A systematic review and meta-analysis of hyperbaric oxygen therapy for diabetic foot ulcers with arterial insufficiency

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ABSTRACT

Background: Diabetic foot ulcers (DFUs) are frequently associated with peripheral arterial occlusive disease (PAOD) and may ultimately lead to amputations of the lower extremity. Adjuvant hyperbaric oxygen treatment (HBOT) might foster better wound healing and lower amputation rates in patients with DFU and PAOD. A systematic review was conducted to assess the effects of HBOT as an adjunctive therapy to standard treatment for patients with DFUs with PAOD.

Methods: Systematic review using the MEDLINE, EMBASE, and Cochrane CENTRAL databases (from inception to October 2018). All original, comparative studies on the effect of HBOT on DFUs with PAOD were eligible. The primary outcome measures were amputation rate, amputation-free survival, complete ulcer healing, and mortality.

Results: Eleven studies, totaling 729 patients, were included for analysis, including 7 randomized clinical trials, 2 controlled clinical trials, and 2 retrospective cohorts. Four were used for quantitative synthesis. Meta-analysis showed a significantly fewer major amputations in the HBOT group (10.7% vs 26.0%; risk difference, −15%; 95% confidence interval [CI], −25 to −6; $P = .002$; number needed to treat, 7; 95% CI, 4-20). No difference was found for minor amputations (risk difference, 8%; 95% CI, −13 to 30; $P = .46$). Three studies reporting on complete wound healing showed contrasting results. No significant difference was found for mortality or amputation-free survival.

Conclusions: Current evidence shows that adjuvant HBOT improves major amputation rate, but not wound healing, in patients with DFUs and PAOD. Given the wide range of patients included in the trials, better patient selection may help define which patients with DFUs and PAOD benefit most from HBOT as standard adjunctive treatment. (J Vasc Surg 2020;71:682-92.)

Keywords: Hyperbaric oxygen therapy; Diabetic foot ulcer; Peripheral arterial occlusive disease; Systematic review; Meta-analysis

Diabetes is a major health care problem with an estimated incidence of 422 million people worldwide.[1] Besides blindness, kidney failure, heart attacks, and strokes, a major burden of diabetes is the occurrence of diabetic foot ulcers (DFUs).[1] DFUs, often complicated with sensory neuropathic impairment, have a complex pathophysiology and are often associated with peripheral arterial occlusive disease (PAOD).[2] Standard treatment consists of pressure relief, restoration of skin perfusion, treatment of infection, metabolic control, local wound care, education, and prevention of recurrence.[3] Despite optimal treatments, DFUs are the main cause of lower extremity amputations, especially in the presence of leg ischemia.[4] Two of three amputations are diabetes related, with a yearly amputation rate of 2.5% for diabetic patients.[4,5]

Hyperbaric oxygen therapy (HBOT) has been proposed as a useful adjunct in the complex treatment of DFUs with PAOD, in particular because of the presence of local arterial insufficiency,[6] whereas recent evidence on HBOT for DFUs is still ambiguous.[7-10] HBOT involves breathing 100% oxygen at two to three times the normal atmospheric pressure in a hyperbaric chamber and results in elevated oxygen tension in arteries and tissue.[11] It improves local tissue oxygenation and transcutaneous oxygen pressure measurement ($TcpO_2$).[12-14] Further research also shows that HBOT might improve neovascularization, stimulates stem cells and growth factors, inhibits the inflammatory response, and has a bacteriostatic effect on anaerobic bacteria.[15] HBOT is commonly used as a treatment for a variety of indications as set out in the published recommendation of the Undersea

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and Hyperbaric Medical Society and the European College of Hyperbaric Medicine.[16,17] Treatment with HBOT is considered a cumbersome, but low-risk, therapy. Described side effects are middle ear barotrauma (up to 2%), myopia, and sinus barotrauma.[18]

O'Reilly et al,[19] Stoekenbroek et al,[6] and Zhao et al[10] published literature reviews regarding HBOT as adjunctive treatment in DFU and concluded that there was insufficient evidence, at that time, to support the routine use of HBOT as a standard adjunct to local and systemic wound care in diabetic patients with foot ulcers with and without PAOD. In 2015, Kranke et al[9] updated their Cochrane review and meta-analysis on the treatment of chronic wounds and concluded that HBOT improves the outcome of DFU at 6 weeks, but not after 1 year. Elraiyah et al[8] found low- to moderate-quality evidence to support the use of HBOT to prevent amputations in DFUs. These reviews, however, did not focus on the subgroup of DFUs with PAOD. Furthermore, after publication of these reviews, new evidence has emerged. Three new original studies were published, from which one focused specifically on DFUs with PAOD. Therefore, a new systematic review seems appropriate to appreciate current evidence as to the effect of HBOT in patients with DFUs with PAOD, as adjunctive therapy to standard vascular, diabetic, and wound treatment to promote wound healing and prevent major amputations.

METHODS

The protocol for the review objectives, literature search strategies, inclusion and exclusion criteria, outcome measurements, and methods of statistical analyses was prepared a priori, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[20,21] and is described in the following section.

