REVIEW

Hyperbaric Oxygen for the Treatment of Diabetic Foot Ulcers: A Systematic Review

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WHAT THIS PAPER ADDS

The value of adjunctive hyperbaric oxygen therapy (HBOT) in the treatment of diabetic foot ulcers has been questioned in meta-analyses of randomized clinical trials (RCTs). Yet, because of significant clinical heterogeneity between the trials, pooling of data is considered to be inappropriate. Some evidence was found for HBOT improving rates of complete wound healing in patients with a diabetic foot ulcer and concomitant ischaemia, as opposed to non-ischaemic ulcers. A consistent effect on amputation rates was not found. Additional trials are necessary to justify routine use of HBOT in patients with diabetic ulcers.

Objective: A systematic review of randomized clinical trials (RCTs) to assess the additional value of hyperbaric oxygen therapy (HBOT) in promoting the healing of diabetic foot ulcers and preventing amputations was performed.

Methods: MEDLINE, Embase, and the Cochrane Library were searched to identify RCTs in patients with diabetic foot ulcers published up to August 2013. Eligible studies reported the effectiveness of adjunctive HBOT with regard to wound healing, amputations, and additional interventions.

Results: Seven of the 669 identified articles met the inclusion criteria, comprising 376 patients. Three trials included 182 patients with ischaemic ulcers, two trials studied 64 patients with non-ischaemic ulcers, and two trials comprising 130 patients did not specify ulcer type. Two trials were of good methodological quality. Pooling of data was deemed inappropriate because of heterogeneity. Two RCTs in patients with ischaemic ulcers found increased rates of complete healing at 1-year follow-up (number needed to treat (NNT) 1.8 (95% CI: 1.1 to 4.6) and 4.1 (95% CI: 2.3 to 19)), but found no difference in amputation rates. A third trial in ischaemic ulcers found significantly lower major amputation rates in patients with HBOT (NNT 4.2, 95% CI: 2.4 to 17), but did not report on wound healing. None of the RCTs in non-ischaemic ulcers reported differences in wound healing or amputation rates. Two trials with unknown ulcer types reported beneficial effects on amputation rates, although the largest trial used a different definition for both outcomes. HBOT did not influence the need for additional interventions.

Conclusion: Current evidence shows some evidence of the effectiveness of HBOT in improving the healing of diabetic leg ulcers in patients with concomitant ischaemia. Larger trials of higher quality are needed before implementation of HBOT in routine clinical practice in patients with diabetic foot ulcers can be justified.

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INTRODUCTION

Diabetic ulcers of the lower limb are a major healthcare problem, and a major contributor to societal costs of diabetes. It has been estimated that 347 million people worldwide have diabetes.[1] In 1 year, one in 20 of these patients will develop a foot ulcer, and over 10% of these ulcers will result in an amputation.[2] Indeed, some 50% of all lower limb amputations are done in diabetic patients.[3]

Diabetic ulcers require complex multimodal treatment including glycaemic control, extensive local wound care, revascularization of ischaemic limbs (open and/or endovascular) to improve peripheral circulation, treatment of infections, and off-loading.[4] Despite optimal care, complete wound healing rates are reported to be as low as 60% after 1 year.[5]

Hyperbaric oxygen therapy (HBOT) has been suggested as a valuable addition to conventional treatment for a variety of indications, including delayed radiation injury, necrotizing soft tissue infections and chronic wounds, particularly in

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patients with diabetes.[6] HBOT for diabetic ulcers involves intermittent administration of 100% oxygen, usually in daily sessions of 90 minutes each, at pressures of 1.5—3.0 atmospheres absolute (ATA) in an airtight cabin.[6,7] By increasing the blood oxygen content, HBOT creates a favourable gradient for the diffusion of oxygen into the tissues. In hypoxic tissues, the enhanced oxygen supply has multiple effects that may benefit wound healing.[7] By increasing the expression of, among others, vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), HBOT may enhance angiogenesis and fibroblast proliferation. In addition, the resulting hyperoxia may cause vasoconstriction, thereby decreasing tissue oedema. By reducing the expression of pro-inflammatory cytokines, HBOT reduces inflammation, while simultaneously enhancing the bacterial killing activity of leukocytes.[7—9]

