Hyperbaric oxygen therapy for nonischemic diabetic ulcers: A systematic review

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INTRODUCTION

Diabetes is a growing global health issue. Currently, an estimated 8.5% of the adult population now suffers from this disease.1 With it comes a plethora of complications, including increased risk of heart attack, stroke, and premature death.2 Diabetic foot ulcers (DFUs) are one of the most common diabetes-related complications, affecting up to 25% of patients and leading to major personal and economic consequences.3,4 For example, the reported mortality rates associated with DFUs rival or exceed those of some common cancers.5

The development of DFU is multifactorial, with the most important risk factors being neuropathy and vasculopathy. It is estimated that the majority of ulcers are of neuropathic rather than vascular origin.6 However, even in neuropathic ulcers, these changes are most notable as microvascular disease.7 Once present, ulcer healing is intrinsically impaired due to the physiological and immunological changes associated with diabetes.8

Despite optimal treatment, previous studies have shown that 19% to 35% of diabetic ulcers remain unhealed,8–10 considerably increasing the risk of amputation of the affected limb.11 Even if complete wound healing has been achieved, there is still the risk of recurrence: 40% of patients develop a recurring wound within 1 year.4,12

When it comes to chronic wounds, local tissue hypoxia is one of the most important sustaining factors.13 Hyperbaric oxygen therapy for nonischemic diabetic ulcers: A systematic review

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The development of DFU is multifactorial, with the most important risk factors being neuropathy and vasculopathy. It is estimated that the majority of ulcers are of neuropathic rather than vascular origin.6 However, even in neuropathic ulcers, these changes are most notable as microvascular disease.7 Once present, ulcer healing is intrinsically impaired due to the physiological and immunological changes associated with diabetes.8
oxygen therapy (HBOT) aims to correct this hypoxic state in order to improve wound healing and, consequently, to prevent amputations.

The definition of HBOT is the breathing of 100% oxygen under an atmospheric pressure greater than sea level, or one atmosphere absolute (ATA). The Underwater and Hyperbaric Medical Society (UHMS) states that a pressure of at least 1.4 ATA is required to have a clinical effect. Generally, the treatment is considered safe and cost-effective. In Europe, there are several recognized indications for the therapy, including osteoradionecrosis of the mandible, delayed radiation injury, compromised skin grafts, and diabetic foot lesions. The therapy is usually applied daily for several weeks and can be performed in monoplace or multiplace chambers (i.e. accommodating a single patient or several). It provides several physiological effects beneficial for wound healing, such as increased angiogenesis and leukocyte activity, improved collagen deposition and reduction of edema.

Despite these advantages, the application of HBOT remains controversial. The evidence on clinical effectiveness is low, which is one of the reasons why HBOT is frequently used as a “last-resort” treatment option in the Netherlands. It is generally considered to be cumbersome and time-consuming and, additionally, not all physicians have ready access to a hyperbaric chamber. For the same reasons, few randomized clinical trials (RCTs) have been performed on the effectiveness of HBOT for diabetic and/or ischemic ulcers. Other research is considered to be of questionable quality. The quality of evidence could be bolstered by the use of a control group, but since there is no consensus on the most valid sham treatment, this is not easily implemented.

Previous systematic reviews of the available literature have been inconclusive about the efficacy of HBOT. A Cochrane review by Kranke et al. concluded that HBOT leads to improved wound healing after 6 weeks, but not after 12 months, and does not reduce major amputation rate. In non-ischemic DFUs, O’Reilly et al. found that treatment with HBOT in randomized trials reduced the risk of major amputation but did not significantly affect wound healing. A systematic review by Stoekenbroek et al. found that none of the relevant RCTs reported significant differences, neither in wound healing nor in amputation rates. All reviews, based on RCTs, concluded that there was not enough evidence to support routine use of HBOT for DFUs in clinical practice.

The inconclusiveness of the previous reviews might, at least in part, be explained by the inclusion of both patients with and without peripheral arterial occlusive disease (PAOD). Often, no distinction was made between these groups when reporting on wound healing or amputation rate, despite the varying pathophysiology of ulcers and the fact that PAOD in itself is a risk factor for major amputation.

Hence, the current systematic review aimed to evaluate the current scientific data on the benefits and harms of HBOT adjunctive to local and/or systemic treatments regarding wound healing and amputation rates in patients with DFUs without PAOD.