Literature search strategy. A systematic review of original, comparative articles (published between 1900 and September 2018) on the effects of HBOT in patients with a DFU and ischemia was performed in the MEDLINE, EMBASE, and Cochrane CENTRAL databases. The search strategy was formed with the help of a clinical librarian. In short, the keywords "hyperbaric oxygenation," "diabetes," "leg ulcer," "ischemia," and related MeSH terms and their equivalents were used. The full search strategy is supplemented as Appendix (online only). A hand search was conducted of references in eligible studies. No language restriction was applied.

Inclusion and exclusion criteria, data extraction, and outcomes of interest. Two authors (R.J.B., R.C.L.) independently screened the potentially eligible studies, based on predefined inclusion and exclusion criteria. Comparative studies were included if they performed HBOT in patients with diabetes type 1 or 2 with PAOD and a leg ulcer, in addition to standard treatment regimens. Studies that included both patients with and without PAOD were excluded for quantitative analysis if no subgroup data of ischemic DFUs were given. PAOD was defined as an ankle-brachial pressure index ≤0.9, a toe-brachial pressure index (TBI) ≤0.70, a toe pressure (TBP) <30 mm Hg or $TcpO_2$ on the dorsum of the foot <30 mm Hg.[22] The liberal ankle-brachial pressure index criteria are used because of the common problem of incompressible arteries in this population.[23] Studies were not excluded on the basis of language or publication date.

Outcome measures. Two authors (R.J.B., R.C.L.) independently collected a predefined set of outcome measures. These comprised study characteristics, patient characteristics, and the following primary study outcomes: amputation rate ("major," ie above the ankle, and "minor"), amputation-free survival (AFS), complete ulcer healing, and mortality. As secondary outcome measures, we considered time to complete healing any measure of quality of life as reported by the authors; $TcpO_2$ values before, during, and after the treatment; need for additional (surgical) interventions; adverse effects of HBOT; and costs, if reported. Any discrepancies were resolved by discussion.

Quality assessment. The same authors also independently assessed the quality of the included studies, using the Cochrane Collaboration checklists[24,25] These checklists are abbreviated PRISMA and ROBINS-2 checklists, containing items to appreciate the risk of bias of included studies, such as selection bias, performance bias, detection bias, attrition bias, reporting bias, comparability and outcome bias. Again, discrepancies were resolved by discussion among the authors.

Data analysis. Outcomes are presented as means with standard deviations, medians with interquartile ranges, or percentages, where appropriate. Differences in outcomes between treatment groups are expressed as risk differences (RDs) or differences in means, with their 95% confidence intervals (CIs). For significant differences, the corresponding numbers needed to treat (NNT) were calculated. Review Manager v. 5.3 (Copenhagen, The Nordic Cochrane Centre TCC, 2014) was used to perform a meta-analysis of the primary outcomes, if possible. The I^2 test was used as a measure of statistical heterogeneity. If the I^2 would be below 25%, a fixed effect was used; if between 25% and 75%, a random effect was used. Above 75%, no meta-analysis would be conducted but the reasons for heterogeneity were to be explored.

RESULTS

A total of 11 studies[26-36] were included for qualitative analysis and are presented in Table I. Figure 1 shows the literature search and study selection. Six studies[31-36] did not specify an ischemic subgroup and one study[30] did not measure a clinically relevant outcome measure as specified in the methods. All authors of the studies

Table I. Characteristics of included studies

Author	Year	Study	HBOT size	Control size	PAOD/ mix	HBOT application	Number of sessions (SD)	Follow-up	Outcome measures
Faglia[a]	1996	RCT	35	33	PAOD	90 min, 2.2-2.5 ATA, 5 d/w	38	Unknown	AR, VI, $TcpO_2$
Kalani[a]	2002	CCT	17	21	PAOD	90 min, 2.5 ATA, 5 d/w	40-60	3 years	AR, CUH, $TcpO_2$, HT, M
Abidia[a]	2003	RCT	9	9	PAOD	90 min, 2.4 ATA, 5 d/w	30	1 year	AR, US, CUH, HT, M, QoL
Santema[a]	2018	RCT	60	60	PAOD	90 min, 2.4 ATA, 5 d/w	40	Unknown	AR, AFS, CUH, VI, HT, M
Perren	2018	RCT	13	13	PAOD	120 min, ATA unknown, 5 d/w	40	4 weeks	US, UD
Baroni	1987	CCT	18	10	Unknown	90 min, 2.5/2.8 ATA, 7 d/w	CUH, 34 (22)	13.5 (1-36) months	AR, CUH
Oriani	1990	Retrospective cohort	62	18	Mix	Unknown, 2.5/2.8 ATA, 5-6 d/w	CUH, 72 (29)	Unknown	AR, CUH
Faglia	1998	Retrospective cohort	51	64	Mix	90 min, 2.5 ATA, 7 d/w and 90 min, 2.2-2.4 ATA, 5 d/w	CUH, 32 (11)	3 years	AR
Duzgun	2008	RCT	50	50	Unknown	90 min, 2-3 ATA, daily to 2 d/w	30-45	92 (±12) weeks	AR, CUH
Löndahl	2010	RCT	49	45	Mix	85 min, 2.5 ATA, 5 d/w	40-50	9 months	AR, CUH, VI, M
Chen	2017	RCT	22	20	Unknown	120 min, 2.5 ATA, 5 d/w	20	2 weeks	CUH, QoL

