Hyperbaric oxygen treatment for University of Texas grade 3 diabetic foot ulcers: a retrospective cohort study

Aim: Hard-to-heal diabetic foot ulcers (DFUs) may increase the risk of amputation. This study reports the positive influence of hyperbaric oxygen therapy (HBOT) on hard-to-heal DFUs involving underlying bone. **Method:** A single-centre, retrospective cohort study reporting the results of HBOT and wound care on hard-to-heal University of Texas grade 3 DFUs (i.e., involving underlying bone) between 2013 and 2019. Outcome measures were primarily (near-) complete wound healing (i.e., ≥80% ulcer surface area reduction) and amputation rate (minor or major), and secondarily the number of hyperbaric sessions and improvement in quality of life (QoL) and pain score. **Results:** The study included 206 patients, of whom 74 (36%) achieved complete wound healing, and 75 (36%) near-complete healing. Amputations were performed in 27 patients (13%): 12 (6%) minor and 15 (7%) major. The median number of HBOT sessions was 42. Participants who achieved complete healing received a median of 43 sessions, compared with 10 for those who required major amputation. Patients with at least 30 sessions were less likely to undergo amputation (odds ratio: 0.08; 95% confidence interval (CI): 0.03–0.21). Mean QoL increased by 7.6 points (95%CI: 3.9–11.3; p<0.01) and median pain score fell from 3 to 1 (0–3) (p<0.01). **Conclusions:** The addition of HBOT to standard wound care may lead to a decreased amputation risk, improved wound healing and increased QoL for people with a University of Texas grade 3 DFU. An adequate number of HBOT sessions is required to achieve optimal clinical results. Objective selection criteria and shared decision-making are suggested to improve dropout rates. **Declaration of interest:** The authors have no conflicts of interest to declare. No specific funding was received for this work.

diabetes ● diabetic foot ● foot ulcer ● hyperbaric oxygen therapy ● hyperbaric medicine ● infection ● wound healing ● retrospective study ● ulcer ● wound

Diabetes is a global health issue with an estimated prevalence of 8.5% in the adult population.[1] A diabetic foot ulcer (DFU) is one of the most common complications, and affects more than 2% of all patients annually.[2] Despite adequate treatment, an estimated 19–35% of DFUs remain unhealed,[3,4] and mortality rates due to DFU rival or exceed those of certain types of cancer.[5] Hard-to-heal wounds are more prone to infection and may eventually lead to amputation of the affected digit, foot or even limb. As many as 50–70% of all non-traumatic lower extremity amputations are due to diabetes.[6] A systematic review by Narres et al.[7] reported up to a 26-fold increased risk for lower extremity amputation in the diabetic population compared to the non-diabetic population.

Several classification systems exist to describe the severity of a DFU. They can be used as a prognostic tool, guidance for treatment or for communication between professionals. One such system is the (University of) Texas wound classification,[8] in which DFUs are classified based on the presence of ischaemia, infection and extent of tissue penetration (see Table 1). The deeper the tissues that are involved, the higher the grade (0–3). The presence of ischaemia and/or infection (stage) is scored with an additional letter (A–D). Patients with a DFU with involvement of the underlying bone (i.e., Texas grade 3) are 11 times more likely to require amputation.[9]

Tissue hypoxia and infection are important sustaining factors in these hard-to-heal wounds.[10] Hyperbaric oxygen therapy (HBOT) improves tissue oxygenation and thereby provides several beneficial effects for wound healing,[11] such as increased angiogenesis and decreasing inflammation,[12] improved collagen deposition[13] and antibiotic penetration in micro-organisms.[11] The therapy is defined as breathing 100% oxygen under increased ambient pressure, which is achieved in pressure chambers, accommodating either single or multiple persons. Nowadays, HBOT is accepted for several indications, including osteoradionecrosis of the mandible, delayed radiation injury, compromised skin grafts and diabetic foot lesions.[14] There are a few, usually mild, side-effects with a small risk of barotrauma of the ears or sinuses, reversible visual acuity changes and a very small risk (<0.03%) of acute cerebral oxygen toxicity.[15]