Although pooled estimates from randomized clinical trials (RCTs) on HBOT in patients with diabetic ulcers in early systematic reviews demonstrated increased rates of wound healing and decreased major amputation rates when HBOT was added to standard care,[10—12] the reduction in amputation rates was not confirmed in a recent large trial.[13] The subsequently updated Cochrane review reported increased rates of ulcer healing in the short term (risk ratio (RR) 5.20, 95% CI: 1.25 to 21.66) but not in the long term (RR 9.53, 95% CI: 0.44 to 207.76), and no significant difference in major amputation rates (RR 0.36, 95% CI: 0.11 to 1.18).[14] These results were confirmed in the meta-analysis by O'Reilly et al.[15] Given that the findings of an additional RCT were recently reported, a systematic review of all currently available RCTs has been performed to assess whether HBOT, when added to current best practice, can effectively improve wound healing and prevent amputations in patients with diabetic foot ulcers. As it was hypothesized that the presence of foot ischaemia may be a discriminating factor for the effectiveness of HBOT, the evidence on the effectiveness of HBOT in RCTs that included patients with compromised versus normal peripheral circulation was specifically compared.

METHODS

This review was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, which has been updated to address several conceptual and practical advances for performing a systematic review of RCTs.[16]

Search strategy

A clinical librarian assisted in formulating a search strategy for the MEDLINE, Embase, and Cochrane databases to identify RCTs on the effectiveness of HBOT in the treatment of diabetic leg ulcers, published up to August 2013. Medical Subject Headings (MeSH) terms were used, and accompanying entry terms for the patient group and intervention. The keywords 'leg ulcers', 'diabetes', and 'hyperbaric oxygenation' were used, along with their synonyms. The full search strategies are given in Appendix I. There were no language restrictions. Reference lists of retrieved studies were used to complete the search. In addition, www.clinicaltrials.gov was searched for ongoing or terminated, yet unpublished, trials. The aim was to contact the authors of unpublished data (abstracts, conference proceedings, or trials recorded in trial registers).

Trial selection

Titles and abstracts of potentially eligible articles were independently screened by two of the authors (RS, MK) to select potentially relevant articles. Studies were selected if they met the following criteria: the patients had diabetes and an ulcer of the lower extremity, and were randomly allocated to standard care with or without HBOT, irrespective of the use of sham treatment, and the study reported on amputation rates, wound healing, or additional interventions. Any selection disagreements were resolved by discussion. Agreement between the selecting authors was good (Kappa value of 0.97). Subsequently, the full texts of these potentially relevant articles were retrieved.

Data extraction

Two reviewers (RS, MK) independently extracted the data using predefined extraction forms. Data from multiple reports of the same study were extracted on one data collection form. Disagreement was handled by discussion.

Recorded study characteristics included publication type, country and year, total number of patients included and excluded, age, sex distribution, vascular status, single-centre or multicentre design, duration of follow-up, time of randomization, and details about the HBOT regimen used.

Recorded outcome measures included amputation rate, which was reported separately for major (above ankle joint) and minor (below ankle joint) amputations, proportion of healed wounds, mean changes in ulcer size, surgical debridement during follow-up, other additional interventions, antibiotic therapy, and adverse events related to HBOT. Authors of published trials were contacted when additional information was required.

Quality assessment

The methodological quality of the included studies was assessed by two reviewers (RS, MK) independently using a modified version of the Cochrane checklist.[17] The following sources of bias were assessed: randomization; allocation concealment; blinding of patients, clinicians, and assessors to the received treatment; similarity of baseline characteristics; completeness of follow-up of a sufficient number of patients; intention-to-treat analysis; and similarity of other treatments beside the allocated treatment. Any discrepancies were resolved by discussion.

Data analysis

Differences in dichotomous outcomes between the treatment groups (e.g. rates of amputations and wound healing) are expressed as risk differences (RD) and numbers needed

to treat or harm (NNT or NNH) with 95% CI. Differences in continuous outcomes (e.g. ulcer size) are reported as weighted mean differences including 95% CI.

It was planned to perform a meta-analysis using a random effects model a priori because of anticipated clinical and statistical heterogeneity. If the I^2 was above 70%, meta-analysis was avoided and the reason for the study differences was explored.[18] To assess publication bias, an Egger test and contour-enhanced funnel plots were performed.[19] A sensitivity analysis was planned to assess the effects of including only studies of high methodological quality, and subgroup analyses were considered to assess the effects of different HBOT regimens and the presence of foot ischaemia.

RESULTS

669 potentially eligible articles were identified from the databases. Fig. 1 presents the flowchart of study inclusion and reasons for exclusion. Finally, seven articles reporting on seven RCTs fulfilled the inclusion criteria.[13,20–25] These articles were used for data extraction. Also identified was the study protocol for a RCT in patients with diabetic foot lesions persisting at least 3 weeks after optimal revascularization on the www.oxynet.org website.[26] This study was started in 2002. The principal investigator involved was contacted in this COST B14 project diabetic foot lesion study. Although some 30 patients were included, the study was prematurely terminated, and a final report has never been published (personal communication).