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**Figure 1.** PRISMA flowchart for meta-analysis up to October 1, 2018.
METHODS

The review protocol was developed beforehand. The review was conducted and described according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.30,31

Search strategy

A clinical librarian helped develop a search strategy to identify the literature concerning diabetic wounds and HBOT using the Embase, MEDLINE, and Cochrane CENTRAL databases, from inception up to September 2018. The search included MeSH and free text terms as 'ulcer,' 'diabetes mellitus,' and 'hypobaric oxygen therapy' and synonyms. The complete search strategy is supplemented in Appendix . Hand search was conducted of references in eligible studies and also of nonpublished trials from digital sources (e.g. www.clinicaltrials.gov). No language restriction was applied to prevent publication bias.

Inclusion and exclusion criteria

Two researchers (RB and RL) independently screened the titles and abstracts of the articles found. Comparative studies were included if they concerned patients with type I or II diabetes who had a DFU without PAOD, and who received HBOT in addition to standard wound care. PAOD was defined as an ankle-brachial pressure index (ABI) ≤0.9, a toe-brachial pressure index (TBI) ≤0.70, a toe blood pressure (TBP) <30 mmHg on the dorsum of the foot <30 mmHg.32,33 If studies did not provide criteria that measured PAOD, or did not discern ischemic and nonischemic wounds, the corresponding author was emailed to provide these data. If there was no response or the data were not available, the study was excluded. In case of discrepancies, consensus was reached through discussion among authors.

Data collection

Study characteristics and outcome measures were extracted by two reviewers (RB and RL) independently and entered into predefined electronic tables for the purpose of data checking by the authors. Study characteristics reported were number of patients included, details of HBOT treatment including (mean) number of sessions, outcome measures, type of study design, and year of publication. Primary outcomes of interest were complete wound healing and amputation rate (major (i.e. above the ankle joint) or minor). Secondary outcomes of interest were amputation-free survival, mortality, any measure of quality of life (QoL) as reported by the authors, number of sessions performed, adverse events, and costs of HBOT. Any discrepancies were resolved by discussion. When consensus was reached, the final data were entered into the Review Manager 5.3 software package (Copenhagen: The Nordic Cochrane Centre TCC, 2014).

Quality assessment

Two of the authors (RB and RL) independently assessed the quality of the selected studies using the Cochrane checklist44 for randomized studies and the ROBINS-I checklist35 for non-randomized interventional studies. These checklists assess the risk of bias on several domains, including selection bias,
allocation bias and performance bias. Risks scores on the ROBINS-I scale were judged as 'low,' 'moderate,' 'serious' or 'critical,' or if not enough information was available, as 'NI' (no information). The reviewers calculated total scores for each study (columns) and each domain (rows). Again, any differences in assessment were resolved by discussion.

### Statistical analysis

Results are given as means with standard deviations (SD) for normally distributed data or medians with interquartile ranges (IQR) for nonnormally distributed data. Percentages are provided when describing proportions of the study population. Differences between treatment groups are presented as mean

### Table 2. Baseline patient characteristics

| Author      | N   | Age (mean) | Sex (% male) | Ulcer size (cm²) | Duration DM (years) | HbA1c (%) | TcpO2 (mmHg) | Wagner grade (% of patients) |
|-------------|-----|------------|--------------|------------------|---------------------|-----------|--------------|------------------------------|
| Akgül HBOT  | 27  | 55         | 70.4         | -                | 12                  | -         | -            | 92.5 7.5 0                    |
| Control     | -   | -          | -            | -                | -                   | -         | -            | -                            |
| Kessler HBOT| 14  | 60.2       | 71.4         | 2.31             | 18.2                | 9.4       | 45.2         | -                            |
| Control     | 13  | 67.6       | 69.2         | 2.82             | 22.1                | 8.1       | 45.6         | -                            |
| Khandelwal HBOT | 20  | 43.8       | 50           | 14.91            | -                   | -         | -            | -                            |
| Control     | 20  | 43.35      | 55           | 9.90             | -                   | -         | -            | -                            |
| Lyon HBOT   | 13  | 69         | -            | -                | -                   | - >30     | -            | -                            |
| Control     | 25  | 71         | -            | -                | -                   | - >30     | -            | -                            |
| Ma HBOT     | 18  | 59.8       | 61.1         | 4.21             | 24.8                | -         | 37.06        | 22.2 22.2 55.6 - -            |
| Control     | 18  | 60.4       | 66.7         | 4.35             | 23.1                | -         | 35.61        | 27.8 33.3 38.9 - -            |
| Margolis HBOT | 793 | 61.6*      | 64.4*        | 1.9*             | -                   | -         | -            | -               45.7*† - -          |
| Control     | 5,466 | 63.0      | 55.7         | 1.6              | -                   | -         | -            | -               18.4† - -           |
| Zamboni HBOT | 5   | 63.6       | 80           | 6.02             | -                   | -         | 53.4         | -                            |
| Control     | 5   | 53.8       | 80           | 4.4              | -                   | -         | 60.0         | -                            |

