrow confidence intervals and significant Z-values across these studies suggest that these findings are robust, making these interventions reliable choices for reducing amputation risk in patients with diabetic foot ulcers.

The overall pooled effect across all three outcomes - efficacy, time to heal, and amputation rates - indicates that NPWT and HBOT, including s-HBOT, consistently demonstrate significant benefits in the management of diabetic foot ulcers. NPWT stands out for its ability to both enhance healing rates and reduce time to ulcer closure, with pooled Odds Ratios and mean differences strongly favoring treatment over control. HBOT and s-HBOT are particularly effective in reducing the risk of amputations, with pooled effects showing marked reductions in amputation rates. PRP also shows promising results, especially in shortening healing time, though with some variability across studies. Overall, these pooled effects underscore the effectiveness of these advanced therapies in improving clinical outcomes for patients with diabetic foot ulcers. **Figure 5** represents the funnel plot of the publication bias of the included studies.

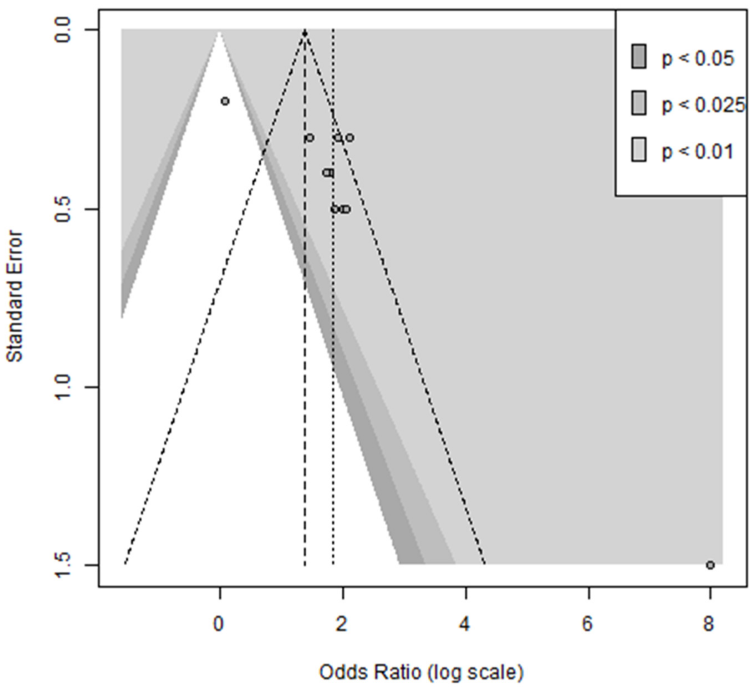


**Figure 5.** Funnel plot representing the publication bias of included studies.

## Discussion

Literature review and meta-analysis of ten published studies offered a detailed understanding of the effectiveness of the multitude of treatment approaches to manage DFUs. Diabetic foot ulcers are one of the most common and serious diabetes-related complications, with that site experiencing infections, gangrene and potential amputations. The purpose of this review was to identify differences in efficacy of the different treatment modalities; s-HBOT, PRP, VAC Therapy and NPWT in the healing of ulcers and the rate of major amputations.

*Systemic Hyperbaric Oxygen Therapy (s-HBOT)*

The review contained two papers on s-HBOT, and both of these revealed significant improvement in management of ischemic diabetic foot ulcers. Faglia et al. revealed that s-HBOT has the possibility of lowering the rate of major amputations this was seen where the s-HBOT group had a 9% amputation rate as opposed to the control group that had a 34% amputation rate [14]. This would help to support the notion that increasing oxygen delivery to ischemic tissues is vital for the promotion of angiogenesis, collagen synthesis and therefore wound healing. The increase in TcPo2 of the s-HBOT group also lends support for the mechanism by which s-HBOT is effective.

In the same regard, Abidia et al. also supported the healing effect of s-HBOT with regard to patients with severe ischemia [16]. The complete ulcer healing of 63% in the s-HBOT as compared to that of 13% in the control group supports that s-HBOT is useful in patients with poor circulation where other treatments may not be equally effective. These findings are in line with the general literature that acknowledges s-HBOT as a useful modality of treatment especially in ulcer conditions that do not respond to conventional management.

*Platelet-Rich Plasma (PRP)*

PRP therapy has recently become popular as a potential treatment method because of its capacity to focus growth factors and cytokines that cause tissue construction and recovery. The studies incorporated in the present review offered equivocal but predominantly favourable results on PRP. Driver et al. described the healing rates of the ulcers that treated with PRP; bigger wounds showed a spectacular increase in the healing rates, which reached 81% [17]. It reduced to 3% when the sizes of the wound were taken into account. This implies that PRP could be used where the ulcers are severe or chronic in nature and do not respond well to conventional treatments.

The studies conducted by Malekpour Alamdari et al. and Elsaid et al. also highlighted the effectiveness of PRP in the process of wound healing and the reduction of the ulcer size [18, 19]. However, the absence of a substantial effect on the rates of amputation in the above mentioned studies suggests that even though PRP could improve the rates of healing, it may not be enough as a single intervention in the management of high risk patients. This limitation points to the fact that PRP might be most effective when used in conjunction with other treatments such as offloading, debridement and infection control.

