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.
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. As a result, previous systematic reviews of available literature have been inconclusive about the efficacy of HBOT. 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. 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).

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 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)

<table>
<thead>
<tr>
<th>Wound classification</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage A</td>
<td>No wound complete epithelialisation</td>
<td>Superficial wound</td>
<td>Wound involving tendon or capsule</td>
<td>Wound involving bone or joint</td>
</tr>
<tr>
<td>Stage B</td>
<td>With infection</td>
<td>With infection</td>
<td>With infection</td>
<td>With infection</td>
</tr>
<tr>
<td>Stage C</td>
<td>With ischaemia</td>
<td>With ischaemia</td>
<td>With ischaemia</td>
<td>With ischaemia</td>
</tr>
<tr>
<td>Stage D</td>
<td>With infection and ischaemia</td>
<td>With infection and ischaemia</td>
<td>With infection and ischaemia</td>
<td>With infection and ischaemia</td>
</tr>
</tbody>
</table>

### Table 2. Baseline patient characteristics

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

### Table 3. Wound healing results and number of sessions

<table>
<thead>
<tr>
<th>Wound classification</th>
<th>n</th>
<th>Number of sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete wound healing</td>
<td>74 (36)</td>
<td>43 (33–57)</td>
</tr>
<tr>
<td>≥80% wound healing</td>
<td>75 (36)</td>
<td>56 (40–60)</td>
</tr>
<tr>
<td>&lt;80% wound healing</td>
<td>25 (12)</td>
<td>45 (8–58)</td>
</tr>
<tr>
<td>Wound deteriorated</td>
<td>5 (2)</td>
<td>28 (12–45)</td>
</tr>
<tr>
<td>Minor amputation</td>
<td>12 (6)</td>
<td>24 (16–38)</td>
</tr>
<tr>
<td>Major amputation</td>
<td>15 (7)</td>
<td>10 (8–19)</td>
</tr>
<tr>
<td>Total</td>
<td>206 (100)</td>
<td>42 (28–58)</td>
</tr>
<tr>
<td>Values are median (Q1–Q3) or n (%)</td>
<td>Number of patients with ≥30 sessions=152 (74%)</td>
<td></td>
</tr>
</tbody>
</table>
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 questionnaire23 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 increased to 7.6 points (range: 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 classification27 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 clinics28 because it is better at predicting outcomes.29

Earlier systematic reviews17–19 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 Santerma 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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{37} Other factors also contribute to QoL,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{3} The presence of ischaemia and infection are thought to be the most important prognostic factors.\textsuperscript{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,\textsuperscript{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.

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

- If hyperbaric oxygen treatment (HBOT) is able to improve wound healing, why is it not more commonplace in clinical practice?
- Because there seems to be no difference between wound-duration groups for outcomes, should patients be referred earlier, if no adequate wound healing is achieved with conventional care?
- How can clinicians and researchers increase the likelihood that patients return questionnaires after an extended amount of time after therapy?


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