*significant difference.
†Wagner grade ≥ 3.
DM, diabetes mellitus; HbA1c, glycated hemoglobin; HBOT, hyperbaric oxygen therapy; TcpO2, transcutaneous oximetry.

### Figure 2. Risk of bias in RCTs.

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differences (MD) or risk differences (RD) with their 95% CI. For significant differences, the number needed to treat (NNT) or number needed to harm (NNH) are also provided.

Data were pooled if clinically homogeneous and if statistical heterogeneity was limited, as expressed by an I^2 statistic of <75%. A fixed-effects model was used if I^2 < 25% and a random effects model if 25% ≤ I^2 < 75. Both RCTs and observational studies were to be included in the meta-analyses but are shown separately for a more in-depth evaluation of the available evidence.39 Meta-analysis, if meaningful, was performed using the Review Manager 5.3 software package (Copenhagen: The Nordic Cochrane Centre TCC, 2014).

RESULTS

The literature search yielded a total of 818 eligible articles; see also Figure 1. After screening, six studies37–42 met the inclusion criteria for PAOD and were selected for qualitative analysis. These studies included two RCTs,37,40 two prospective studies,38,42 and two retrospective studies.39,41 Akgül et al.43 provided additional data on patients without PAOD in a retrospective study and was therefore included as well. A total of 6,438 patients were included in this review.

Eight studies,44–51 including two RCTs,46,50 were excluded because we received no response on our request for additional data from the authors. One of the larger RCTs performed by Fedorko et al.52 was excluded as well. In contradiction to the study protocol, the need for amputation was not evaluated by a vascular surgeon in person but by using photographs of the wounds, and evaluations were made by a single, albeit experienced, surgeon. No actual amputations were performed in this study. Therefore, the exclusion of this study appears justified.53–55

Characteristics of included studies

Table 1 gives an overview of the characteristics of the included studies. HBOT protocols varied between 60 and 120 minutes and between 2.0 and 2.5 ATA, for three to 6 days a week. The two RCTs by Kessler et al.37 and Ma et al.40 used the same protocol of 90 minutes at 2.5 ATA twice daily, which enabled them to perform 20 sessions in a short amount of time. These two studies reported the shortest follow-up periods of four and two weeks, respectively, while the longest follow-up period was twelve months.43 The total numbers of sessions as mentioned in non-randomized studies ranged from 15 to 110, while both RCTs37,40 used a fixed number of 20 sessions. The number of included patients varied greatly between studies. The prospective study by Zamboni et al.42 contained 10 patients, while the retrospective study by Margolis et al.41 had 6,259 patients.

Characteristics of included patients

Table 2 shows the baseline patient characteristics of the included studies. From the study by Akgül et al.43 only the data on patients without PAOD are presented. Margolis et al.41 is the only study to report significant differences between groups at baseline, namely for sex, age, ulcer size, and Wagner grade, but for which they did not correct in their analysis. TcpO2 was reported by four studies.37,39,40,42 Wagner grade, whenever reported, varied among studies. One study included patients with ulcer grades I-III40 and two studies included grades III-V.

| Study     | Selection of patients | Classification of interventions | Deviation from intervention | Measurement errors | Missing data | Overall risk of bias |
|-----------|------------------------|---------------------------------|-----------------------------|--------------------|-------------|---------------------|
| Akgül     | Low                    | Moderate                        | Low                         | Low                | Low         | Low                 |
| Khandelwal| Moderate               | Low                             | Low                         | Moderate           | Low         | Moderate            |
| Lyon      | Moderate               | Low                             | Low                         | Low                | Low         | Moderate            |
| Margolis  | Serious                | Low                             | Low                         | Low                | Low         | Serious             |
| Zamboni   | Serious                | Moderate                        | Low                         | Low                | Low         | Serious             |
| Overall score | Moderate               | Moderate                        | Moderate                   | Moderate           | Moderate     | Moderate            |

Table 3. ROBINS-I checklist for risk of bias
Quality assessment

Because of different HBOT protocols and number of HBOT sessions performed, as well as wound grades and sizes at inclusion, clinical heterogeneity was high.