Rutger C Lalieu,[1,2] MD*; **Willem Mulder**,[1] MD; **René D Bol Raap**,[1] MD; **Saskia Stolk**;[1] **Casper Smit**,[1,3] MD, PhD; **Emile FL Dubois**,[1] MD, PhD; **Rob A van Hulst**,[2,4] MD, PhD
*Corresponding author email: r.lalieu@hgcrijswijk.nl
1 Hyperbaar Geneeskundig Centrum, Rijswijk, the Netherlands. 2 Amsterdam University Medical Centers, Department of Anesthesiology, Amsterdam, the Netherlands. 3 Reinier de Graaf Gasthuis, Department of Surgery, Delft, the Netherlands. 4 Amsterdam University Medical Centers, Department of Surgery, Hyperbaric Dept, Amsterdam, the Netherlands.

Despite the beneficial effects and low risks, HBOT is not routinely applied in wound care. Hyperbaric facilities are not yet widely accessible for most physicians, and the therapy itself is presumed to be time-consuming and cumbersome. For similar reasons, randomised clinical trials (RCTs) are complicated, and therefore not frequently performed.[16] As a result, previous systematic reviews of available literature have been inconclusive about the efficacy of HBOT.[17–19] In the current study, we specifically aim to describe the effect of the addition of HBOT to wound care for patients with a Texas grade 3 wound. Since these wounds lead to a profound risk of amputation, exploring additional treatment options to standard wound care is essential.

Methods

Ethical approval
No ethical approval was necessary because the patients were receiving routine treatment. All patients provided written consent for the use of anonymised data in this study.

Study design
The study design was a single centre, retrospective cohort study without a control group, according to the STROBE guidelines.[20] All principles of the Declaration of Helsinki were followed.

Patients were referred from surrounding regional and university hospitals, when no significant wound healing was observed despite optimal wound care for longer than three months. Some patients were referred earlier than three months at the discretion of the treating physician, for example, due to the fast deterioration of the wound. Optimal wound care encompasses surgical debridement, antibiotic therapy, compression therapy, negative pressure wound therapy (NPWT) and optimisation of offloading with a total contact cast when indicated. Prior to starting HBOT, the vascular status was analysed and optimised (if possible) by the vascular surgeon at the referring hospital.

Patients were included in the current study when they met the following inclusion criteria:
- Diabetes mellitus type 1 or type 2
- DFU grade 3 (Texas classification: ulcer penetrating to bone or joint).[8]

Upon starting, during and after treatment, the ulcer was photographed regularly and manually measured. These photographs were evaluated weekly with the entire wound care team to achieve consensus regarding the wound healing progress. Quality of life (QoL) questionnaires were filled out by all participants before the first and after the last HBOT session.

Treatment took place in a multiplace chamber (IHC Hytec, HYOT/2200/20/2/RD, Royal IHC, the Netherlands) and consisted of once daily sessions of HBOT, five days per week, for a duration of 110 minutes per session in total. During the first 10 minutes of each session, the chamber was pressurised to the working

pressure of 2.4 atmospheres absolute (ATA; 240kPa). With 5-minute air-breaks in between, patients breathed 100% oxygen for three blocks of 20 minutes. Then a fourth and final block lasting 15 minutes, after which decompression was started. During decompression, patients still breathed 100% oxygen for 8 minutes. In the last 2 minutes of decompression, patients breathed air. In addition, standard wound care, as defined above, was continued once weekly.

Table 1. Texas Wound Classification system (adapted from Lavery et al.[8])

	Grade 0	Grade 1	Grade 2	Grade 3
Stage A	No wound or complete epithelialisation	Superficial wound	Wound involving tendon or capsule	Wound involving bone or joint
Stage B	With infection	With infection	With infection	With infection
Stage C	With ischaemia	With ischaemia	With ischaemia	With ischaemia
Stage D	With infection and ischaemia	With infection and ischaemia	With infection and ischaemia	With infection and ischaemia

