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Research Article

Effectiveness and Safety of Hyperbaric Oxygen Therapy (HBOT) in Treating Diabetic Foot Ulcers (DFUs)

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Abstract

Introduction: Diabetic Foot Ulcers (DFUs) are one of the more dangerous complications of diabetes, contributing to morbidity, mortality, and major financial strain, potentially affecting patients' quality of life. Therefore, an effective DFU treatment is needed to both heal and reduce severe consequences, such as amputation. Studies into effective multiple therapeutic interventions for DFUs indicate that Hyperbaric Oxygen Therapy (HBOT) may be a current alternative for treating patients presenting with DFUs.

Here, we seek to determine whether HBOT is clinically effective in wound healing of DFUs and reducing associated high amputation levels. Further, it examines whether HBOT is a safe therapy for treating diabetes patients with foot ulcers.

Methods: A comprehensive search strategy was applied to eight databases (CINAHL, Medline, EMBAS, PsycINFO, Joanna Brigg's Institute (JBI), Ovid, Cochrane Library and PubMed) to obtain relevant Randomised Controlled Trials (RCTs). Stringent pre-defined inclusion and exclusion criteria were applied regarding eligibility of the retrieved studies. A manual search of the references contained in these studies was performed alongside a search of e-libraries and medical websites. Eight RCTs were included, shown in a PRISMA flow diagram; data were extracted using the JBI's data extraction tool before being critically appraised using the JBI critical appraisal tool. Findings were then summarised and interpreted using narrative synthesis.

Results: Three main themes emerged from the included studies: the effect of HBOT on ulcer healing, its effect on amputation rate, and HBOT safety (i.e., concerns about adverse events and oxidative stress). Most studies concluded that HBOT assists in size reduction and accelerates healing of DFUs.

Conclusion: HBOT is an effective, safe treatment, as an additional therapy for standard wound care, for DFUs in the short term, if at least 20 sessions are completed. HBOT reduces the risk for severe consequences, not the consequences per se, i.e. infection. Further rigorous examination by larger, well-designed RCTs is required to investigate the relative efficacy and cost-effectiveness of HBOT.

Introduction

The advent of diabetes has been documented regionally and globally by the International Diabetes Federation since 2000, as diabetes was estimated the fifth major cause of death [1]. Diabetes affects 25% of those 65 years and older, while half of those below 65 suffer from pre-diabetes [2]. Prevalence of both types gradually rose until 2017, when 4 million people worldwide had died from diabetes [3]. By 2019, the number of cases stood at 463 million, with 578 cases predicted for 2030, and 700 million for 2045 [4].

The lifetime risk of foot ulcers was estimated at 25% for diabetes patients [5]. Epidemiologically, global Diabetic Foot Ulcers (DFU) prevalence was roughly 6.3% higher in males (4.5%) than females (3.5%), and higher in T2DM patients at 6.4% and 5.5% in T1DM [6]. Physical, psychological, and productive consequences reducing patients' quality of life make ulcers an alarming risk [7]. In the US, DFU care costs Medicare approximately $25 billion in 2008 [8]. Around £662 million was spent by the UK National Health Services (NHS) on managing

DFUs in 2012 [9]. More worryingly, DFUs have been closely associated with an elevated risk of mortality. According to [8], 10.7% of DFU patients died in 2008 in the American Medicare community. In terms of physical complications, 85% of DFUs caused lower limb amputations [10].

The greatest consequence of DFU is foot amputation, equating to medical and financial burdens. [11-13] reported that 75% of DFU-related amputations are the major global source of non-trauma amputations, which increase hospital admissions [14] and deaths [15].

Hyperbaric Oxygen Therapy (HBOT) is an inhalation and diffusion therapy using high-dose and short-term oxygen, administrated systemically via patient blood circulation and airways [16] with devices pressurised with air up to 2 to 2.5 atmospheres (ATA) and patients breathe 100% oxygen [17]. HBOT can enhance oxygen in hypoxic tissues, decrease oedema, generate collagen, encourage perfusion, and reduce inflammatory cytokines [18].

Pathophysiology of DFUs

Hyperglycaemia is a biochemical aberration inhibiting endothelial nitric oxide synthase production and activation, and interaction of protein with sugar (Millard reaction), leading to accelerated development of neuropathy and vascular changes [19]. The main factors which affect the underlying pathophysiology of foot ulcers include peripheral neuropathy, ischemia from vascular diseases, inflammatory cytokines and susceptibility to infection [20].