Figure 2 shows the results of the Cochrane checklist for risk of bias of the randomized studies. Hypothetical example: The general quality of the RCTs was good, although the authors did not provide adequate information on blinding of the researchers or assessors or stated to have performed an open-label study. Hypothetical example: Table 3 shows the categories for risk of bias for the non-randomized studies, according to the ROBINS-I tool. Two studies presented a serious risk of bias due to confounding, while other studies showed a moderate risk of bias in all domains.

Table 4. Outcome measures

| Author       | HBOT (N) | Control (N) | Complete ulcer healing, N (%) | Amputation rate, N (%) | Mortality, N (%) |
|--------------|----------|-------------|-------------------------------|------------------------|-----------------|
|              |          |             | HBOT                          | Control                | Minor           | Major           |          |
| Akgül        | 27       | -           | 16 (59.2)                     | 5 (18.5)               | 1 (3.7)         | 5 (18.5)        |          |
| Kessler      | 15       | 13          | 2 (13.3)                      | 0 (0)                  | -               | -               |          |
| Khandelwal   | 20       | 20          | 12 (60)                       | 8 (40)                 | -               | -               |          |
| Lyon         | 13       | 25          | 0 (0)                         | 0 (0)                  | -               | -               |          |
| Ma           | 18       | 18          | 0 (0)                         | 0 (0)                  | 0 (0)           | 0 (0)           |          |
| Margolis     | 793      | 5,466       | 1,210                         | 7,311*                 | -               | 26 (3.28)*      | 70 (1.28) |
| Zamboni      | 5        | 5           | 4 (80)*                       | 1 (20)                 | 0 (0)           | 0 (0)           |          |

*Significant difference.

HBOT, hyperbaric oxygen therapy.

Figure 3. Forest plot of complete ulcer healing results.

Figure 4. Forest plot of major amputation rates.
Outcome measures

All studies reported on complete ulcer healing, while amputation rate was reported by four studies. Mortality was reported by two studies. Results of these outcome measures are shown in Table 4. Margolis et al. did report on complete ulcer healing but reported healing of multiple wounds per patient. A percentage of patients with healed wounds could therefore not be given in Table 4. Lyon et al. only reported on reduction of ulcer size, which was not a predefined outcome measure because it is less clinically relevant than complete ulcer healing. The two RCTs mention adverse events. Most studies reported number of sessions used. None of the included studies reported on QoL, cost of therapy, or amputation-free survival.

Complete ulcer healing rate

Meta-analysis could not be performed meaningfully for complete wound healing due to clinical heterogeneity. Neither the RCTs nor the nonrandomized studies reported significant differences in wound healing. The results are shown in a Forest plot in Figure 3. Akgül et al. reported that 16 of 27 (59.3%) patients in the HBOT group achieved complete wound healing at the end of the treatment course.

Major amputation rate

Four studies reported on amputation rates. Meta-analysis could not be performed meaningfully due to clinical heterogeneity. The only RCT showed no significant differences, while the large retrospective study by Margolis et al. did show a difference in favor of the control treatment but failed to correct for significant differences between the patient groups at baseline in their analysis. Akgül et al. reported that 1 out of 27 (3.7%) patients undergoing HBOT needed major amputation in a 24-month follow-up. See also the Forest plot in Figure 4.

Minor amputation rate

Minor amputations were registered by Ma et al. and Zamboni et al., but these did not occur during the follow-up period of two weeks and six months, respectively. In the study by Akgül et al., 5 of 27 (18.5%) patients needed minor amputations.

Mortality rate

Mortality rate was only described in two studies. Ma et al. reported no deaths during the study period of two weeks and Akgül et al. reported an 18.5% mortality rate in the HBOT-treated patients in the 24-month follow-up period.

Adverse events

Adverse events were mentioned in both RCTs. None occurred in the study by Ma et al. Kessler et al. reported that 1 of the 14 patients (7.1%) was discharged after developing barotraumatic otitis, which resolved without sequelae.