Table 2. Baseline patient characteristics

Characteristic	n=206
Age (years)	67±12
Female gender	47 (23)
Male gender	159 (77)
University of Texas stage	
A (no infection or ischaemia)	33 (16)
B (infection)	71 (34)
C (ischaemia)	34 (17)
D (both infection and ischaemia)	68 (33)
Ulcer duration	
0–3 weeks	20 (10)
3–6 weeks	34 (17)
6 weeks–3 months	56 (27)
3–18 months	77 (37)
>18 months	19 (9)
Values are mean±standard deviation or n (%)	

Table 3. Wound healing results and number of sessions

Wound classification	n	Number of sessions
Complete wound healing	74 (36)	43 (33–57)
≥80% wound healing	75 (36)	56 (40–60)
<80% wound healing	25 (12)	45 (8–58)
Wound deteriorated	5 (2)	28 (12–45)
Minor amputation	12 (6)	24 (16–38)
Major amputation	15 (7)	10 (8–19)
Total	206 (100)	42 (28–58)
Values are median (Q1–Q3) or n (%); Number of patients with ≥30 sessions=152 (74%)		

Table 4. Quality of life scores before and after treatment, per outcome category

Treatment results	n (%)	Health score (mean±standard deviation)				
		Before	After	Mean difference	95% confidence interval	p-value
Complete healing	74 (36)	63.2±20.1	71.4±21.4	+8.4	3.1 to 13.7	0.02*
≥80% wound healing	75 (36)	58.9±16.8	69.1±16.9	+6.5	0.7 to 12.3	0.03*
<80% wound healing	25 (12)	65.1±21.8	69.9±19.1	+3.0	−11.4 to 17.4	0.66
Wound deteriorated	5 (2)	58.0±31.1	75.0±13.2	+8.3	−64.5 to 81.1	0.67
Minor amputation	12 (6)	57.3±24.4	64.4±25.3	+8.6	−16.0 to 33.1	0.43
Major amputation	15 (7)	51.0±21.2	75.0±7.1	+21.0	−17.9 to 59.9	0.21
Total	206 (100)	60.5±19.9	69.6±19.2	+7.6	3.9 to 11.3	<0.01*
*statistically significant (p<0.05)						

Table 5. Pain scores before and after treatment, per outcome category

Treatment results	n (%)	Pain score (median (interquartile range))				
		Before	After	Mean difference	95% confidence interval	p-value
Complete healing	74 (36)	3.0 (2.0 to 6.0)	1.0 (0.0 to 3.0)	−1.3	−2.1 to −0.5	<0.01*
≥80% wound healing	75 (36)	3.0 (1.0 to 6.0)	0.0 (0.0 to 4.0)	−1.0	−1.6 to −0.5	<0.01*
<80% wound healing	25 (12)	4.0 (1.0 to 5.8)	3.0 (0.8 to 4.5)	−1.3	−2.9 to 0.3	0.09
Wound deteriorated	5 (2)	3.0 (0.5 to 9.0)	0.0 (0.0 to 0.0)	−3.7	−13.1 to 5.7	0.11
Minor amputation	12 (6)	3.0 (1.0 to 6.0)	0.5 (0.0 to 4.0)	−1.7	−4.1 to 0.7	0.11
Major amputation	15 (7)	5.0 (4.0 to 6.5)	1.0 (0.0 to 4.3)	−3.5	−10.6 to 3.6	0.19
Total	206 (100)	3.0 (1.0 to 6.0)	1.0 (0.0 to 3.0)	−1.4	−1.8 to −0.9	<0.01*
* statistically significant (p<0.05)						

Outcome parameters

Primary outcome parameters were wound healing and amputation rate (minor (i.e., below ankle joint) or major (i.e., above ankle joint)). Both complete (group 1) and near-complete wound healing (group 2) were considered a favourable outcome. Near-complete wound healing is a surrogate outcome measure, defined as no clinical signs of infection, ≥80% ulcer surface area reduction, superficial wound (i.e., ≤0.5cm), 100% granulating tissue and complete re-epithelialisation of wound borders. When these characteristics were achieved, they provided a robust predictor for complete healing in the weeks thereafter.[21,22] Further outcome categories were <80% ulcer surface area reduction (group 3), deterioration of the wound (group 4), and minor (group 5) and major amputation (group 6), which are all considered negative outcomes.