Neuropathy is accountable for over 60% of DFUs [20], where the metabolic disorders caused by hyperglycaemia precipitate neuropathy in patients [21]. The polyol path is among the most prevalent disorders [22], in which intracellular glucose is converted into sorbitol and fructose as a consequence of increased activity of aldose reductase and sorbitol dehydrogenase enzymes [23]. The risk of accumulating sugar products lies in the decrease of nerve cell myoinositol synthesis necessary for normal neuron conduction [24]. Conversion of chemical glucose leads to depletion of phosphate stock of nicotinamide adenine dinucleotide, vital for detoxifying Reactive Oxygen Species (ROS) and synthesising vasodilator Nitric Oxide (NO) [19]. Consequently, oxidative pressure inside the neuron and vasoconstriction are increased, causing ischemia, which contributes to cell damage, abnormal activation of protein kinase C, and nerve death [25].

Neuropathy impacts motor, autonomic and sensory components of the nervous system in diabetes patients [20]. With regards to the motor aspect, the damage to the affected foot's intrinsic muscles contributes to a disturbance between its flexion and extension [26]. Deformities (i.e., bony prominence and pressure points) arise in the anatomy of the foot, which then lead to skin breakdown and ulceration [27]. The autonomic nervous system is adversely influenced by the neuropathy by disrupting the oily and sweat gland functions, thus, the foot lacks its natural skin moisturising ability and becomes drier and thus more prone to infection [28]. As neuropathy weakens sensation in the affected limb, patients do not notice the wounds to which they are exposed and continue to put pressure on them, thus, exacerbating these ulcers [29].

Peripheral Artery Disease (PAD), which accounts for approximately 50% of patients presenting with diabetic foot, affects the tibial and peroneal arteries of the calf (gastrocnemius muscle) [30]. In addition, persistent hyperglycaemia often triggers smooth cell defects and endothelial cell impairment of the peripheral arteries [21]. As a result, vasodilators produced from the endothelium diminish and cause constriction. Further, the rise in thromboxane A2, a vasoconstrictor and platelet aggregation agonist, is also linked to hyperglycaemia in diabetes, which contributes to elevated plasma hypercoagulability risks [31]. The vascular extracellular matrix may also be subject to changes in arterial lumen stenosis [19]. These responses may interfere with other factors common to diabetes patients, such as hypertension and hyperlipidaemia, causing occlusive artery disease that ultimately leads to lower extremity ischemia and increased risk of DFUs [32].

Here, we seek to determine whether HBOT is clinically effective in wound healing of DFUs and reducing associated high amputation levels. Further, it examines whether HBOT is a safe therapy for treating diabetes patients with foot ulcers.

Methodology

Search Strategy

A three-step search strategy was applied and aimed at identifying all eligible published studies. First, CINAHL, Medline, EMBAS, PsycINFO, JBI, Ovid, Cochrane Library, and Pubmed were searched by one of the research team. An initial limited search was first undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were then used to develop a full search strategy for the report. The search strategy, including all identified keywords and index terms, were adapted for each included information source. Initial keywords used in this review were: Adult diabetes AND/OR Diabetic foot ulcers patients AND/OR Diabetic patients; Hyperbaric oxygen therapy AND/OR Hyperbaric Oxygenation AND/OR Hyperbaric oxygen chamber AND/OR Hyperbaric AND/OR HBOT safety AND/OR HBOT effectiveness AND/OR Ulcers healing AND/OR Ulcers treatment AND/OR Adverse effects AND/OR Complications. Second, a process of screening, supplementary search parameters were used to ensure relevance to the topic, duplicate articles and those

not relevant were removed (n=1936). Following abstract review, studies were excluded if they were not primary research, unrelated, excluded human participants, non-English language and did not have full text availability for the review.

Finally, the full text of selected citations was assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full text studies that did not meet the inclusion criteria was recorded and reported in the systematic review. Disagreements between the reviewers at each stage of the study selection process were all resolved through discussion, and by including a third reviewer if required. The results of the search were reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram [33]. Of the 2,022 papers generated using the keywords, a final 8 papers were included for analysis. The PICOS tool focused on the Population, Intervention, Comparison, Outcomes and Study (PICOS) type to identify suitable primary research studies to be included.

Critical appraisal tools such as CASP and JBI, were utilised to thoroughly examine the relevant primary studies to verify the probability of errors and biases in the design and reliability of findings, which ultimately serve as the bases for assessing study quality [34,35]. The JBI data extraction tool for experimental/observation studies was used in this study. Data was subsequently tabulated and designed according to JBI tool items, to facilitate the writer's data handling synthesis and results' reporting stages. The eight included studies were evaluated using the new JBI-MAStARI critical appraisal tool and ranged between high and moderate.