Number of sessions performed

The total number of HBOT sessions patients received differed among studies. Most studies used a fixed number of either 20 or 30 sessions. Akgül et al. report a range of 25 to 110 sessions and Margolis et al. report administering 15 to 48 sessions. It is not reported in either study why some patients received less sessions than others. Akgül et al. mention that most patients were treated as outpatients and Khandelwal et al. treated patients as inpatients first and later as outpatients (not otherwise defined). Other studies did not mention if study participants were either in- or outpatients.

DISCUSSION

This is the first systematic review that aggregated all available evidence for the specific subgroup of patients with nonischemic DFU. From the currently available evidence, it seems that these patients, when treated with HBOT, do not achieve faster wound healing and do not benefit in terms of prevention of major or minor amputations but are at risk of possible HBOT-related adverse effects. The RCTs demonstrate this are of good quality. However, the amount of research focusing exclusively on non-ischemic diabetic ulcers and HBOT is scarce and this result should therefore be viewed with caution. Until additional research has been performed for this specific subgroup, physicians will have to weigh the expected risks and benefits of the therapy and inform patients in this regard, to reach a decision that best fits the patients’ preferences.

Earlier systematic reviews, which did not specifically differentiate between the presence or absence of PAOD, arrived at more favorable conclusions concerning wound healing with HBOT. In the Cochrane review on chronic diabetic wounds and HBOT by Kranke et al., which included studies with and without PAOD, complete wound healing was achieved more frequently with HBOT at 6 weeks (although no differences were observed anymore after 6 and 12 months). The reviews by Stoekenbroek et al. and O’Reilly et al. also included patients with and without PAOD and reported findings similar to those of Kranke et al. While Stoekenbroek et al. did not find an increase in complete wound healing, they did report that wound size was reduced in those treated with HBOT. O’Reilly et al. found some evidence of increased wound healing after HBOT but could not draw definite conclusions from the available evidence. Furthermore, major amputation rate decreased after HBOT in the Cochrane review by Kranke et al. and in the review by Stoekenbroek et al. O’Reilly et al. found a decreasing, but not significant trend in both major and minor amputation rates. Possibly, an effect of HBOT may become manifest in DFU patients if PAOD is present, which may account for the different outcomes of the current and earlier reviews. Quantifying the extent of PAOD in patients may help physicians make an informed decision to apply HBOT in wound healing.

In the current review, one large retrospective cohort study found an increase in major amputation rate for patients treated with HBOT. Since this result is contrary to earlier evidence, it warrants further exploration. Possibly due to the lack of randomization, patients in the HBOT group had a larger wound and more ulcers had a Wagner grade ≥ 3 at inclusion than in the standard wound care group. These patients have an inherently increased risk of major amputation, which may have contributed to the observed effect. It also exemplifies the problem of HBOT.
within the course of treatment. In light of this, one of the primary aspects of further research should be concerned with the relationship between HBOT and its timing within the course of treatment.

As indicated in an earlier study by D’Agostino et al., 58 30 sessions of HBOT appear to be the minimally appropriate number of sessions to achieve the desired effect. This was also suggested by the results from another trial. 59 Therefore, performing less than 30 sessions might decrease the efficacy of HBOT. However, in the included studies, 37–43 the number of sessions performed varied. Both RCTs 37, 40 prescribed 20 sessions and report no differences in complete wound healing or either major or minor amputation rate. Margolis et al. 41 reported an average of 29 sessions, with a range of 15 to 48 sessions. They reported an increase in major amputation rate in the HBOT group. However, they did not report on the number of sessions performed before amputation occurred. In contrast, Khandelwal et al. 38 used 30 sessions and found a positive, albeit not significant, trend toward complete wound healing, while Zamboni et al. 32 used 30 sessions as well and reported an increase in complete wound healing after HBOT. These results also suggest that for HBOT to be clinically effective a minimal number of 30 sessions is required.

However, some patients may not be able to complete 30 sessions for various reasons. Protocols with a shorter HBOT-period might be able to improve patient adherence. However, in the studies by Kessler et al. 37 and Ma et al. 40 HBOT was applied twice daily, which led to shorter protocols than other studies used. However, this did not lead to improved wound healing. In fact, complete healing rate was lower than in other studies. Apparently, more than one session of HBOT per day does not lead to better results.