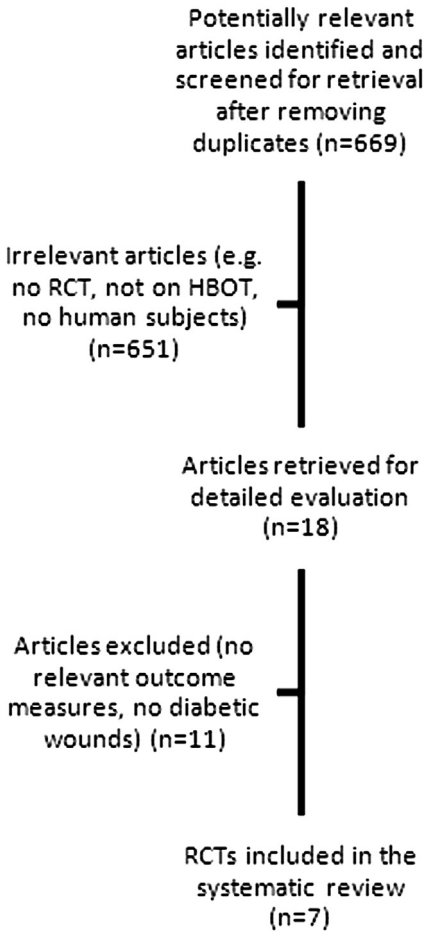

Figure 1. Flow diagram of article inclusion in the systematic review.

Study characteristics

Study characteristics are listed in Table 1. Sample sizes ranged from 18 to 100 patients, and follow-up varied between 2 weeks and more than 1 year. Most patients had type II, as opposed to type I diabetes. The three largest trials included only patients with ulcers classified as Wagner 2, 3, and 4.[13,22,23] Wounds had been present for at least 4 weeks, and infected ulcers were not excluded. The trial by Doctor et al. did not state how many of the 30 included patients were allocated to each study arm.[21]

Study populations were heterogeneous, particularly as to the wound characteristics and presence of ischaemia. All included trials employed different definitions of ischaemia. The study by Abidia et al. specifically investigated ischaemic ulcers, defined as an ankle-brachial pressure index less than 0.8 or great toe-brachial pressure index less than 0.7.[20] The study population of the Faglia trial primarily consisted of patients with compromised peripheral circulation, as judged by the mean ankle blood pressure and transcutaneous oxygen pressure ($TcpO_2$), although it is not apparent if patients with adequate perfusion were excluded from participation.[23] The Löndahl trial included patients with adequate distal perfusion as well as patients with non-reconstructable peripheral arterial disease (PAD).[13] Foot ischaemia, defined as a toe blood pressure of less than 60 mmHg, was present in 57% of their study population. The median toe blood pressure was 52 mmHg. Kessler et al. and Ma et al. specifically included non-ischaemic ulcers, as judged by palpable pulsations, normal Doppler signals, and $TcpO_2$.[24,25] Doctor et al. and Duzgun et al. did not specify the presence of ischaemia.[21,22]

Risk of bias

The results of the risk of bias assessment of the seven RCTs are presented in Table 2. The overall methodological study quality was mediocre. Most studies lacked proper reporting of the treatment allocation procedure and two trials did not report the blinding of assessors. Only two trials were of high quality.[13,20]

Interventions

Two trials compared HBOT with 100% oxygen to hyperbaric air, enabling blinding of patients and physicians with regard to the treatment given.[13,20] The other trials compared HBOT plus standard care to standard care alone. HBOT regimens were quite different among the trials, as the number of HBOT sessions varied between 4 and 45. Table 3 summarizes the HBOT characteristics in each trial.

Study outcomes

Because the populations, interventions, and outcome measures were widely heterogeneous, pooling of data was

Table 1. Baseline patient characteristics.