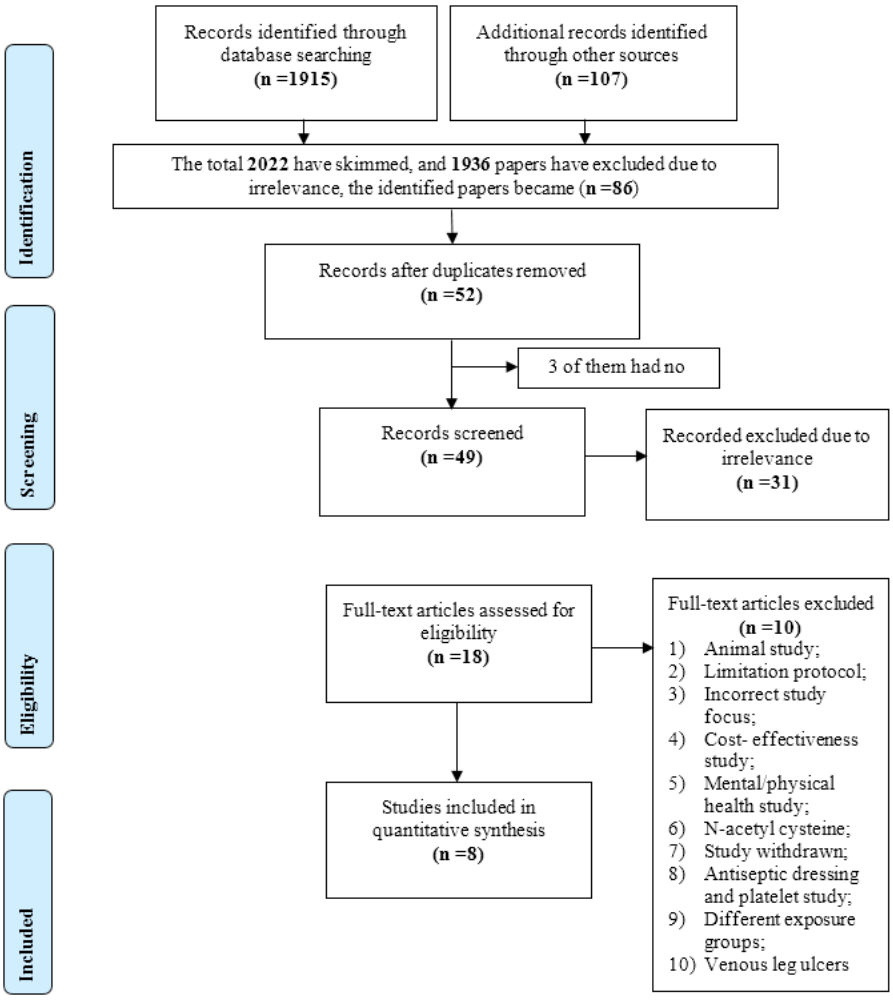

Figure 1: PRISMA Flow Diagram indicating included studies (adapted from [33]).

Results

Characteristics of the Included Studies

The participants in the eight studies totalled 609, with [16] having the highest sample size (n=164), and [36] having the smallest one (n=30). All trials identified the participants' age group to be 18 years or above. Diabetes patients who had DFUs that had remained for more than four weeks were the united criterion used in these studies. The study by [36] is exceptionally confined only to participants who have non-ischemic DFUs.

The classification of these DFUs on Wagner's scale was nevertheless slightly different across the studies. To further explain that point, three of the trials selected patients with 3rd grade ulcers or less [37-39], while four extended further to involve 4th grade DFU patients as well [16,40-42]. In addition, [36] only targeted patients diagnosed with grade two or three of DFUs.

Study Number	Author and Year	Study Design	Participants			Intervention	Clinical Outcomes
			Setting	Population	Sample Size		
1	Löndahl M, Katzman P, Nilsson A, Hammarlund, C (2010)	A (Double-Blind) RCT	An ambulatory setting, Sweden.	Patients with diabetes and chronic foot ulcers (at least one full-thickness wound below the ankle for 3 months.).	164 TG= 49 CG= 45	TG: HBOT CG:Placebo (Hyperbaric air) Treatments were given in a multi-place hyperbaric chamber for 85-min daily (session duration 95 min), five days a week for eight weeks (40 treatment sessions).	* **Effect on ulcer healing** Complete healing of the index ulcer was achieved in 37 patients at 1-year of follow-up: 25/48 (52%) in the TG and 12/42 (29%) in the CG (P 0.03). ***Effects on amputation** 3 major amputations were performed in the TG as compared with 1 in the CG within the 1st year. ***The frequency of adverse events was low** **In TG:** 1 fatal outcome, 2 post-session hypoglycaemia, 1 endured post-traumatic otitis, 2 my- ringotomy needed with tube placement, 1 HBOT session-related dizziness, 1 worsening of cataracts **In CG:** 1 post-session hospitalisation due to losing consciousness, 4 post-session hypoglycemia, 2 my- ringotomy needed with tube placement, 1 minor head injury after fall inside the hyperbaric chamber in CG.