A limitation of this review is the small size and number of RCTs and nonrandomized studies that were available for inclusion. Unfortunately, most authors did not respond to our request for additional data, which also led to the exclusion of two major RCTs. 46, 50 Nevertheless, this review currently represents the best available evidence for this specific subgroup of patients. However, until additional data become available, our results should be interpreted with caution, especially because no meaningful meta-analyses could be performed due to high clinical heterogeneity.

For future research, we strongly advocate the importance of differentiating between patients with major clinical determinants, such as PAOD. Furthermore, additional patient selection criteria (e.g. TepO2-values) and (patient-reported) outcome measures are needed to better phenotype, or identify, patients that might benefit from this treatment modality. The use of a single, standardized HBOT protocol may also facilitate aggregation of study results in future meta-analyses. Cooperation with healthcare policy makers may help with implementing such a standardized protocol. For the current clinical practice, physicians treating DFUs might also use their patients’ characteristics and clinical determinants to help them make an informed decision on the application of HBOT.

In conclusion, the currently available evidence suggests that HBOT does not accelerate wound healing and does not prevent major or minor amputations in patients with DFU without PAOD. Based on this evidence, routine clinical use of this therapy cannot be recommended. However, the available evidence for this specific subgroup of patients is scarce, and physicians should counsel patients on expected risks and benefits. Additional research, focusing especially on patient selection criteria, is needed to better identify patients that might profit from this therapy modality.

CONFLICT OF INTEREST
The authors declare no conflict of interest in writing this manuscript.

APPENDIX A.

Complete Search Strategy

MEDLINE (Ovid).

January 1946 – October 1, 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).

January 1947 – October 1, 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.)

Cochrane Library.

Up to October 2018.

(diabet*.ti,ab,kw OR [Diabetes Mellitus]) AND ((Hyperbaric Oxygenation] OR (high* near3 (pressure or tension*)) AND oxygen*.ti,ab,kw OR (hyperaric* OR barotherap*) AND oxygen*.ti,ab,kw OR HBO OR HBOT.ti,ab,kw) AND (ulcer* OR wound* OR diabetic foot:ti,ab,kw)

REFERENCES

1. WHO. Global report on diabetes. WHO, Geneva, Switzerland, 2016.
2. Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D, et al. Changes in diabetes-related complications in the United States, 1990-2010. N Engl J Med 2014; 370: 1514–23.
3. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet (London, England) 2005; 366: 1719–24.
4. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med 2017; 376: 2367–75.
5. Armstrong DG, Wrolsel J, Robbins JM. Guest editorial: are diabetes-related wounds and amputations worse than cancer? Int Wound J 2007; 4: 286–7.
6. Prompers L, Huijberts M, Apelqvist J, Jade E, Piaggesi A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia 2007; 50: 18–25.
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7. Fiordaliso F, Clerici G, Maggioni S, Caminiti M, Bisighini C, Novelli D, et al. Prospective study on microangiopathy in type 2 diabetic foot ulcer. *Diabetologia* 2016; 59: 1542–8.

8. Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers. *Am J Surg* 1998; 176: 5–10s.

9. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Armstrong DG, Harkless LB, et al. The effects of ulcer size and site, patient’s age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. *Diab Med: J British Diabetic Assoc* 2001; 18: 133–8.

10. Gershater MA, Londahl M, Nyberg P, Larsson J, Thorne J, Eneroth M, et al. Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. *Diabetologia* 2009; 52: 398–407.

11. Narres M, Kvitikina T, Claessen H, Droste S, Schuster B, Morbach S, et al. Incidence of lower extremity amputations in the diabetic compared with the non-diabetic population: a systematic review. *PLoS One* 2012; 12: e0182081.

12. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA* 2005; 293: 217–28.

13. Schreml S, Szmieles RM, Prantl L, Karrer S, Landthaler M, Babilas P. Oxygen in acute and chronic wound healing. *Br J Dermatol* 2010; 163: 257–68.

14. Weaver JK. *UHMS hyperbaric oxygen therapy indication*, 13th ed. Best Publishing Company, North Palm Beach, Florida, USA, 2014.

15. Hadanny A, Meir O, Bechor Y, Fishlev G, Bergan J, Efrati S. The safety of hyperbaric oxygen treatment-retrospective analysis in 2,334 patients. *Undersea Hyperb Med* 2016; 43: 113–22.