	Doctor 1992[21]	Faglia 1996[23]	Abidia 2003[20]	Kessler 2003[24]	Duzgun 2008[22]	Löndahl 2010[13]	Ma 2013[25]
N	30	70	18	28	100	94	36
Wagner grade							
Grade 1	?		6%	?			25%
Grade 2	?	13%	94%	?	18%	26%	28%
Grade 3	?	25%		?	37%	56%	47%
Grade 4	?	62%		None	45%	18%	
Median wound surface area	?	?	Median 0.92 cm^2	Mean 2.6 cm^2	?	Median 3.0 cm^2	Mean 4.3 cm^2
Wound duration	?	?	>6 weeks	>3 months	>4 weeks	>3 months	>3 months
Median toe blood pressure	?	?	?	?	?	52 mmHg	?
$TcpO_2$			Mean: 45 mmHg[a]				
Dorsum of foot	?	Mean 22.3 mmHg		Mean 45.4 mmHg	?	Median 49 mmHg[c]	Mean 36.3 mmHg
Wound vicinity	?	?		Mean 21.9 mmHg[b]	?	?	Mean 37.1 mmHg
ABI	?	Mean 0.65	Mean GTPI 0.46	?	?	?	?
Ischaemic ulcers included	?	Yes	Yes	No	?	Yes	No
Diabetes type II (%)	?	?		86%	?	67%	86.1%
Insulin therapy	?	63%	56%	93%	86%	90%	91.7%

$TcpO_2$ = Transcutaneous oxygen pressure; ABI = Ankle/brachial pressure index; GTPI = Great toe pressure index.
[a] Measurement location unknown.
[b] Only measured in the HBOT group.
[c] Values for patients who completed >36/40 sessions; obtained from different report of same study.

deemed inappropriate. Therefore, the results of individual studies are reported separately. For a detailed summary of the main study outcomes see Table 4. In this table, the NNT is given only for studies with a significant difference between HBOT and control groups.

Wound healing and wound size reduction

In both of the two trials that included patients with ischaemic ulcers and reported on wound healing, HBOT resulted in improved rates of wound healing at the final follow-up visit compared with control patients, with an NNT of 1.8 (95% CI: 1.1 to 4.6) and 4.1 (95% CI: 2.3 to 19), respectively (Table 4).[13,20] No increased rate of complete wound healing has been demonstrated in either of the two trials that excluded patients with ischaemic diabetic ulcers. HBOT resulted in improved wound healing compared with the control treatment in one of the two trials with unknown leg perfusion (NNT 1.5 (95% CI: 1.3 to 1.9)).[22]

Three studies reported on reduction in wound size.[20,24,25] In the study by Abidia et al. the median decrease in wound surface area at 6 weeks was significantly higher in the HBOT than in the control group (100% vs. 52%, $p = .027$).[20] Kessler et al. found no difference in wound size reduction after 4 weeks (62% vs. 55%).[24] Ma et al. found an increase in average reduction in ulcer size after 2 weeks in patients treated with HBOT (42% vs. 18%, $p < .05$).[25]

Table 2. Risk of bias assessment of the included trials.

	Doctor 1992[21]	Faglia 1996[23]	Abidia 2003[20]	Kessler 2003[24]	Duzgun 2008[22]	Löndahl 2010[13]	Ma 2013[25]	Total (%)
Adequate randomization method	?	+	+	+	+	+	+	86
Allocation concealment	?	?	+	?	?	+	?	29
Patient blinding	−	−	+	−	−	+	−	29
Clinician blinding	?	?	+	?	?	+	?	29
Assessor blinding	?	+	+	+	?	+	+	71
Baseline similarity	+	+	+	+	−	+	+	86
Complete follow-up available	?	+	+	+	?	+	+	71
All patients accounted for	?	+	+	+	−	+	+	71
Intention-to-treat analysis	?	+	+	?	?	+	?	43
Similar co-interventions	+	+	+	+	+	+	+	100

Table 3. HBOT regimens and follow-up duration.

	Doctor 1992[21]	Faglia 1996[23]	Abidia 2003[20]	Kessler 2003[24]	Duzgun 2008[22]	Löndahl 2010[13]	Ma 2013[25]
HBOT sessions	4	38	30	20	30–45	40	20
Sham treatment	No	No	Yes	No	No	Yes	No
Times daily	?	1, 5/7 days in 'second phase'	1	2	2 and 1 (alternating)	1	2
HBOT duration (minutes)	45	90	90	90	90	85	90
HBOT pressure (ATA)	3	2.5, 2.2–2.4 in 'second phase'	2.4	2.5	2–3	2.5	2.5
Duration of follow-up	?	?	1 year	4 weeks	Mean: 92 weeks	1 year	2 weeks

Amputations

All seven trials reported major and minor amputation rates, as listed in Table 4.

HBOT resulted in a significant decrease in major amputations, with a NNT of 4.2 (95% CI: 2.4 to 17), in one of the three studies that included patients with ischaemic ulcers.[23] However, significantly more minor amputations were performed in patients who received additional HBOT in this study. No effect on amputation rates was observed in the other trials which included ischaemic ulcers.