AFS, Amputation free survival; *AR,* amputation rate; *CCT,* controlled clinical trial; *CUH,* complete ulcer healing; *d/w,* days per week; *HBOT,* hyperbaric oxygen treatment; *HT,* healing time; *M,* mortality; *PAOD,* peripheral arterial occlusive disease; *QoL,* quality of life; *RCT,* randomized clinical trial; *SD,* standard deviation; *$TcpO_2$,* transcutaneous oxygen pressure; *US,* ulcer size; *UD,* ulcer depth; *VI,* vascular intervention.
[a]Included in quantitative analysis.

with an ischemic subgroup[32,33,35] or unknown vascular status[31,34,36] were approached by e-mail, if possible, to share the data of the ischemic subgroup for inclusion in the quantitative synthesis (meta-analysis) and narrative summary. After this selection, four studies[26-29] were included for quantitative synthesis.

Characteristics of included studies. The study characteristics for the 11 included studies are shown in Table I, comprising 7 randomized controlled trials (RCTs),[26,28-30,34-36] 2 controlled clinical trials,[27,31] and 2 retrospective cohort studies.[32,33] Three studies[29,30,36] were recently published and therefore not included in previous reviews. Five studies focused on ischemic DFUs only,[26-30] 3 studies had a mix of ischemic and nonischemic DFUs,[32,33,35] and 3 studies did not report on vascular status.[31,34,36] The studies mostly used a protocol of 90 minutes of HBOT with pressures between 2.2 and 2.8 ATA for 5 of 7 days a week, aiming for a total of 20 to 60 sessions. Three studies applied HBOT until complete ulcer healing.[31-33] Follow-up time varied greatly between just 2 weeks and 3 years. Study sizes varied from 18[24] to 120[25] patients.

Nine studies[26-29,31-35] described amputation rates, mostly divided into minor and major amputations. None of the studies distinguished between below or above the knee amputations for major amputations. Duzgun et al[34] was the only study that classified amputations in proximal and distal from the metacarpophalangeal joint. Eight studies[27-29,31,32,34-36] reported on complete ulcer healing. Mortality was described in four studies.[27-29,35] Two studies[28,30] reported on the reduction of ulcer size or ulcer depth, which were not predefined as an outcome in this review as it is a surrogate and less patient-relevant outcome. Three studies[26,29,35] assessed the need for additional vascular interventions. Another two studies[26,27] reported on $TcpO_2$ measurements measured on the dorsum of the foot. Santema et al[29] was the only study describing AFS. Only Löndahl et al[35] used a sham treatment, consisting of breathing room air through double-blinded pipes under the same atmospheric pressure as the HBOT group.

Characteristics of included patients. Baseline patient characteristics of the included studies are shown in Table II. Six studies[31-36] did not provide baseline statistics for the subgroup containing PAOD separately. Three studies found a significant difference in baseline characteristics.[27,33,34] In the controlled trial of Kalani et al,[27] patients in the HBOT group had a significantly lower mean age and a significantly larger mean ulcer size, which was not adjusted for in their analyses. The retrospective cohort study of Faglia et al[33] found a significantly lower mean age in the HBOT group, which also was not adjusted for. In the RCT of Duzgun et al,[34] there was a significantly higher proportion of male patients in the HBOT group. Only three studies[27,29,35] reported a toe pressure. The Wagner grade of the included ulcers varied between studies, if reported. Four studies included