16. Chuck AW, Hailey D, Jacobs P, Perry DC. Cost-effectiveness and budget impact of adjunctive hyperbaric oxygen therapy for diabetic foot ulcers. *Int J Technol Assess Health Care* 2008; 24: 178–83.

17. Guo S, Counte MA, Gillespie KN, Schmitz H. Cost-effectiveness of adjunctive hyperbaric oxygen in the treatment of diabetic ulcers. *Int J Technol Assess Health Care* 2003; 19: 731–7.

18. Mathieu D, Marroni A, Kot J. Tenth European consensus conference on hyperbaric medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. *Diving Hyperb Med* 2017; 47: 24–32.

19. Andre-Levigne D, Modarressi A, Pignol R, Bochaton-Piallat ML, Pittet-Cuenod B. Hyperbaric oxygen therapy promotes wound repair in ischemic and hyperglycemic conditions, increasing tissue perfusion and collagen deposition. *Wound Repair Regen* 2016; 24: 954–65.

20. Londahl M. Hyperbaric oxygen therapy as adjunctive treatment of diabetic foot ulcers. *Med Clin North Am* 2013; 97: 957–80.

21. Kranke P, Bennett MH, Martyr-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* 2015; 6: CD004123.

22. Miltiaguoli M, Uzun G, Bennett M, Germonpre P, Smart D, Mathieu D. Poorly designed research does not help clarify the role of hyperbaric oxygen in the treatment of chronic diabetic foot ulcers. *Diving Hyperb Med* 2016; 46: 133–4.

23. Sherlock S. Control groups in hyperbaric trials. *Diving Hyperb Med* 2012; 42: 183.

24. Lansdorp CA, van Hulst RA. Double-blind trials in hyperbaric medicine: a narrative review on past experiences and considerations in designing sham hyperbaric treatment. *Clin Trials* 2018; 15: 462–76.

25. O’Reilly D, Pasricha A, Campbell K, Burke N, Assasi N, Bowen JM, et al. Hyperbaric oxygen therapy for diabetic ulcers: systematic review and meta-analysis. *Int J Technol Assess Health Care* 2013; 29: 269–81.

26. Stoenzekrook RM, Santema TB, Legemate DA, Umbink DT, van den Brink A, Koellemay MJ. Hyperbaric oxygen for the treatment of diabetic foot ulcers: a systematic review. *Eur J Vasc Endovasc Surg* 2014; 47: 647–55.

27. Guo S, DiPietro L. Factors affecting wound healing. *J Dent Res* 2010; 89: 219–29.

28. Sun JH, Tsai JS, Huang CH, Lin CH, Yang HM, Chan YS, et al. Risk factors for lower extremity amputation in diabetic foot disease categorized by Wagner classification. *Diabetes Res Clin Pract* 2012; 95: 58–63.

29. Adler AL, Boyko EJ, Ahroni JH, Smith DG. Lower-extremity amputation in diabetes. The independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. *Diabetes Care* 1999; 22: 1029–35.

30. Moher D, Liberati A, Tetzlaff J, Altmann DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Syst Res* 2010; 8: 336–41.

31. Liberati A, Altmann DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ (Clinical Research ed)*. 2009; b2707: 339.

32. Gerhard-Herman MD, Gornik HL, Barrett C, Bashe RS, Corriere MA, Drachman DE, et al. AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2016; 135: e726–e79.

33. Umbink DT, Kitslaar PJ, Tordor JH, Reneman RS, Jacobs MJ. Skin microcirculation in diabetic and non-diabetic patients at different stages of lower limb ischaemia. *Eur J Vasc Surg* 1993; 7: 659–66.

34. Higgins JP, Altmann DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane collaboration’s tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research ed)* 2011; d5928: 343.

35. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ (Clinical research ed)* 2016; 355: 1–7.

36. Shrier I, Boivin J-F, Steele RJ, Platt RW, Furlan A, Kakuma R, et al. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. *Am J Epidemiol* 2007; 166: 1203–9.

37. Kessler L, Bilbault P, Ortega F, Grasso C, Passeram P, Stephhan D, et al. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. *Diabetes Care* 2003; 26: 2378–82.

38. Khandelwal S, Chaudhary P, Poddar DD, Saxena N, Singh RA, Biswal UC. Comparative study of different treatment options of grade III and IV diabetic foot ulcers to reduce the incidence of amputations. *Clin* 2013; 3: e9.