In both trials that only included patients with adequate peripheral blood circulation, no difference in amputation rates was demonstrated.[24,25]

A reduction in amputation rates was reported in both trials with patients with unknown vascular status. Doctor et al., who reported the number of amputations but did not specify the number of patients in each treatment group or percentages, reported a statistically significant reduction in the number of major amputations (2 vs. 7, $p < .05$) in patients treated with HBOT, but not of minor amputations (4 vs. 2, p is non-significant).[21] In the trial by Duzgun et al. HBOT resulted in a reduction in the number of major amputations, with an NNT of 2.9 (95% CI: 2.1 to 4.8).[22] In addition, in this study there was a reduction in the rates of minor amputations in HBOT-treated patients. However, the authors of this trial employed a different definition of major and minor amputations from the other trials. Specifically, amputations proximal to the metatarsophalangeal joint (MTPJ) were defined as major amputations. Therefore, transmetatarsal amputations were classified as major amputations, whereas these amputations were classified as minor amputations in the other trials. Unfortunately, the authors did not respond to our request for additional information on the number of patients with an above-ankle amputation.

None of the other studies found significant differences in minor amputation rates between HBOT and control treatment.

Additional interventions

The need for additional interventions was reported in four trials. Two of the trials reported on percutaneous transluminal angioplasty (PTA) or peripheral bypass surgery.[13,23] In the Löndahl trial, which excluded patients who were candidates for revascularization at baseline, a vascular reconstruction was performed during follow-up in 6/49 (12%) of patients in the HBOT group and in 4/45 (9%) of patients in the control group.[13] Revascularization rates were also not significantly different in the Faglia trial: 13/36 (36%) vs. 13/34 (38%), although patients who were candidates for revascularization at inclusion were not excluded, and no distinction was made between patients in whom revascularization was performed prior to HBOT or only during follow-up.[23]

Two trials reported on skin graft or flap closure.[21,22] In the trial by Doctor et al., six skin grafts were used in the HBOT group compared with two in the control group.[21] In the study by Duzgun et al., skin grafts or flap closures were only used in patients with Wagner grade IV ulcers, significantly more often in patients treated with HBOT: 4/25 (16%) versus 0/20 (0%) ($p < .05$).[22]

Two trials reported on surgical debridement.[22,23] Duzgun et al. reported significantly higher rates of surgical debridement in the control group: 0/50 (0%) versus 9/50 (18%).[22] In the study by Faglia et al., aggressive surgical debridement was performed in all patients.[23] Other studies did not state the frequency of debridement or did not distinguish between bedside debridement and debridement performed in the operating room.

Complications

Five trials reported on adverse events of HBOT.[13,20,23–25] Two trials reported no adverse events.[20,25] Three trials reported 1/49 (2%), 1/36 (3%), and 2/15 (13%) cases of barotraumatic otitis, respectively, which was a reason for termination of treatment in at least one case.[13,23,24] In the Löndahl trial, myringotomy with tube placement due to pain caused by the inability to equilibrate air pressure through the Eustachian tube was performed in 2/49 (4%) patients in the HBOT group, and in 2/45 (4%) in the hyperbaric air group.[13] Hypoglycaemia was reported in 2/49 (4%) and 4/45 (9%) patients in the HBOT group and the hyperbaric air group, respectively.[13] Dizziness and worsening of cataract were each described in 1/49 (2%) patients.[13]

DISCUSSION

The available evidence on the effectiveness of HBOT for the treatment of diabetic leg ulcers is not solid, both because of clinical heterogeneity and methodological shortcomings of

Table 4. Outcomes of the individual RCTs.