Secondary outcome measures were number of HBOT sessions and QoL, appraised with the EQ-5D questionnaire[23] before the first and after the last HBOT session. As part of the questionnaire, people scored self-perceived QoL on a 100-point scale and pain on a 10-point visual analogue scale (VAS).

Statistical analysis

All statistical analyses were performed with SPSS version 26 (IBM, US). For normally distributed variables, the mean and standard deviation (SD) are given; for non-normally distributed values the median and interquartile range (IQR) are given. Frequencies are displayed as an amount and percentage. Comparisons between groups were performed with a one-way analysis of variance (ANOVA) for normally distributed outcomes or Kruskal–Wallis tests for non-parametric outcomes, and presented with a 95% confidence interval (95%CI). Both separate outcome groups and dichotomised groups (positive and negative outcome) were tested against each other, since outcome groups 3 to 6 contained fewer patients than groups 1 and 2. A Tukey post-hoc test was used to compare data before and after therapy, when possible. A p-value <0.05 was considered statistically significant for all tests.

Results

From January 2013 to December 2019, 206 patients with a Texas grade 3 ulcer were treated with HBOT and standard wound care and were included in the current study. Baseline characteristics are shown in Table 2. Of the 206 patients, 139 (67%) had an infected wound and 102 (50%) had a wound with (local) ischaemia, as per the Texas wound classification stage. In about 47% of the population, the wound had existed for three months or longer.

Treatment results are displayed in Table 3. A

favourable outcome was seen in 149 (72%) patients: 74 (36%) achieved complete wound healing, while 75 (36%) patients achieved near-complete healing. Amputations were performed in 27 patients (13%): 12 (6%) minor and 15 (7%) major.

Patients who achieved a favourable outcome completed more sessions than those with an unfavourable outcome (p<0.01), especially those with more than 30 sessions (p<0.01). The median number of HBOT sessions for the entire population was 42 (range: 28–58), with 152 patients (74%) completing at least 30 sessions. Patients in this category were less likely to undergo an amputation (odds ratio (OR) 0.08; 95%CI: 0.03–0.21). The wound duration before start of therapy did not influence the number of sessions performed (p=0.33) or the result of treatment (p=0.77). Patients in the Texas 3A and 3B groups had a better outcome overall than patients in the Texas 3D group (p<0.01 and p=0.01, respectively), although the number of sessions performed was comparable between these groups (p=0.55).

Table 4 shows the difference between health scores, before and after treatment, between the different wound healing categories. Table 5 shows the pain scores for the same categories. No significant differences in QoL and pain scores at the start of treatment were found between outcome groups, even when dichotomised for positive and negative outcome. The mean difference in QoL and pain after treatment was similar across all groups but only achieved statistical significance for patients with a favourable outcome, which are the largest groups. For the EQ-5D at baseline, the average QoL score was 60.5±19.9 and the median pain score 3 (range: 1–6). After treatment, the average QoL score was increased to 7.6 points (95%CI: 3.9–11.3; p<0.01) and median pain score reduced to 1 (range: 0–3) (p<0.01). A Tukey post-hoc test revealed significant differences between patients who achieved (near-) complete healing, plus those who did not achieve significant healing, and those who required major amputation. Although the overall pain score was also lowered in the major amputation group, this result was not statistically significant. A Tukey post-hoc test could not be performed.

Discussion

In this study, the addition of HBOT to standard wound care results in a majority of patients achieving complete or near-complete wound healing. The patients who eventually required amputation (minor or major) did not complete as many HBOT sessions as those who achieved complete healing. Patients categorised without local ischaemia according to the Texas classification achieved overall better results than those with local ischaemia.