39. Lyon KC. The case for evidence in wound care: investigating advanced treatment modalities in healing chronic diabetic lower extremity wounds. *J Wound Ostomy Continence Nurs* 2008; 35: 585s–90.

40. Ma L, Li P, Shi Z, Hou T, Chen X, Du J. A prospective, randomized, controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer. *Ostomy Wound Manage* 2013; 59: 18–24.
41. Margolis DJ, Gupta J, Hoffstad O, Papdopoulos M, Glick HA, Thom SR, et al. Lack of effectiveness of hyperbaric oxygen therapy for the treatment of diabetic foot ulcer and the prevention of amputation: a cohort study. Diabetes Care 2013; 36: 1961–6.

42. Zamboni WA, Wong HP, Stephenson LL, Pfeifer MA. Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. Undersea Hyperb Med 1997; 24: 175–9.

43. Akgul EA, Karakaya J, Aydin S. Role of comorbidities as limiting factors to the effect of hyperbaric oxygen in diabetic foot patients: a retrospective analysis. Diabetes Ther 2014; 5: 335–44.

44. AbdulAal A, Hermosilla JPD, Smart H. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes Care 2010; 33: 998–1003.

45. Bishop AJ, Mudge E. A retrospective study of diabetic foot ulcers treated with hyperbaric oxygen therapy. Int Wound J 2012; 9: 665–76.

46. Chen CY, Wu RW, Hsu MC, Hsieh CJ, Chou MC. Adjunctive hyperbaric oxygen therapy for healing of chronic diabetic foot ulcers: a randomized controlled trial. J Wound Ostomy Continence Nurs 2017; 44: 536–45.

47. Duzgun AP, Satir HZ, Ozozan O, Saylam B, Kulah B, Coskun F. Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. J Foot Ankle Surg 2008; 47: 515–9.

48. Erdogan A, Duzgun AP, Erdogan K, Ozkan MB, Coskun F. Efficacy of hyperbaric oxygen therapy in diabetic foot ulcers based on Wagner classification. J Foot Ankle Surg 2018; 57: 1115–9.

49. Kaya A, Aydin F, Altay T, Karapinar L, Ozturk H, Karakuzu C. Can major amputation rates be decreased in diabetic foot ulcers with hyperbaric oxygen therapy? Int Orthop 2009; 33: 441-6.

50. Londahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes Care 2010; 33: 998–1003.

51. Oliveira N, Rosa P, Borges L, Dias E, Oliveira F, Cassio I. Treatment of diabetic foot complications with hyperbaric oxygen therapy: a retrospective experience. J Foot Ankle Surg 2014; 20: 140–3.

52. Fedorko L, Bowen JM, Jones W, Oreopoulos G, Goeree R, Hopkins RB, et al. Hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with non-healing ulcers of the lower limb: a prospective, double-blind. Randomized Controlled Clinical Trial Diabetes Care 2016; 39: 392–9.

53. Huang ET. Comment on Fedorko et al. hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. Diabetes Care 2016; 39: e133–4.

54. Londahl M, Fagher K, Katzman P. Comment on Fedorko et al. hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. Diabetes Care 2016; 39: 392–399. Diabetes Care 2016; 39: e131–2.

55. Murad MH. Comment on Fedorko et al. hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. Diabetes Care 2016; 39: 392–399. Diabetes Care 2016; 39: e135.

56. Imran S, Ali R, Mahboob G. Frequency of lower extremity amputation in diabetics with reference to glycemic control and Wagner’s grades. J College Phys Surg—Pakistan: JCPSP 2006; 16: 124–7.

57. Ozan F, Gurbuz K, Celik I, Bestepe Dursun Z, Uzun E. Evaluation of major and minor lower extremity amputation in diabetic foot patients. Turk J Med Sci 2017; 47: 1109–16.

58. D’Agostino Dias M, Fontes B, Poggeti RS, Birolini D. Hyperbaric oxygen therapy: types of injury and number of sessions—a review of 1500 cases. Undersea Hyperb Med 2008; 35: 53–60.

59. Santema KTB, Stoeckenbroek RM, Koellemay MJW, Reekers JA, van Dortmont LMC, Oomen A, et al. Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: results of the DAMO2CLES multicenter randomized clinical trial. Diabetes Care 2018; 41: 112–9.