2	Fedorko L, Bowen JM, Jones W, Oreopoulos, G, Goeree R, et al. (2016)	A Prospective (Double-Blind) RCT	A single-center, Canada.	Patients with diabetes and foot lesions (Wagner grade 2–4) persisting for a minimum of 4 weeks.	103 TG = 49 CG = 54	TG: HBOT (Breathing oxygen) CG: Sham (Breathing air) Treatments were given to participants as 5 days per week for 6 weeks (30 sessions), each session takes 90 min of HBOT (breathing oxygen at 244 kPa) or sham (breathing air at 125 kPa). Patients were followed for 6 weeks after the end of hyperbaric sessions and returned to the clinic every week for wound assessment and treatment.	[*]**Meeting Criteria of Need for Amputation or Undergoing Amputation** Criteria for major amputation were met in 13 of 54 patients in the CG and 11 of 49 in the TG (odds ratio 0.91 [95% CI 0.37, 2.28], P = 0.846). The percentage of amputations recommended of any type (major or minor) was 51% in TG and 48% in CG (1.12 [0.52, 2.43], P = 0.771). Beyond the adjudicated indication for amputations, only 1 actual amputation occurred during the 12-week study period, and this was the removal of a toe in CG. 10 of the 11 participants who received HBOT treatment and met the criteria for major amputation were recommended to have a below-knee amputation, and all of those assessed to require major amputation in CG (n = 13) were recommended to have below-knee amputation. 14 (28.6%) and 13 (24.1%) participants were adjudicated to undergo minor amputations in TG and CG, respectively (1.26 [0.52, 3.04], P = 0.605). [*]**Wounds healing** Twelve (22%) patients in the CG and 10 (20%) in the TG were healed (0.90 [0.35, 2.31], P = 0.823). All other indices of wound healing were also not statistically significantly different between groups. [*]**Adverse events** **In TG:** 1 an episode of CHF, 9 cases of inability to equalise middle ear pressure during treatment, 4 hypoglycaemic episode. **In CG:** 3 cases of inability to equalise middle ear pressure during treatment, 2 hypoglycaemic episode.

3	Ma L, Li P, Shi Z, Hou T, Chen X, et al. (2013)	A Prospective (Blind) RCT	The author's unit of the hospital, China.	Diabetic patients with diabetic foot ulcers, at least one full-thickness wound below the ankle (Wagner grades III or less) for >3 months.	36 TG = 18 CG = 18	TG: SC+ HBOT CG: Standard care including offloading, wound debridement, and glucose control. Treatments were given via a multi-person hyperbaric chamber twice-daily for 90 minutes at 2.5 atmospheres absolute (ATA) 5 days a week for 2 weeks.	*__Effects on Ulcers healing__ $TcPo_2$ in the HBO group increased on day 7 (477.8 ± 118.2 mm Hg versus 37.06 ± 5.23 mm Hg, P <0.01) and day 14 (501.1 ± 137.7 mm Hg versus 35.61 ± 4.85 mm Hg, P <0.01). Ulcer size reduction in the HBO group was greater than that of the control group (42.4% ± 20.0% versus 18.1% ± 6.5%, P <0.05). *__Effects on oxidative stress__ MDA levels, SOD, and CAT were all significantly higher in the HBO than in the control group on day 14 (P<0.05). *__Adverse events__ No serious complications such as death or amputation or other adverse reactions such as barotraumatic otitis, dizziness, seizures, or pneumothorax occurred.
4	Chen CY, Wu RW, Hsu MC, Hsieh CJ, Chou, MC (2017)	A Prospective RCT	A medical center in Kaohsiung City, Taiwan.	Diabetic patients with nonhealing DFUs (Wagner wound classification of grade 1, 2, and 3 ulcers) who were deemed poor candidates for vascular surgery.	38 TG = 20 CG = 18	TG: Standard care plus HBOT CG: Standard care alone HBOT was administered in a hyperbaric chamber under 2.5 absolute atmospheric pressure for 120 minutes; for 5 days a week for 4 consecutive weeks.	*__Effects on ulcers healing__ Complete DFU closure was achieved in 5 patients (25%) in the HBOT group (n = 20) versus 1 participant (5.5%) in the routine care group (n = 18) (P = .001). The HBOT group showed statistically significant improvements in inflammation index, blood flow, and health-related quality of life from pretreatment to 2 weeks after the last therapy ended (P < .05). Hemoglobin A1c was significantly lower in the HBOT group following treatment (P < .05) but not in the routine care group. *__Effects on amputation rate__ The AR was 5% for the HBOT group and 11% for the routine care group (χ^2= 15.204, P = .010).