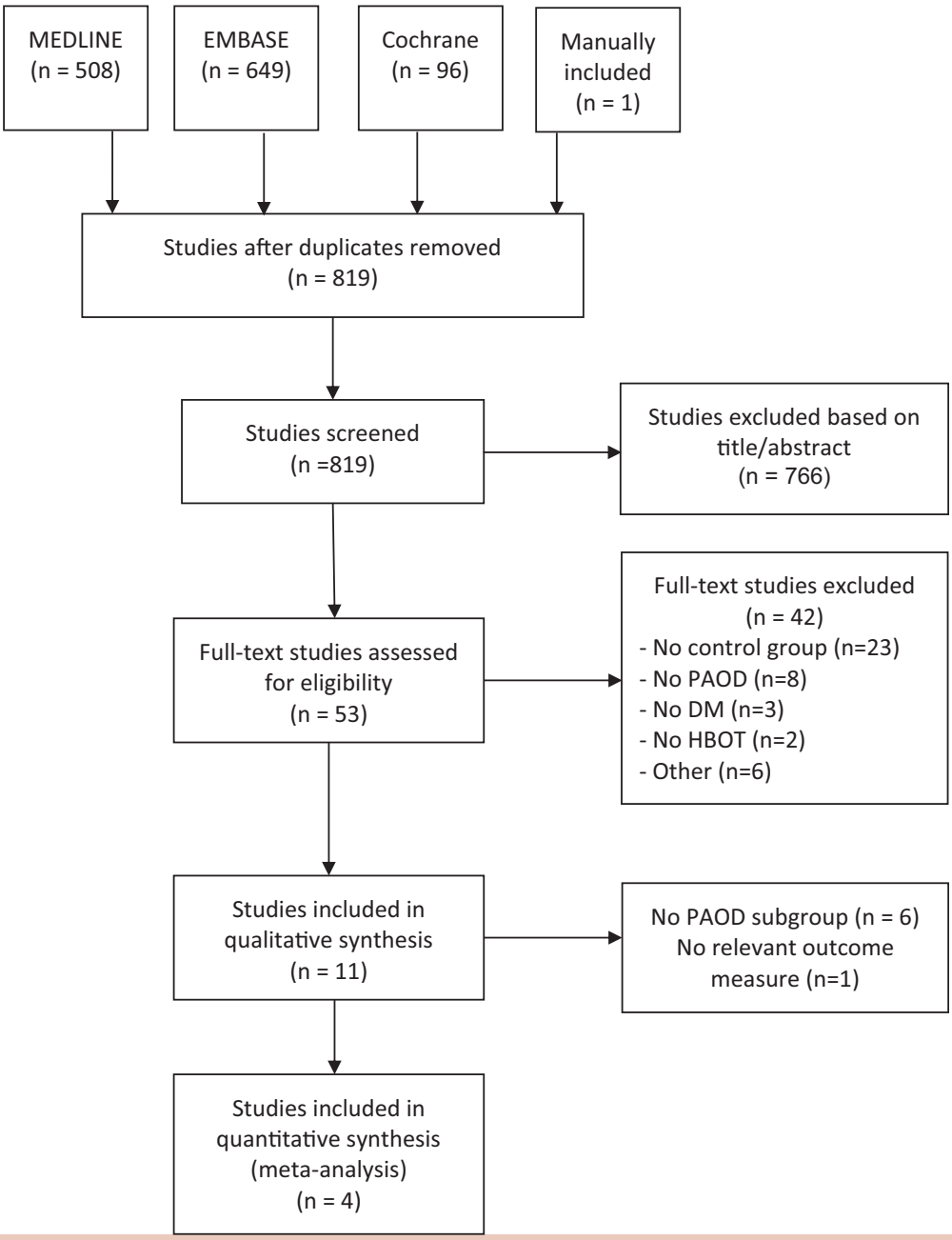

Fig 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart for meta-analysis. *DM*, Diabetes mellitus; *HBOT*, hyperbaric oxygen therapy; *PAOD*, peripheral arterial occlusive disease.

patients with ulcers in Wagner grades II-IV,[26,29,34,35] one study included Wagner grade I-III patients[30] and other patients from Wagner grades I and II.[28] Five studies[26,28,29,31,32] reported on polyneuropathy (PNP), of which three studies[26,31,32] found high percentages of PNP (94% to 100% in the HBOT groups vs 90% to 95% in the control groups), whereas Santema et al[29] reported lower PNP rates: 41 (68%) patients in the HBOT group and 32 (53%) patients in the control group. Abidia et al[28] used a biothesiometer to assess PNP and found an average of 47 (95% CI, 14.6-79.4) in the HBOT group and 55 (95% CI, 27.6-82.4) in the control group.

Quality assessment. Assessment of the methodological quality of the seven randomized studies[26,28-30,34-36] was conducted using the Cochrane checklist for RCTs and is shown in Table III, *A*. The quality assessment of the four nonrandomized studies[27,31-33] was performed using the ROBINS-I tool[37] and is shown in Table III, *B*. The overall quality of the included randomized studies was good, whereas three nonrandomized studies[27,31,32] were at serious risk of bias. Four randomized studies[26,30,34,36] did not blind the doctor, patient, and outcome assessor and three studies[26,28,36] did not use an intention-to-treat analysis. All studies[26-36]

Table II. Baseline patient characteristics

Author	Sex (% Male)	Age, years	Ulcer size, mm^2	Duration DM, years	HbA1c, %	$TcpO_2$, mm Hg	PNP, %	Wagner grade I	Wagner grade II	Wagner grade III	Wagner grade IV	Toe pressure
Faglia 1996												
HBOT	77	62	–	16	9.3	–	100		12	26	63	–
Control	63	66	–	19	8.5	–	94		15	24	61	–
Kalani												
HBOT	71	54[a]	1077[a]	28	7.1	22	–		–	–	–	48
Control	86	65[a]	449[a]	26	7.3	25	–		–	–	–	54
Abidia												
HBOT	67	72	106	13	–	46	[b]	0	100	0	0	–
Control	33	70	78	10	–	43	[b]	13	88	0	0	–
Santema												
HBOT	85	68	–	17	–	23	68	0	45	33	22	45
Control	77	71	–	19	–	23	53		58	27	15	41
Perren												
HBOT	77	–	1173	–	–	–	–	15	15	79	0	–
Control	77	–	1060	–	–	–	–	15	15	79	0	–
Baroni												
HBOT	61	58	3340	17	–	–	94	–	–	–	–	–
Control	60	60	2810	14	–	–	90	–	–	–	–	–
Oriani												
HBOT	58	53	–	15	9.5	–	95	–	–	–	–	–
Control	67	58	–	16	8.2	–	94	–	–	–	–	–
Faglia 1998												
HBOT	–	62[a]	–	–	–	–	–	–	–	–	–	–
Control	–	65[a]	–	–	–	–	–	–	–	–	–	–
Duzgun												
HBOT	74[a]	58	–	17	8	–	–	0	12	38	50	
Control	54[a]	63	–	16	8.7	–	–	0	24	36	40	
Löndahl												
HBOT	78	69	–	20	7.8	–	–	0	24	51	24	50
Control	84	68	–	23	8.1	–	–	0	27	62	11	55
Chen												
HBOT	50	64	–	–	8.8	–	–	–	–	–	–	–
Control	61	61	–	–	8.3	–	–	–	–	–	–	–