	Ischaemic ulcers included						Non-ischaemic ulcers				Unknown vascular status			
	Faglia 1996[23]		Abidia 2003[20]		Löndahl 2010[13]		Kessler 2003[24]		Ma 2013[25]		Doctor 1992[21]		Duzgun 2008[22]	
Ischaemia	Mean ABI 0.65, mean $TcpO_2$ 22.3 mmHg		Mean GTPI 0.46, mean $TcpO_2$ 45 mmHg		Median TBP 52 mmHg		Palpable pulses, normal Doppler signals and $TcpO_2$		Palpable pulses, normal Doppler signals and $TcpO_2$		Unknown		Not distinguished	
	HBOT	Control	HBOT	Control	HBOT	Control	HBOT	Control	HBOT	Control	HBOT	Control	HBOT	Control
	N = 36	*N* = 34	*N* = 9	*N* = 9	*N* = 49	*N* = 45	*N* = 15	*N* = 13	*N* = 18	*N* = 18	*N* = ?	*N* = ?	*N* = 50	*N* = 50
Wound healing, *n* (%)	—	—	5 (56%)	0 (0%)	25 (51%)	12 (27%)	2 (13%)	0 (0%)	0 (0%)	0 (0%)	—	—	33 (66%)	0 (0%)
Risk difference % (CI)			56% (22% to 89%)		24% (5.3% to 43%)		13% (−6.9% to 34%)		0% (−10% to 10%)				66% (53% to 79%)	
NNT/NNH (CI)			NNT 1.8 (1.1 to 4.6)		NNT 4.1 (2.3 to 19)								NNT 1.5 (1.3 to 1.9)	
Major amputations, *n* (%)	3 (8%)	11 (32%)	1 (11%)	1 (11%)	3 (6%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2	7	0 (0%)	17 (34%)
Risk difference % (CI)	−24% (−42% to −5.9%)		0% (−29% to 29%)		3.9% (−4.1% to 12%)		0% (−13% to 13%)		0% (−10% to 10%)				−34% (−47% to −21%)	
NNT/NNH (CI)	NNT 4.2 (2.4 to 17)												NNT 2.9 (2.1 to 4.8)	
Minor amputations, *n* (%)	21 (58%)	12 (35%)	1 (11%)	0 (0%)	4 (8%)	4 (9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4	2	4 (8%)	24 (48%)
Risk difference % (CI)	23% (0.3% to 46%)		11% (−15% to 37%)		−0.73% (−12% to 11%)		0.0% (−13% to 13%)		0% (−10% to 10%)				−40% (−56% to −24%)	
NNT/NNH (CI)	NNH 4.3 (2.2 to 345)												NNT 2.5 (1.8 to 4.1)	

ABI = Ankle/brachial pressure index; $TcpO_2$ = Transcutaneous oxygen pressure; GTPI = Great toe pressure index; TBP = Toe blood pressure; HBOT = Hyperbaric oxygen therapy; NNT = Number needed to treat; NNH = Number needed to harm; CI = Confidence interval.

the clinical trials. Within and between study clinical heterogeneity was substantial with regard to wound characteristics and vascular status. Most studies were probably underpowered, and only one study provided a sample size calculation.[23] Moreover, HBOT regimens varied widely among the trials, as well as the definitions used for the outcome measures major amputation and wound healing. In addition, the duration of follow-up of some studies was either not defined or too short to yield meaningful, patient-relevant outcomes. For these reasons it would be inappropriate to pool data in a meta-analysis.

By exploring the results of the individual studies some evidence was found that HBOT improves wound healing in ischaemic diabetic ulcers in the longer term, as opposed to non-ischaemic diabetic ulcers. However, HBOT should not be considered a substitute for optimal revascularization,[27] and in all trials patients underwent revascularization if indicated prior to HBOT. Given that optimal revascularization is considered a prerequisite before using HBOT, it may be noted that angiosome-directed revascularization has increasingly been reported to achieve optimum perfusion of ulcers.[28,29] Although both of the trials that included patients with ischaemic ulcers with improved wound healing were well-designed sham-controlled RCTs, the number of patients was too small and the populations were too diverse to draw definite conclusions.[13,20] One of the trials with unknown ulcer type reported a beneficial effect on wound healing, although this trial defined wound healing as healing without an intervention in the operating room.[22] Remarkably, none of the 50 patients in the control group reached this endpoint during the mean follow-up of 22 months. It should be noted that this trial was at an overall unclear risk of bias, including blinding of caregivers and outcome assessors, and that the outcome measure may be particularly prone to performance bias.

It might be that the effectiveness of HBOT in patients with ischaemic diabetic ulcers is underestimated. Two of the trials used air at hyperbaric pressure in the control groups, thus enabling the blinding of patients and clinicians.[20,23] Although a study designed as such is ideal to prove the concept of the effectiveness of HBOT, breathing air at hyperbaric pressure might also increase the blood oxygen concentration, thereby possibly diluting a treatment effect, as opposed to when standard wound care would have been the comparator treatment.