5	Salama SE, Eldeeb AE, Elbarbary AH, Abdelghany SE (2019)	A Prospective RCT	In the Vascular Surgery Department and the Physical Medicine, Rheumatology and Rehabilitation Department, Tanta University Hospitals.	Diabetic patients having Wagner's grade 2 or 3 chronic DFU, in whom the response to 30 days of standard wound care was not favorable.	30 TG = 15 CG = 15	TG: HBOT plus conventional treatment CG: Conventional treatment alone HBOT was administered via monoplace chamber once daily for 5 days a week with 2 days off, for a total number of 20 to 40 sessions according to the ulcer response. The session began with a gradual pressure increase to the designated treatment pressure of approximately 2.5 ATA over about 10 to 15 min- utes in a 100% oxygen environment (compression phase). The treatment period "at pressure" lasted for 1 hour. Then, gradual decompression over about 10 to 15 minutes was made.	*__Effects on ulcers healing__ A significantly greater percentage of HBOT-treated wounds (33.3%, 5/15) achieved complete closure than conventional therapy–treated wounds (0%, 0/15; P = .014) at the end of treatment. This significant difference was maintained throughout the 8 weeks of follow-up. At the end of all HBOT sessions and 2 months of conventional treatment, the median ulcer surface area was significantly reduced in TG but not in CG. This significant ulcer size reduction in TG was maintained at 4 and 8 weeks of follow-up. Complete healing of the target ulcer, at the end of the treatment, was observed in 5 cases in TG versus no case in the CG, P = .014*. At 4 and 8 weeks of follow-up, these numbers were increased to 7 and 10 cases versus 2 and 3 cases in TG versus the CG p, P = .046*, .025*, respectively. On bivariate analysis, it was found that a significantly higher wound healing rate was associated with more HBOT sessions completed (r = 0.888, P = .0001, 95% confidence interval = 0.6904-0.9626).] *Adverse events Complications frequency was non-significantly different between both groups. [Mild to moderate wound infections were observed in 3 (20%) versus 5 (33.3%) cases of TG versus CG, respectively, during the period of treatment. This was cleared after surgical debridement, and culture and sensitivity with appropriate antibiotics administrated accordingly]. *__Amputation rate__ There was no major amputation in both groups while minor (toes) amputations were done to one patient in each group.

6	Santema KT, Stoekenbroek RM, Koelemay MJ, Reekers JA, Van Dortmont LM, et al. (2018)	A randomized, parallel-group superiority trial	Multicenter (24 hospitals in the Netherlands and one in Belgium + all nine public HBOT fa- cilities in the Netherlands and one affili- ated to the Antwerp University Hospital in Belgium).	Diabetic patients who have an ischemic ulcer of the lower extremities (graded as Wagner grades 2–4), present for at least 4 weeks.	120 TG: 60 CG: 60	TG: Standard care with HBOT GG: Standard care alone HBOT was administered as sessions of 90min in a multi-placed chamber, pressurised at 2.4 or 2.5 atmospheres absolute during which patients were breathing 100% FiO_2 except for three blocks of 5 min during which ambient air was administered to prevent oxy- gen intoxication. HBOT was scheduled for 5 days per week until a maximum of 40 sessions was reached or until complete wound healing was achieved.	* **Effects on Limb salvage** Limb salvage was achieved in 47 patients in the CG vs. 53 patients in the TG (risk difference, 10% [95% CI24to23]). * **Effects on Wound healing** After 12months, 28 index wounds were healed in the CG vs. 30 in the TG (RD 3% [95% CI 214 to 21]). No statistically significant difference was found in the time to complete ulcer healing of the index ulcer between both groups. * **Effects on Amputation** - Freedom From Any Amputation of the Index Limb. 31 patients (52%) in the CG remained free of any amputation (i.e., including minor amputations), compared with 38 (63%) patients in the TG group (RD 12% [95% CI 26to 28]). - Amputation-Free Survival AFS was achieved in 41 patients in the CG and 49 patients in the TG (RD 13% [95% CI 22 to 28]). ***Adverse Events and Mortality** A total of 14 participants died during the follow-up period (9 [15%] in the CG vs. 5 [8%] in the TG; RD 7% [95% CI 25 to 19]). 2 serious adverse events occurred that were attributable to HBOT: an oxygen- induced seizure and barotraumatic perforation of the tympanicmembrane. Both recovered without lasting consequences. 3 cases had required preventive myringotomy with tube placement due to the inability to equalise the pressure of the middle ear during HBOT.