DM, Diabetes mellitus; *HbA1c,* hemoglobin A1c; *HBOT,* hyperbaric oxygen therapy; *PNP,* polyneuropathy; *$TcpO_2$,* transcutaneous oxygen pressure.
[a]Significant difference.
[b]Used biothesiometer.

had a limited loss to follow-up, had a similar standard treatment, and did not receive sponsoring or only received sponsoring from independent institutions.

Quantitative analysis (meta-analysis). The included studies[26-36] primarily focused on amputation rate, complete ulcer healing, and healing time as primary outcome measures and are shown in Table IV. Some studies also reported on $TcpO_2$, vascular interventions, quality of life, costs, mortality, and adverse effects. The outcomes of the four studies included for quantitative synthesis[26-29] are described in the following section. Meta-analyses could be performed meaningfully for major amputation rate, minor amputation rate, and mortality. Clinical heterogeneity was too large to perform a meta-analysis for the other outcomes. Therefore, these will be described later.

Amputation rate. Amputation rates reported in the four clinical trials comprising only patients with ischemic DFUs could be pooled.[26-29] They are subcategorized in major and minor amputations. The forest plots are

Table III. A, Quality assessment using Cochrane risk of bias tool

	Faglia (1996)	Abidia	Santema	Perren	Duzgun	Löndahl	Chen	Total, %
Randomization	+	+	+	+	+	+	+	100
Treatment allocation concealed	−	+	+	+	+	+	+	86
Patient/doctor blinded	−	+	+	−	−	+	−	43
Outcome assessors blinded	−	+	+	−	−	+	−	43
Study groups comparable	+	+	+	+	−	+	+	86
Lost to follow-up limited	+	+	+	+	+	+	+	100
ITT analysis	−	−	+	+	+	+	−	58
Standard treatment comparable	+	+	+	+	+	+	+	100
Selective publication excluded	+	+	+	+	+	+	+	100
No sponsorship	+	+	+	+	+	+	+	100
Total, %	70	90	100	80	70	100	70	

+, Complied to item; −, did not comply to item; *ITT*, intention to treat.

Table III. B, Quality assessment using ROBINS-I risk of bias tool

	Confounding	Patient selection	Classification of interventions	Deviation from interventions	Missing data	Measurement errors	Selective reporting	Overall risk of bias
Kalani	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Baroni	Serious	Low	Low	Low	Low	Low	Low	Serious
Oriani	Serious	Low	Low	Low	Low	Low	Low	Serious
Faglia (1998)	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Overall score	Serious	Moderate	Low	Low	Low	Low	Low	

shown in Figs 2 and 3. Major amputation rate was significantly lower in the group treated with HBOT than in the control group 10.7% vs 26.0% (RD, −15%; 95% CI, −25 to −6, $P = .002$; NNT, 7; 95% CI, 4-20). Minor amputation rates did not differ significantly (RD, 8%; 95% CI, −13 to 30; $P = .46$).

Healing time. Abidia et al[28] and Kalani et al[27] assessed healing time as the mean time needed for an ulcer to heal. Santema et al[29] also reported on healing time, defined as the median time the wounds needed to fully heal. The mean healing time was obtained from the authors of Santema et al.[29] The pooled results are shown in Fig 4 and shows no significant difference between the HBOT and control group.

Mortality. Mortality was described by three studies[27-29] and is shown as a forest plot in Fig 5, showing no significant differences when pooled. Mortality ranged from 0% to 8.3% in the HBOT groups and from 0% to 15% in the control groups.

Qualitative analysis. The four studies included for quantitative synthesis[26-29] also reported on complete ulcer healing, AFS, vascular interventions, $TcpO_2$, completion of treatment, adverse events, quality of life, and costs, but were due to clinical heterogeneity not suitable for meta-analysis. These results are presented as a narrative review in the following section.

Complete ulcer healing. Abidia et al,[28] Santema et al,[29] and Kalani et al[27] reported on complete ulcer healing after 1 year. Because of a high heterogeneity of 76%, no meta-analysis was performed. This heterogeneity was, at least partly, due to the inclusion of patients with different Wagner grades. Abidia et al[28] included patients with only Wagner grades I and II, where Santema et al[29] included patients with Wagner grades II-IV. Kalani et al[27] did not describe the Wagner grade of the included patients. Abidia et al[28] reported that significantly more ulcers (5; 56%) healed in the HBOT group vs no healed ulcers in the control group, being statistically significant (RD, 56%; 95% CI, 22-89). Santema et al[29] found no significant difference in wound healing: 30 (50%) ulcers had healed after 1 year in the HBOT group vs 28 (47%) in the control group (RD, 3%; 95% CI, −15 to 22). Kalani et al also found no significant difference: 13 (76%) ulcers fully healed in the HBOT group vs 10 (48%) in the control group (RD, 29%; 95% CI, −1 to 58).