We did not find consistent evidence for HBOT preventing major or minor amputations, either in patients with and without concomitant foot ischaemia. Two out of the three RCTs which included patients with foot ischaemia, which were of acceptable methodological quality, reported no significant difference in major amputation rates.[13,20] The third trial on ischaemic ulcers did report significantly decreased major amputation rates, which was accompanied by a significant increase in minor amputations.[23] The increase in minor amputations may reflect limb salvage at the expense of minor amputations. Two trials in patients with unknown vascular status reported decreased major amputation rates, although these results cannot be compared

because of inconsistency in the definition of major versus minor amputations.[21,22]

HBOT did not seem to decrease the need for revascularization in patients in whom revascularization was not indicated prior to HBOT, although this observation is derived from a single RCT.[13] Although revascularization rates were reported in one additional trial, the report of this trial does not distinguish between patients in whom revascularization was performed at baseline, prior to HBOT, or during follow-up, in patients who were not candidates for revascularization at baseline.[23]

HBOT can generally be considered a safe treatment modality, which is reflected by the low frequency of adverse events in the trials included in this review. Reported side effects include barotraumatic otitis, hypoglycaemia, and worsening of cataract, as well as oxygen-induced seizures, although the occurrence of such an event was not described in the included RCTs.

It has been postulated that the addition of HBOT to standard care in chronic diabetic foot ulcers is an effective way of decreasing the overall costs of diabetic wounds.[30] Yet, although insurance companies in the USA and Europe reimburse HBOT for treatment of diabetic ulcers irrespective of their origin, the evidence for the effectiveness of HBOT, at least in non-ischaemic diabetic ulcers, is limited and therefore its cost-effectiveness remains to be established.[31,32]

Recently, a retrospective cohort study of 6259 patients with non-ischaemic diabetic foot ulcers which were managed by a wound care company in the USA was published.[33] The results indicated that patients who were treated with HBOT ($n = 793$) had an increased risk of any amputation (6.7% vs. 2.1%), a major amputation (3.3% vs. 1.3%), and a lower probability of wound healing (43.2% vs. 49.6%) after 16 weeks follow-up compared with patients who did not have HBOT. These differences remained statistically significant after adjustment for confounders. The strength of this study is in the large number of patients receiving HBOT who were included. Yet, several points of criticism of the design and reporting of the study have been expressed in a number of recent commentaries.[34–38] First, although the authors corrected for wound severity and patient comorbidities through propensity scoring, many known and unknown confounding factors may have introduced selection bias, inherent to the retrospective design of the study. Second, the majority of patients had Wagner Grade II ulcers, whereas prospective trials have focussed mainly on more severe ulcers. Third, follow-up was limited to 16 weeks, and a longer follow-up may be required before the maximal effect of HBOT can be demonstrated.[13] Fourth, the proportion of patients that completed all HBOT sessions was unknown. Finally, although HBOT should only be considered after optimal limb perfusion has been achieved,[27] it is unclear if all patients underwent thorough vascular examination to determine the indication for revascularization, as the study report only states that adequate perfusion was 'determined by a physician'. In a response, the authors of the study rightly state that the results from RCTs often mirror the effectiveness of a study treatment in an idealized, highly controlled setting, whereas a cohort study may provide more reliable estimates of the effectiveness of a study-treatment in a 'real-world' setting.[39] This remark is important in light of the burdensome nature of a full HBOT regimen, which may also limit the feasibility and effectiveness of HBOT in practice. The authors did not report information on the proportion of patients who dropped out.

Liu et al. recently performed a meta-analysis of 13 controlled trials including RCTs, non-randomized controlled trials and case-control studies, comprising a total of 624 patients with both ischaemic and non-ischaemic ulcers, and reported significantly increased healing rates (RR 2.33, 95% CI: 1.51 to 3.60) and decreased major amputation rates (RR 0.29, 95% CI: 0.19 to 0.44).[40] Results from observational studies have also been summarized by O'Reilly et al.[15] In their pooled analysis of four comparative observational studies comprising a total of 191 patients, additional HBOT significantly decreased the risk of major amputation (RR 0.39, 95% CI: 0.21 to 0.73). Although including observational studies increases sample size and decreases the risk of publication bias, studies designed as such are obviously biased, and the positive results could not be reproduced in their meta-analysis of RCTs.[15]

A possible limitation of this systematic review is that some RCTs in the field might not have been located, leading to publication bias. Yet, the search was extensive, and it is believed that no important studies were missed. Unfortunately, the unpublished data from the prematurely stopped trial could not be included in this review. Another possible limitation is that only RCTs were included. Although such studies provide the highest level of evidence, the total number of patients included in the RCTs was low, which may limit the external validity of the summarized data. Moreover, the strength of the evidence provided by this review is limited because only two of the included RCTs were considered to be of acceptable quality.