7	Yazid MB, Ayesyah A, Nurhanani AB, Rohaizat MH (2017)	A prospective RCT	A tertiary hospital, Malaysia.	Diabetic patients with foot or ankle ulcer (Grade 1 or 2 or 3 on Wanger system) for at least four weeks of duration.	60 TG = 30 CG = 30	TG: standard treatment with HBOT CG: Standard treatment alone HBOT was administered five days a week in mono- place chamber. (20- 30 treatment sessions). A session consisted of a duration of compression in air for 5 mins, subsequently at 2.5 atmosphere absolute (ATA) treatment period for 85 mins, and then a 5 mins decompression period.	* **Effects on inflammatory markers** Reduction of WCC and CRP in TG were significant throughout the treatment (p=0.046 and p=0.039, respectively). * **Effects on ulcers healing** With the treatment, reduction in size of the ulcer was observed in both groups, and it was significant (p<0.001) in TG. Using Pairwise comparison, wound reduction in every ten days of measurement was significant (p<0.001) in TG compared to the CG. A total of 26 patients (86.7%) from the TG achieved complete ulcer healing at six months' follow-up, while 18 patients (60%) in CG's ulcer healed completely.

8	Nik NH, Wan WMZ, Mohd BY, Rahmah S (2019)	A RCT	Two tertiary centers and one private hyperbaric healthcare facility.	Diabetic patients with non-healing foot ulcers (2 grade or above on Wagner scale) which was treated at the study centers for more than thirty days and failed to achieve wound size reduction of more than 30%.	58 TG = 29 CG = 29	TG: Conventional wound care with HBOT CG: Conventional wound care HBOT was given at 100 percent concentration of 2.4 atmospheres absolute (ATA) as an adjunctive therapy with conventional wound care. This treatment was performed daily from Mondays to Fridays for thirty sessions. Patients underwent a hyperbaric treatment of 90 minutes in each session in a mono-place hyperbaric chamber.	* **Effects on wound healing** The means of wound size over time points (Day 0, 10, 20 and 30) among patients under TG were statistically significantly different [$F(1,61)=30.86$, $p<0.001$)] compared to CG. Multiple logistic regression analysis showed that TG has nearly 44 times higher odds to achieve at least 30% wound size reduction within the study period (95%CI: 7.18, 268.97, $p<0.001$).

Table 1: Characteristic of Included Studies.

Intervention/Comparator Characteristics

In six of the included trials, a standard diabetic foot treatment in conjunction with HBOT was compared with standard care alone. In the studies by [16] and [40], the intervention was HBOT, while the placebo/sham air was the comparator. With respect to the types of HBOT chambers, half of the experiments were performed in single-seater chambers and the remaining half in multi-person chambers. The HBOT session varied between 60 and 120 min throughout the studies. The frequency of intervention was given as a daily session five days a week. A different intervention dosage (twice a day) was given by [37]. The average length of the intervention across the eight trials was 20 to 40 sessions. The follow-up phase was completed in five of the eight studies [16,36,39-41].

Outcomes Characteristics

The eight studies mainly measured the effectiveness of the intervention on ulcer healing, which is the primary outcome of this review. As a secondary outcome, five studies measured the effect of HBOT on the amputation rate. Another secondary outcome was the intervention safety and its subsequent adverse events, as reported by the five studies. In addition, [37] was unique in examining oxidative stress as a side effect of HBOT.

Results and Discussion

Theme 1: Effect of HBOT on Ulcer Healing

The most clinically important theme was the effectiveness of HBOT on ulcer healing, which was measured by all of the included studies. Six of the eight studies noted the beneficial effects of HBOT for accelerating healing and reducing the size of DFUs [16,36-39,42]. Most studies supporting HBOT's effectiveness have a quality score of 8 to 13 on JBI, thereby rendering their findings trustworthy. Interestingly, in all six studies, the favourable effect was conditional on the administration of HBOT as an adjunct therapy to the standard care for DFUs. This result can be explained by the fact that the treatment of DFUs is complex and requires an integrated approach to achieve the desired healing. This is precisely what previously led the Society for Vascular Surgery to choose a range of adjunctive interventions—including HBOT—to investigate their efficacy [43]. The application of our review results

indicates that HBOT should be administered supplementary to standard DFU care. This finding is consistent with the results of a previous prospective randomised investigation conducted by [44], who lauded the efficacy of HBOT as a concomitant therapy with standard care for improving the healing of DFUs. The outcome of our review is also supported by the findings of a previous SR [43], who investigated the best available evidence supporting the use of different adjuvant therapies for DFUs. They concluded that HBOT was superior to other interventions for accelerating DFU wound healing. Despite their large final sample (n=1526), the restricted quality (low to medium) of the included studies weakens the reliability of their review findings. Our outcome is also in agreement with a more recent study, by [45], whose meta-analysis yielded findings confirming the helpful impact of HBOT on the promotion of DFU healing. However, their small sample size (n=585) demands caution when using this result.