The results of the current study were compared with those in recent literature on HBOT and wound healing.[17–19,24–26] It should be noted that most of these studies use the Wagner wound classification[27] to describe DFUs. Comparable with Texas grade 3, Wagner grade 3 and 4 also encompasses DFUs with involvement of deeper tissues, including the underlying bone. Although the classification systems are similar, the newer Texas Wound Classification is currently more widely used in wound clinics[28] because it is better at predicting outcomes.[29]

Earlier systematic reviews[17–19] reported improved wound healing and fewer amputations after HBOT combined with standard wound care, compared with standard wound care alone, although the effects were not statistically significant. Variability of the quality of the included studies, not the treatment itself, is cited as one of the main reasons for this.[17–19]

An observational study by Ennis et al.,[24] with a similar patient population to the current study, reported an improved wound healing rate in Wagner grade 3 and 4 ulcers after HBOT (60.01%), when compared with wound healing alone (56.04%). The result was even more pronounced when patients completed the prescribed amount of sessions (75.24%).

The current results are also comparable with those of earlier RCTs on HBOT and wound healing of DFUs. Löndahl et al.[25] included a total of 94 participants of similar age and sex distribution compared with the current study population, who had had a DFU for at least three months. In the intention-to-treat analysis they reported an improved wound healing rate of DFUs with Wagner grade 2–4 (the majority being Wagner 3 or 4) when comparing HBOT to sham treatment (52% versus 29%, p=0.03). In a sub-analysis of patients completing >35 sessions, the wound healing rate was 61% versus 27% (p=0.009).

In contrast, the recent DAMOCLES study by Santema et al.,[26] reported that, in a population with ischaemic DFUs classified as Wagner 2–4, adding HBOT to standard wound care does not decrease amputation rate (amputation free survival risk difference (RD): 13%; 95%CI: −2 to 28) or improve wound healing results (RD: 3%; 95%CI: −14 to 21). Nevertheless, longer amputation-free survival (RD: 26%; 95%CI: 10–38) was reported in the per-protocol analysis when 30 or more sessions of HBOT were used. Although this may be due to selection bias of patients with an overall better medical condition, it is in line with the study by D'Agostino et al.,[30] who suggested at least 30 sessions are needed for healing hard-to-heal wounds. In the DAMOCLES study,[26] 35% of participants in the HBOT group were not able to complete a full regimen of treatment, possibly due to their generally bad medical condition. A similar effect can be seen in the current study—patients who required an amputation completed fewer sessions than those who had a favourable outcome. Improved patient selection for HBOT and shared decision-making may reduce drop-out rates.[31] Examples of selection criteria are wound classification and transcutaneous oxygen measurements. Shared decision-making should include informing the patient of the expected risks and outcomes, the amount of

sessions required and alternative treatment options. These same principles should be applied during therapy as well, i.e., when patients have trouble completing the prescribed amount of sessions, they should be counselled on the underlying reasons for this and alternative treatment options.

Crucially, our results show an improved wound healing rate compared with the literature on treatment of DFUs with standard wound care only. A recent review by Fife et al.[32] estimates that wound healing rates in a typical outpatient wound clinic for DFUs in general may be as low as 30.5%. Other small-scale studies show that increased depth of the ulcer, concomitant infection and longer referral time for extended treatment are risk factors for lower extremity amputation.[33,34] In our population, duration of the wound before HBOT did not influence the result of treatment. Around half of the population presented with an ulcer that had been present for <3 months. HBOT is usually recommended for wounds that fail to heal after three months of standard wound care. However, they may be treated earlier when the wound is expected to deteriorate before this term. These are usually critical wounds (for example, ischaemic ulcers) which are harder to heal. This would explain why these wounds did not heal faster. This implies that, while standard wound care may be able to heal low-grade ulcers, earlier and more extensive treatment is warranted in high-grade ulcers and comorbidities, such as infection, to prevent outcomes such as amputation. Duration of the wound should therefore not be a selection criterion for referral for HBOT.

Concerning the secondary outcome measures, a recent meta-analysis[35] has shown that QoL is decreased in the presence of a DFU, as measured by several validated questionnaires, such as the SF-36 and EQ-5D questionnaires. When amputation is required, this may lead to additional mental health problems, such as anxiety or even post-traumatic stress disorder.[36] Our study shows a high frequency of healed wounds, and relatively low frequencies of minor and major amputation, in a population with an otherwise high risk of amputation.[9] Unsurprisingly, people who achieved (near-) complete wound healing reported a higher health score after treatment.