In conclusion, considering the low quality of current evidence, the high costs of HBOT, and the burdensome nature of a full HBOT regimen, there is insufficient evidence to support the routine use of HBOT as an adjunct to standard wound care in diabetic patients with foot ulcers. Although there is some indication of a beneficial effect on wound healing, it is currently unknown which patients are likely to benefit from HBOT and which patients are not. Before large-scale implementation of HBOT in routine practice can be justified, its effectiveness needs to be confirmed in large RCTs of strong methodological quality using uniform outcome measures to enable comparison of outcomes. Moreover, future trials should identify the subgroup of patients who are most likely to benefit from HBOT, establish the optimal HBOT regimen, and should be adequately powered to identify a possible effect on amputation rates. Given that previous RCTs have indicated beneficial effects of HBOT particularly in diabetic patients with ischaemic leg ulcers, future research should

specifically focus on these patients. Two multicentre trials have recently started. The O'Reilly study (NCT00621608) will include only patients without large vessel disease and who are not candidates for revascularization, and the DAMOCLES-trial (NTR3944) will specifically study patients with ischaemic diabetic ulcers.[41,42] The results of these trials will contribute to evidence-based decision making on the use of HBOT as an adjunctive therapy in patients with a diabetic foot ulcer.

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CONFLICT OF INTEREST

None.

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APPENDIX 1. FULL SEARCH STRATEGY

MEDLINE (Pubmed)

January 1962 – August 2013. (Diabetic Foot[Mesh] OR Foot Ulcer[Mesh] OR Leg Ulcer[Mesh] OR ((diabetes[tiab] OR diabetic[tiab]) AND (foot[tiab] OR feet[tiab] OR ulcer*[tiab] OR wound*[tiab])) OR (foot[tiab] AND ulcer*[tiab]) OR (feet [tiab] AND ulcer*[tiab]) OR plantar ulcer*[tiab] OR leg ulcer*[tiab] OR ulcus cruris[tiab] OR crural ulcer*[tiab]) AND (Hyperbaric Oxygenation[Mesh] OR (hyperbaric[tiab] AND oxygen*[tiab]) OR HBO[tiab] OR HBOT[tiab] OR (oxygen* [tiab] AND (high pressure[tiab] OR high tension[tiab])) OR hyperbaric chamber*[tiab]) NOT case report

Embase

January 1973 – August 2013. ('leg ulcer'/OR 'foot ulcer'/OR 'diabetic foot'/OR 'diabetic feet'.ti,ab. OR (diabetes adj3 ulcer*).ti,ab. OR (diabetic adj3 ulcer*).ti,ab. OR (diabetic adj3 wound*).ti,ab. OR (diabetes adj3 wound*).ti,ab. OR (leg* adj3 ulcer*).ti,ab. OR (foot adj3 ulcer*).ti,ab. OR (ulcer* adj3 feet).ti,ab. OR (plantar* adj3 ulcer*).ti,ab. OR 'ulcus cruris'.ti,ab. OR 'crural ulcer'*.ti,ab. OR (diabetic adj3 foot).ti,ab. OR (diabetic adj3 feet).ti,ab.) AND ('hyperbaric oxygen'/exp OR 'hyperbaric and oxygen*'.ti,ab. OR hbo.ti,ab. OR hbot.ti,ab. OR 'hyperbaric chamber*'.ti,ab. OR (oxygen* and (high pressure or high tension)).ti,ab.) NOT case report/

Cochrane library

To August 2013. #1 MeSH descriptor Diabetic Foot explode all trees

#2 MeSH descriptor Foot Ulcer explode all trees

#3 MeSH descriptor Leg Ulcer explode all trees

#4 (diabet*):ti,ab,kw (foot):ti,ab,kw or (feet):ti,ab,kw or (ulcer*):ti,ab,kw or (wound*):ab

#5 (feet):ti,ab,kw and (ulcer*):ti,ab,kw

#6 (plantar ulcer*):ti,ab,kw

#7 (ulcus cruris):ti,ab,kw

#8 (crural ulcer):ti,ab,kw

#9 MeSH descriptor Hyperbaric Oxygenation explode all trees

#10 (hyperbaric):ti,ab,kw and (oxygen*):ti,ab,kw

#11 (hbo):ti,ab,kw or (hbot):ti,ab,kw

#12 (oxygen*):ti,ab,kw

#13 (high pressure):ti,ab,kw or (high tension):ti,ab,kw or (hyperbaric chamber*):ti,ab,kw

(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) AND (#9 OR #10 OR #11 OR #12 OR #13 OR #14)

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