AFS. Santema et al[29] is the only study reporting on AFS, defined as being alive and free from major amputation. They reported an AFS of 49 (81.7%) patients in the HBOT group and 41 (68.3%) patients in the control group (RD,

Table IV. Primary outcome measures

Author	Completion of treatment, %	Amputation rate, %						Complete ulcer		Healing time, days		Mortality, %	
		Major		Minor		Total		Healing, %					
		HBOT	Control	HBOT	Control	HBOT	Control	HBOT	Control	HBOT	Control	HBOT	Control
Faglia 1996	U	8.6[a]	33.3[a]	60	36.3	68.6	69.6	–	–	–	–	–	–
Kalani	100	11.8	33.3	–	–	–	–	76	48	150	150	11.7	14.3
Abidia	100	11.1	11.1	11.1	0	22.2	11.1	55.5[a]	0[a]	180	270	0	0
Santema	82	11.7	21.7	6.7	10	18	32	50	47	169	176	8	15
Perren	U	–	–	–	–	–	–	–					
Baroni	–	11.1	40	–	–	11.1	40	88.9	10	–	–	–	–
Oriani	–	–	–	–	–	4.8[a]	33.3[a]	96[a]	66.7[a]	–	–	–	–
Faglia 1998	–	12.9[a]	32.7[a]	–	–	–	–	–	–	–	–	–	–
Duzgun	U	–	–	–	–	8[a]	82[a]	66[a]	0[a]	–	–	–	–
Löndahl	54	6.1	2.2	8.2	8.9	14.3	11.1	52[a]	29[a]	–	–	2	6.7
Chen	91	–	–	–	–	4.5	10	22.7	5	–	–	–	–

HBOT, Hyperbaric oxygen therapy; *U,* unknown
[a]Significant difference.

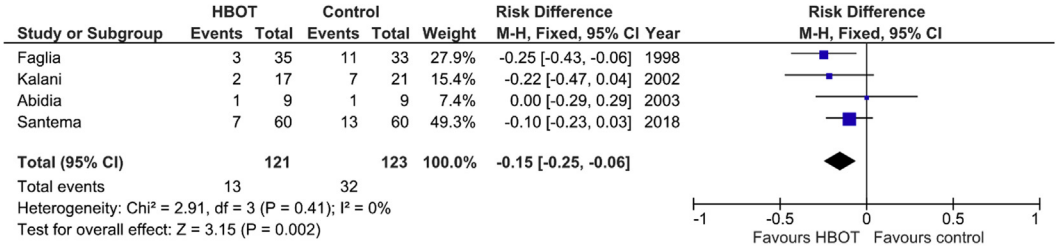

Fig 2. Forest plot showing the effect of hyperbaric oxygen therapy (*HBOT*) on major amputations. *CI,* Confidence interval; *M-H,* Mantel-Haenszel test.

13.3%; 95% CI, −2.2 to 28.1). In their subgroup of patients who underwent at least 30 HBOT sessions, AFS was significantly different in favor of HBOT (RD, −23%; 95% CI, −71 to −7).

Vascular interventions. Faglia et al[26] and Santema et al[29] observed the need for additional vascular interventions. Faglia et al[26] reported that 37% of the patients in the HBOT vs 39% in the control group underwent vascular procedures (RD, 2%; 95% CI, −20 to 24%). Santema et al[29] described the need for additional revascularization in 23% of the patients in the HBOT group and 28% patients in the control group (RD, 5%; 95% CI, −11 to 20).

$TcpO_2$. Faglia et al[26] analyzed the $TcpO_2$ values and found an increase from start until completion of treatment or amputation of 14 mm Hg (95% CI, 2.2-25.8) in the HBOT group vs 5 mm Hg (95% CI, −0.6 to 10.4) in the control group, being statistically significant (mean difference, 9.0; 95% CI, 6.7-11.3; $P < .001$). Kalani et al[27] found no significant difference in $TcpO_2$ at the end of follow-up between the group with complete ulcer healing and the group that underwent amputation (mean $TcpO_2$, 26 mm Hg [95% CI, 6-46] vs 24 mm Hg [95% CI, 4-44], respectively). Kalani et al[27] also reported on the $TcpO_2$ during oxygen inhalation at the end of follow-up and found a mean of 234 mm Hg (95% CI, 14-354) in the healed group and 142 mm Hg (95% CI, 12-272) in the amputated group, being statistically significant (mean difference, 92.0; 95% CI, 11.7-172.3; $P = .03$).

Completion of treatment. Three studies reported on completion rates of HBOT. Abidia et al[28] and Kalani et al[27] described a 100% completion of treatment, using 30 sessions and 40 to 60 sessions, respectively. Santema et al[29] reported completion of at least 30 treatments by 79.6% of the patients who started with HBOT.