In relation to discovering the circumstances in which HBOT was useful in treating ulcers, the six supported studies revealed near-consistent results regarding intervention characteristics. In brief, the studies combined resulted in a session lasting between 60 and 120 minutes, administered 5 times weekly for 6–8 weeks (20–40 sessions). Only three of the six studies addressed the follow-up duration [16,36,39]. These data did not reveal any confirmed correlations between the circumstances of HBOT intervention and its beneficial effect on ulcer healing, since the oppositional studies had the same HBOT characteristics. It should be noted that the six studies have advocated that a minimum of 20 sessions should be conducted to gain this benefit of HBOT. However, in [38], HBOT was conducted twice weekly, resulting in a study period limited to only two weeks. This can be attributed to that study's intention of testing an HBOT-associated oxidative stress risk hypothesis, which resulted in the intervention dosage being doubled to avoid prolonging the overall intervention time, thereby reducing the possibility of this risk in the treatment group. This exceptional finding supports the need for future studies that emphasise the link between short-and-long-term HBOT efficacy in ulcer healing, taking into account other factors such as oxidative stress and inflammatory markers. In terms of inflammatory markers, [39] study was unique in evaluating the effect of HBOT on WBCs and CRP, and they concluded that there was a significant reduction in their levels in the HBOT group. This result reflects what had previously been known about the physiological effect of HBOT in providing an anti-inflammatory effect that reduces inflammatory biomarkers and enhances the immune response [46].

The characteristics of patients who would potentially benefit from HBOT remain controversial. The frequent criteria for response to HBOT was having a chronic DFU (more than 4 weeks) and a grade 4 or less on the Wagner Ulcer Classification System. The beneficiaries in one study [36] were patients with chronic non-ischemic DFUs. It is hard to determine if there is a correlation between this patient category and the efficacy of HBOT based on this single inclusion of non-ischemic ulcers.

In contrast to the above, two studies [40] and [41] repudiated the efficacy of HBOT, finding no differentiation in ulcer healing between their HBOT and standard wound care groups. However, in addition to the large sample sizes (n=103 and n=120, respectively), the high JBI scores of these studies (13 and 10, respectively) implies that their findings should not be underestimated. In addition, the studies used follow-up periods of 6 weeks and 12 months, respectively. In [40], there was a 2% greater healing rate in the control group compared to the treatment group; this could have been caused by the unequal sample populations in the two study groups (CC:54; TG:49). Another important discovery was the inclusion of patients with ischemic DFUs only [41]. Their results found no additional benefit to using HBOT for achieving significant improvement of ulcer healing. With this in mind, it could conceivably be suggested that this finding indicates HBOT may not be beneficial for DFU patients with severe ischemia, which had previously been noted in the review findings of [43]. This could be attributed to the assumption that, in a state of sufficient tension, oxygen cannot reach ischemic areas to induce angiogenesis, so it is doubtful that HBOT would be effective in cases of severe ischemia.

Our review highlights the need for further research to investigate the types of DFUs likely to respond to HBOT. Notwithstanding these observations, the outcomes of both studies were consistent with the SR [47], who concluded that there was no difference in ulcer healing rates between HBOT and conventional wound treatment. What strengthens the reliability of their results is the methodological quality of the studies used in the review. Their meta-analysis found, however, that HBOT was superior to conventional treatment for reducing the size of an ulcer wound. One of the main issues that emerged from the finding that HBOT effectiveness is similar to standard care is the need to examine the HBOT's cost-effectiveness, such that a complete profile of its efficacy can be provided, which will then help clinicians to make decisions about using or dispensing with the practice.

Theme 2: Effect of HBOT on Amputation Rates

The second theme identified in this review was that the effect of HBOT on amputation rates, since five of the eight included studies reported it as a secondary endpoint. Most studies agreed that HBOT provides no benefit in reducing amputation rates [36,40,41], although [38] confirmed HBOT's advantage in reducing the risk of amputation. Interestingly, [16] observed that HBOT was correlated with a high incidence of major amputations (three cases) and a similar rate of minor amputations (four cases). This may be attributed to lower blood pressure levels in the toe (15 mm Hg) observed in their study's amputees, indicating a poor perfusion status. Patients with DFUs and peripheral arterial

occlusive disease typically have poor conditions that exacerbate clinical consequences, including amputations. An evidence for that multi-centre trial [41], which primarily included patients with limb ischemia and HBOT, also found no improvements in amputation rates.