However, the other categories also showed an increased QoL, albeit not statistically significant. The same is true for reduction of pain scores. The lower number of patients in the outcome categories other than (near-) complete healing may explain the non-statistical significance. The difference in the major amputation group is even more pronounced than in other groups, including complete wound healing. A possible explanation for the improved QoL and decreased pain scores after amputation is that amputation itself decreases pain and other complaints of a non-healing wound. Before amputation, even though no complete wound healing was achieved, the condition of the wound may improve enough to decrease pain, and thereby increase QoL. Since pain relief is contextual (patient-dependent), it should be interpreted with care.[37] Other factors also contribute to QoL,[35] so improvement may be possible without wound healing or pain relief. This may also explain the improved QoL scores in the negative outcome groups. It is therefore paramount that patients with high-risk ulcers, such as those with positive probing to bone, are treated early and aggressively, to prevent a reduction in physical and mental functioning.

The benefits of expedient ulcer healing are clearly outlined in these outcome parameters. However, they exist not just on the patient level. They are also reflected by the long-term cost-effectiveness of HBOT for diabetic ulcers.[38,39] While the initial high cost of the therapy is often cited as a reason not to apply it, it stands in contrast to the high cost of not just amputation surgery, but also the physical therapy and other health care expenditures afterward.[40,41] A more prominent hindrance is access to therapy. Usually, HBOT takes place in specialised centres or hospitals, which may not be within reach for many physicians or patients, either geographically or logistically. Providers should therefore focus on increasing the number of locations where HBOT can be applied or improve access to existing locations.

Limitations

There are some limitations to this study. Firstly, since this is a retrospective study, not all data for certain covariates or confounders were available. Although our population is similar to those in RCTs and other studies,[17–19,24–26] the addition of more parameters would have provided a more robust description of our study population. However, there has been no association between the patient's age, sex, type and duration of diabetes, or location of the ulcer and the outcome of a DFU.[3] The presence of ischaemia and infection are thought to be the most important prognostic factors.[42] In the current study, this can be seen as the difference in the number of favourable outcomes of the Texas 3A and 3B groups, compared with the Texas 3D group.

Secondly, the duration of follow-up is short, with the outcome measures reported being the situation directly after treatment (i.e., 12–16 weeks after start of therapy). While we do send out questionnaires after 3, 12 and 24 months to every patient, unfortunately these are seldom returned. Since recurrence is reported to be as high as 40% within a year,[2] it is possible that some people still require amputation at a later time point. We would argue that this is not a failure of HBOT since it is a curative and not a preventative treatment. People still require optimal glycaemic control, adequate offloading and effective treatment of concurrent comorbidities to prevent new ulceration or recurrence.

Lastly, we would like to address the fact that one patient in our database received 112 sessions of HBOT. This patient was referred to prevent a second major amputation and received two series of 60 and 52 sessions, respectively. The treatment was extended by request from the patient's surgeon, who had no

alternative treatment options due to the severe peripheral arterial vascular disease and contralateral leg amputation. In six months, the patient achieved 60% wound healing and was downgraded from Texas 3C to 2A. No minor or major amputation was performed during treatment.

Conclusions

In conclusion, in a population with Texas grade 3 DFUs that did not heal with standard wound care, the addition of HBOT led to a large proportion of patients achieving (near-)complete wound healing. In half of this population, the wound existed longer than three months. Patients who completed >30 sessions were less likely to undergo an amputation. Objective selection criteria and shared decision-making are suggested to reduce dropout rates. Improving accessibility to the therapy remains crucial. **JWC**

References

1 World Health Organization. Global report on diabetes. 2016. https://tinyurl.com/j6ef4fch (accessed 10 December 2018)

2 Armstrong DG, Boulton AJ, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med 2017; 376(24):2367–2375. https://doi.org/10.1056/NEJMra1615439

3 Oyibo SO, Jude EB, Tarawneh I 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. Diabet Med 2001; 18(2):133–138. https://doi.org/10.1046/j.1464-5491.2001.00422.x