Adverse events. Kalani et al[27] reported two cases of adverse events. One of the patients developed cataracts, which was ascribed to the HBOT treatment. Another patient had middle ear barotrauma and had ear pain, which diminished after local treatment with a decongestant. Santema et al[29] described five cases of adverse events. Three patients needed a

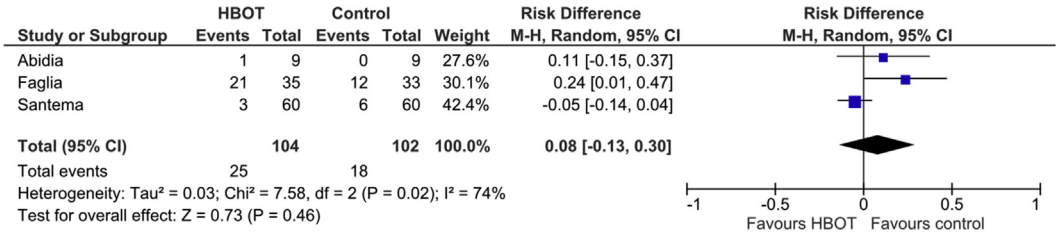

Fig 3. Forest plot showing the effect of hyperbaric oxygen therapy (*HBOT*) on minor amputations. *CI,* Confidence interval; *M-H,* Mantel-Haenszel test.

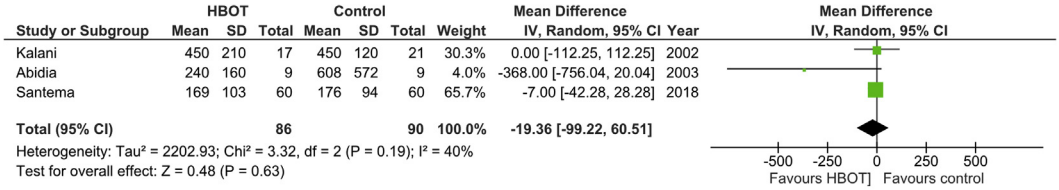

Fig 4. Forest plot showing the effect of hyperbaric oxygen therapy (*HBOT*) on mean healing time. *CI,* Confidence interval; *IV,* inverse variance test.

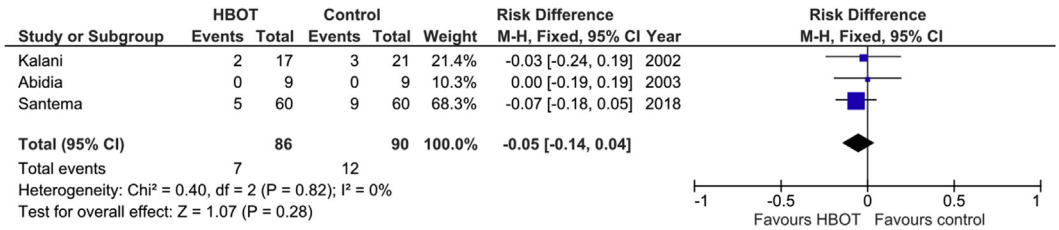

Fig 5. Forest plot showing the effect of hyperbaric oxygen therapy (*HBOT*) on mortality. *CI,* Confidence interval; *M-H,* Mantel-Haenszel test.

myringotomy, one patient had an oxygen-induced seizure, and one patient had a middle ear perforation. Faglia et al[26] reported two cases of barotraumatic otitis. Abidia et al[28] reported that no adverse events occurred.

Quality of life. Abidia et al[28] was the only study including quality of life in their analysis using the SF-36 and Hospital Anxiety and Depression Scale (HADS). The authors observed a significant improvement, without providing numbers, in the general health and vitality domains of the SF-36 in the HBOT group ($P = .12$ and $P = .018$), but found no significant differences between the HBOT and control groups. Abidia et al[28] also found a significant improvement in the depression score of the HADS in both the HBOT and the control group ($P = .011$ and $P = .023$), but without reporting actual scores. They found a significant reduction in the anxiety score of the HADS in the control group ($P = .042$). Overall, no difference in quality of life was found between the HBOT and control group as measured by the Short Form-36 and HADS scores.

Costs. Abidia et al[28] performed a cost-effectiveness analysis and estimated a potential cost saving of $3760. Unpublished data from Santema et al[29] obtained from the authors shows that the total clinical and outpatient treatment costs and out-of-pocket costs did not differ significantly between the HBOT and standard treatment groups. The chance of HBOT being cost-effective was 32%, whereas the cost per QALY gained was nearly $90,000. The other four studies did not report on costs.[26,27,38,39]

DISCUSSION

This is the first systematic review that focuses specifically on patients with DFUs in combination with PAOD. It shows that HBOT as an adjunct to standard wound care in patients with DFU and PAOD leads to a decrease in major amputations, but no difference in minor amputation rates, mortality, or healing time. For the additional outcomes, for which no meta-analysis was performed, no overall significant differences were observed in complete wound healing, AFS, need for vascular interventions, quality of life, and costs.