It is challenging to understand the discrepancy of this theme's outcomes; they may be due to the lack of differentiation between ischemic and non-ischemic patients in most of the studies. Our findings are compatible with [48], which included only ischemic ulcer patients and found no impact of HBOT on amputation rates. [49] also found no effect on amputation rates when studying patients with non-ischemic DFUs. This finding was replicated in [47], which found no changes in major and minor amputation rates between HBOT and standard care.

The variations in amputation indications adopted by the studies is another possible explanation for the diverse findings of this theme. For example, the amputation indications that triggered major amputations in [16] were life-threatening infection and refractory pain. This finding challenges the amputations to be undertaken in this study as their amputation indications are underestimated and limited to infection. The study for amputation indicated [40]: persistent deep infections involving bones and tendons, pain that impedes movement, no significant progress in wound healing during the follow-up period and the inability to bear weight on the affected limb. Notwithstanding the drawback of not conducting actual amputations on the basis of the findings of the study, their use of a blinded-expert vascular surgeon minimised the risk of bias associated with amputation decisions.

[44] confirmed the beneficial impact of HBOT for minimising major and minor amputations. More recently, [45] concluded that the requirements for a major amputation have been lowered by HBOT, roughly by half. One possible reason for [38] finding could be the inclusion of patients with Grade 3 DFUs and lower. To clarify, the lower the degree of the ulcer, the lower the risk of amputation associated with it. [50] projected the amputation rate at 2% for patients with Grade 1 and 2 DFUs, 30% for Grade 3 and 52% for Grade 4. In response, [16] argued that, regardless of the effect of the therapy, patients with Grade 4 ulcers face an unavoidable risk of amputation. This could indicate a negative correlation between the ulcer grade and the potential effect of HBOT on amputation rates; however, the absence of a follow-up period and restriction of the study to a single centre challenged the reliability of [38] findings.

Theme 3: HBOT Safety (Adverse Events and Oxidative Stress)

In five of the studies, HBOT Safety was reported [16,36,37,40,41]. The findings did not indicate any significant differences in the incidence of adverse effects between HBOT and standard treatment. In addition, the frequency of these HBOT-related harmful effects reported in the studies was low. This finding is consistent with that observed in [51], who concluded that adverse events associated with HBOT were infrequent and reversible and were not distinct from those that occurred in the control group. [52] examined the safety of HBOT, also revealed that adverse events accompanying it were harmless and occurred infrequently. These results were reiterated in [47], which showed no significant variations in the frequency of harmful incidents between two groups.

Exceptionally, oxidative stress was reported as a potential risk associated with long-term HBOT [37], which stated that after 20 sessions a significant elevation in oxidative stress parameters was noted in the HBOT group. Oxidative stress is defined as the condition of the imbalance between Reactive Oxygen Species (ROS) production and the capacity of a biological system to effectively remove or repair reactive intermediates [53]. The concern in the context of our topic is that the over-production of ROS, or the failure to detoxify this aggressive molecule, contributes to oxidative stress, an essential element in the pathogenesis of chronic, non-healing wounds. Most importantly, oxidative stress is the unavoidable by-product of the metabolism cycle, which can lead, if not inhibited, to apoptosis or necrosis in the large number of oxygen radicals which threaten all types of life [54]. Regardless of the pioneering work in considering this critical aspect [37], the limited sample size and the short length of that study hindered their results' external validity. Moreover, it is suspected that increasing an HBOT dosage to two sessions a day was the cause for their results, which was contradictory to the intervention model utilised in the remaining studies. It is, however, a significant point that requires further study to obtain further compelling findings on HBOT's oxidative stress impact.

Conclusion

Although HBOT has a long-standing history, it remains a controversial approach for treating diabetes-related foot ulcers. Therefore, our research investigated the effectiveness and safety of HBOT as a therapeutic intervention for DFUs. With respect to HBOT's effectiveness, evidence has determined that HBOT is an intervention that has a positive influence on accelerating the healing of DFUs and decreasing their size, when used as an adjunctive therapy to standard wound care. The findings have also indicated the necessity of completing at least 20 sessions of HBOT—that is, reserving it for short-term use—to attain patient benefit.

Nevertheless, the findings have also demonstrated that there is no added benefit of HBOT, when compared with standard treatment alone, in minimising the risk of minor or major amputations. Regarding the safety of HBOT, the findings confirm that the incidence of HBOT-related adverse effects is low.

Additional large, multi-centre and well-designed trials to

rigorously evaluate the efficacy and safety of this intervention, particularly its relative effectiveness are required.

Our study also recommends further studies to examine HBOT's cost-effectiveness, in an effort to compare its clinical advantages to its expenses. Finally, studies that target physicians' and nurses' perceptions of HBOT's effectiveness and patients that are eligible for its benefit are required.

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