4 Gershater MA, Löndahl M, Nyberg P et al. Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. Diabetologia 2009; 52(3):398–407. https://doi.org/10.1007/s00125-008-1226-2

5 Armstrong DG, Wrobel J, Robbins JM. Guest editorial: are diabetes-related wounds and amputations worse than cancer? Int Wound J 2007; 4(4):286–287. https://doi.org/10.1111/j.1742-481X.2007.00392.x

6 Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005; 366(9498):1719–1724. https://doi.org/10.1016/S0140-6736(05)67698-2

7 Narres M, Kvitkina T, Claessen H et al. Incidence of lower extremity amputations in the diabetic compared with the non-diabetic population: a systematic review. PLoS One 2017; 12(8):e0182081. https://doi.org/10.1371/journal.pone.0182081

8 Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. J Foot Ankle Surg 1996; 35(6):528–531. https://doi.org/10.1016/s1067-2516(96)80125-6

9 Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system: the contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care 1998; 21(5):855–859. https://doi.org/10.2337/diacare.21.5.855

10 Schreml S, Szeimies RM, Prantl L et al. Oxygen in acute and chronic wound healing. Br J Dermatol 2010; 163(2):257–268. https://doi.org/10.1111/j.1365-2133.2010.09804.x

11 Hopf HW, Kelly M, Shapshak D. Chapter 11: Oxygen and the basic mechanisms of wound healing. In: Neuman TS, Thom SR (eds). Physiology and medicine of hyperbaric oxygen therapy. Philadelphia: WB Saunders, 2008:203–228

12 Lam G, Fontaine R, Ross FL, Chiu ES. Hyperbaric oxygen therapy: exploring the clinical evidence. Adv Skin Wound Care 2017; 30(4):181–190. https://doi.org/10.1097/01.ASW.0000513089.75457.22

13 Andre-Levigne D, Modarressi A, Pignel R et el. Hyperbaric oxygen therapy promotes wound repair in ischemic and hyperglycemic conditions, increasing tissue perfusion and collagen deposition. Wound Repair Regen 2016; 24(6):954–965. https://doi.org/10.1111/wrr.12480

14 Moon RE; for the Undersea and Hyperbaric Medical Society. Hyperbaric oxygen therapy indications (14th ed). Best Publishing, 2019

15 Costa DA, Ganilha JS, Barata PC, Guerreiro FG. Seizure frequency in more than 180,000 treatment sessions with hyperbaric oxygen therapy: a single centre 20-year analysis. Diving Hyperb Med 2019; 49(3):167–174. https://doi.org/10.28920/dhm49.3.167-174

16 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(5):462–476. https://doi.org/10.1177/1740774518776952

17 Golledge J, Singh TP. Systematic review and meta-analysis of clinical trials examining the effect of hyperbaric oxygen therapy in people with diabetes-related lower limb ulcers. Diabet Med 2019; 36(7):813-826. https://doi.org/10.1111/dme.13975

18 Brouwer RJ, Lalieu RC, Hoencamp R et al. A systematic review and meta-analysis of hyperbaric oxygen therapy for diabetic foot ulcers with arterial insufficiency. J Vasc Surg 2020; 71(2):682–692.e1. https://doi.org/10.1016/j.jvs.2019.07.082

19 Lalieu RC, Brouwer RJ, Ubbink DT et al. Hyperbaric oxygen therapy for nonischemic diabetic ulcers: a systematic review. Wound Repair Regen 2020; 28(2):266–275. https://doi.org/10.1111/wrr.12776

20 von Elm E, Altman DG, Egger M et al.; for the STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370(9596):1453–1457. https://doi.org/10.1016/S0140-6736(07)61602-X

21 Cardinal M, Eisenbud DE, Phillips T, Harding K. Early healing rates and wound area measurements are reliable predictors of later complete wound closure. Wound Repair Regen 2008;16(1):19–22. https://doi.org/10.1111/j.1524-475X.2007.00328.x

22 Sheehan P, Jones P, Caselli A et al. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care 2003; 26(6):1879–1882. https://doi.org/10.2337/diacare.26.6.1879

23 Rabin R, Charro F. EQ-SD: a measure of health status from the EuroQol Group. Ann Med 2001; 33(5):337–343. https://doi.org/10.3109/07853890109002087