The benefit of HBOT in terms of a lower amputation risk (NNT of 7) should be weighed against other patient-relevant outcomes, like wound healing, AFS, other interventions needed, iatrogenic injury, and the burden involved in attending and completing the HBOT sessions. The effect of HBOT seems most likely if at least

30 sessions are completed.[40] There is not much evidence assessing the burden of HBOT. However, Santema et al[29] reported that 20.4% of the patients did not complete the full treatment of at least 30 HBOT sessions, implying that it is hard for patients to complete treatment because of comorbidities and travel efforts. Also, in the study of Löndahl et al,[35] only 57% completed the full 40 treatments, whereas 80% did complete at least 35 treatments. Chen et al[36] reported that 91% of the patients completed treatment, Abidia et al.[28] 89%, and Kalani et al.[27] 100%. This is also seen in other larger studies such as the HOT-2 trial (84 patients), which showed an 89% completion of the intended number of sessions.[41] Thus, eligible patients should be informed about the chances of success (one in every seven patients will have the additional benefit from HBOT of saving their leg in the first year, whereas six of seven will have no additional benefit of HBOT), whereas they need to undergo HBOT for at least 6 weeks, including transportation to the HBOT center for 5 days a week. Awareness about these pros and cons should help them decide whether or not they want, and are able to, undergo HBOT treatment.

The success of HBOT might increase by identifying subgroups that may benefit most from HBOT. Kalani et al[27] found that $TcPO_2$ during HBOT was an indicator of the success rate of HBOT. This might help to distinguish patients who may respond to HBOT. The $TcPO_2$ parameter may be combined with the angiosome concept because it shows a connection between the location of the arterial occlusion and the location of the wound site and shows better results after focused treatment.[42] In these studies, no attention was given to the ulcer site or the location of the arterial occlusion. It is possible that these parameters, together with the severity of the PAOD, influence the chances of healing and the benefit from HBOT.

This review and the included literature also have some limitations. First, we did not get a response from the authors who published studies with an ischemic subgroup. Therefore, some evidence is lacking from this and, in fact, from any review. Furthermore, the study of Abidia et al[28] was included in quantitative synthesis, which included only patients with Wagner grades I and II, and reported no healed ulcers in the control group. Also, the included studies for meta-analysis did not use a sham treatment. The only included study that did use sham treatment is Löndahl et al.[35] Although it should be noted that breathing air at 2.5 ATA (which is an equivalent of fraction of inspired oxygen of 0.5 [eg, 50% oxygen]) already shows effect on wound healing and therefore might not be considered an optimal sham treatment.[43] Finding an optimal sham treatment for HBOT remains a challenge because it should give a good placebo effect without any physiological effects.[44] The lack of sham treatment and absence of blinding of the patients makes it hard to exclude possible selection bias by the surgeon who decided whether a patients would undergo a major amputation. Finally, no patient-reported outcomes were measured, which should have been used as important outcome measures, given the patients' substantial comorbidity and the heavy burden of the treatment with HBOT.

Future research should focus on the effect of HBOT, in particular on complete ulcer healing and the reduction in major amputation rate in relation to the costs, patient burden, and adverse events. Patient selection seems essential to identify which patients will benefit most from adjunctive HBOT. More large trials should be performed, measuring at least major amputation rates, complete ulcer healing, $TcpO_2$, quality of life, and other patient-relevant outcomes. A minimum of 30 sessions of HBOT and a uniform definition of criteria for amputation should be used. This might help to design a risk stratification scheme to identify the patients that benefit the most from HBOT. For the time being, shared decision-making should be used, in which patients are involved in weighing the advantage of less major amputations against the burden and side effects of HBOT treatment.[45]

In conclusion, HBOT appears to have some beneficial effect as adjunctive therapy to treat DFUs with PAOD as it decreases the major amputation rate, but requires a good general condition and stamina among eligible patients. Future research should focus on patient selection and the effectiveness of HBOT as standard adjunctive treatment in ischemic DFUs. Shared decision-making should be used to weigh the decreased amputation rate against the burden of HBOT.

AUTHOR CONTRIBUTIONS

Conception and design: RB, RL, RH, RAH, DU
Analysis and interpretation: RB, RL
Data collection: RB, RL
Writing the article: RB, RL
Critical revision of the article: RB, RL, RH, RAH, DU
Final approval of the article: RB, RL, RH, RAH, DU
Statistical analysis: RB, RL, DU
Obtained funding: Not applicable
Overall responsibility: RB
RB and RL equally contributed to this article and share co-first authorship.

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APPENDIX (online only).

Search syntax

MEDLINE (OVID)

01-10-2018. (exp Diabetes Mellitus/ OR diabet*.ti,ab,kw.) AND (Hyperbaric Oxygenation/ OR ((high* adj3 (pressure or tension*)) AND oxygen*).ti,ab,kw. OR ((hyperbaric* or barotherap*) AND oxygen*).ti,ab,kw. OR (HBO or HBOT).ti,ab,kw.) AND (Ulcer/ OR exp Leg Ulcer/ OR "Wounds and Injuries"/ OR diabetic foot/ OR (ulcer* or wound* OR diabetic foot).ti,ab,kw.)

EMBASE (OVID):

01-10-2018. (exp diabetes mellitus/ OR diabet*.ti,ab,kw.) AND (hyperbaric oxygen therapy/ OR ((high* adj3 (pressure or tension*)) AND oxygen*).ti,ab,kw. OR ((hyperbaric* OR barotherap*) and oxygen*).ti,ab,kw. OR (HBO OR HBOT).ti,ab,kw.) AND (ulcer/ OR exp skin ulcer/ OR ulcer healing/ OR leg ulcer/ OR exp wound/ OR diabetic foot/ OR (ulcer* OR wound* OR diabetic foot).ti,ab,kw.) EXCLUDING CONFERENCE ABSTRACTS

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