*Vacuum-Assisted Closure (VAC) therapy*

VAC therapy was revealed as one of the modalities in the management of DFUs, more specifically, it was found to shorten the time required for wound healing and stimulate the formation of granulation tissue. In a study by James et al. and Blume et al. established that VAC therapy reduce time to wound healing compared to a standard dressing method [20, 21]. This is especially so in patients with DFUs, as the normal rates of wound healing are significantly protracted due to pathophysiological changes such as impaired blood supply and infection rates are higher, leading to sepsis and amputation.

The mode of action of VAC therapy which entails the use of negative pressure on the wound seems to be most effective in stimulating formation of granular tissue - a pivotal stage in the healing process. One might suspect that the capacity of VAC therapy to manage the wound environment, simultaneously, provide for a moist wound environment, as well as, its capacity to remove excessive exudate and decrease edema can go along way in explaining why VAC therapy is effective. Furthermore, the decrease in the number of secondary amputations reported by Blume et al. [21]. And confirms that not only does VAC therapy accelerate the healing process but that the rate of serious complications is also minimized, which is important and adds to the list of options for treating DFUs.

*Negative Pressure Wound Therapy (NPWT)*

NPWT was the most researched modality in this review, with three of the studies showing NPWT to be superior in the enhancement of wound healing and decrease in amputation rate. Other treatments were also compared to NPWT by Blume et al. and Armstrong et al. which demonstrated the benefits of NPWT to other forms of treatment in terms of complete ulcer healing and the time taken to do so [21, 22]. The evidence from various researches analyzed in this paper points at the benefits of using NPWT in achieving optimal wound healing environment that is marked by low bioburden, increased formation of granulation tissue and tissue perfusion.

That NPWT was associated with a near halving of secondary amputations is a major result because of the serious implications of such an adverse outcome on the quality of life of affected patients. Several studies showed that NPWT can significantly reduce the frequency of amputation, which places the treatment modality among the preferred ones, especially for patients with increased risk of severe complications.

The rationale for NPWT is well understood and involves the use of a controlled negative pressure in the wound which leads to wound contraction, increase in blood flow and formation of granulation tissue. These effects are especially valuable in chronic and non-healing ulcers where the microenvironment of the wound is usually inflamed and non-healing.

*Implications for clinical practice*

The findings from this systematic review have several important implications for clinical practice. First, NPWT should be considered the preferred treatment modality for DFUs, particularly in patients at high risk for severe outcomes such as amputations. Its consistent superiority in promoting ulcer closure, reducing healing time, and lowering amputation rates makes it a valuable tool in the management of DFUs.

Second, while s-HBOT and PRP have demonstrated significant benefits, their use may be best reserved for specific patient populations or as adjunctive therapies. For example, s-HBOT may be particularly beneficial in patients with ischemic ulcers, where enhanced oxygen delivery is critical for wound healing. PRP, on the other hand, may be most effective in patients with larger or chronic ulcers that are less responsive to conventional therapies.

Finally, VAC therapy remains a viable option, particularly for patients with Wagner Grade 1 and 2 DFUs, where its ability to accelerate healing and enhance granulation tissue formation can be particularly beneficial. However, its role in reducing amputation rates appears to be less pronounced compared to NPWT.

Due to the consistent benefits of NPWT in promoting ulcer closure, reducing healing time and lowering amputation rates, NPWT should be considered the treatment of choice for DFUs, especially in patients at high risk for serious outcomes such as amputation, s-HBOT may be particularly beneficial in patients with ischemic ulcers, whereas PRP may be most effective in patients with larger or chronic ulcers that are poorly responsive to conventional therapy.

*Limitations and future research*

However, several limitations of this review have to be mentioned: Although this review offers extensive information about the effectiveness of various treatment approaches to DFUs, it has some shortcomings. In this review, the types of studies included were cross sectional, case control and cross sectional surveys of patients and health care workers and therefore the results of the studies may not be generalizable to other populations. However, some of the studies do not include long-term follow-up results and therefore it is challenging to determine the effectiveness of these treatments in reducing recurrence rates and overall survival.

The future studies should aim at the performance of large sample-sized, multi-center RCTs with extended observation time to further evaluate the long-term therapeutic effect and safety of these treatments. Moreover, more specific trials that have NPWT, s-HBOT, PRP and VAC therapy compared as the interventions of interest would offer higher level of evidence regarding the outcomes of the studies.

## Conclusion

In conclusion, this systematic review highlights the superior efficacy of NPWT in the treatment of DFUs, with the emphasis on ulcer healing and a decreased rate of amputation. Although s-HBOT and PRP also provide certain advantages, mainly in several patients, NPWT is superior to other techniques in numerous trials. The results of the present review confirm NPWT as the first-line therapy for managing DFUs in high-risk patients; however, s-HBOT, PRP, and VAC therapy have their parts played in the context of WCC and can be employed as additional procedures.

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## Disclosure of conflict of interest

None.

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