24 Ennis WJ, Huang ET, Gordon H. Impact of hyperbaric oxygen on more advanced Wagner grades 3 and 4 diabetic foot ulcers: matching therapy to specific wound conditions. Adv Wound Care 2018; 7(12):397–407. https://doi.org/10.1089/wound.2018.0855

25 Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes Care 2010; 33(5):998–1003. https://doi.org/10.2337/dc09-1754

26 Santema KT, Stoekenbroek RM, Koelemay MJ et al.; for the DAMO$_2$CLES Study Group. Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: Results of the DAMO$_2$CLES multicenter randomized clinical trial. Diabetes Care 2018; 41(1):112–119. https://doi.org/10.2337/dc17-0654

27 Wagner FW Jr. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle 1981; 2(2):64–122. https://doi.org/10.1177/107110078100200202

28 Alavi A, Sibbald RG, Mayer D et al. Diabetic foot ulcers: Part I: Pathophysiology and prevention. J Am Acad Dermatol 2014; 70(1):1.e1–1.e18. https://doi.org/10.1016/j.jaad.2013.06.055

29 Oyibo SO, Jude EB, Tarawneh I et al. A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. Diabetes Care 2001; 24(1):84–88. https://doi.org/10.2337/diacare.24.1.84

30 D'Agostino Dias M, Fontes B, Poggetti RS, Birolini D. Hyperbaric oxygen therapy: types of injury and number of sessions—a review of 1506 cases. Undersea Hyperb Med 2008; 35(1):53–60

31 Huang ET, Mansouri J, Murad MH et al. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. Undersea Hyperb Med 2015; 42(3):205–247

32 Fife CE, Eckert KA, Carter MJ. Publicly reported wound healing rates: the fantasy and the reality. Adv Wound Care 2018; 7(3):77–94. https://doi.org/10.1089/wound.2017.0743

33 Jeong EG, Cho SS, Lee SH et al. Depth and combined infection is important predictor of lower extremity amputations in hospitalized diabetic foot ulcer patients. Korean J Intern Med 2018; 33(5):952–960. https://doi.org/10.3904/kjim.2016.165

34 Smith-Strøm H, Iversen MM, Igland J et al. Severity and duration of diabetic foot ulcer (DFU) before seeking care as predictors of healing time: a retrospective cohort study. PLoS One 2017; 12(5):e0177176. https://doi.org/10.1371/journal.pone.0177176

35 Khunkaew S, Fernandez R, Sim J. Health-related quality of life among adults living with diabetic foot ulcers: a meta-analysis. Qual Life Res 2019; 28(6):1413–1427. https://doi.org/10.1007/s11136-018-2082-2

36 Bhuvaneswar CG, Epstein LA, Stern TA. Reactions to amputation: recognition and treatment. Prim Care Companion J Clin Psychiatry 2007; 9(4):303–308. https://doi.org/10.4088/PCC.v09n0408

37 Lamers LM, McDonnell J, Stalmeier PF et al. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. Health Econ 2006; 15(10):1121–1132. https://doi.org/10.1002/hec.1124

38 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(4):731–737. https://doi.org/10.1017/S0266462303000710

39 Treweek S, James PB. A cost analysis of monoplace hyperbaric oxygen therapy with and without recirculation. J Wound Care 2006; 15(6):235–238. https://doi.org/10.12968/jowc.2006.15.6.26921

40 Tchero H, Kangambega P, Lin L et al. Cost of diabetic foot in France, Spain, Italy, Germany and United Kingdom: a systematic review. Ann Endocrinol (Paris) 2018; 79(2):67–74. https://doi.org/10.1016/j.ando.2017.11.005

41 Graz H, D'Souza VK, Alderson DE, Graz M. Diabetes-related amputations create considerable public health burden in the UK. Diabetes Res Clin Pract 2018; 135:158–165. https://doi.org/10.1016/j.diabres.2017.10.030

42 Prompers L, Huijberts M, Apelqvist J 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(1):18–25. https://doi.org/10.1007/s00125-006-0491-1