IQWiG Reports – Commission N15-02

Hyperbaric oxygen therapy for diabetic foot syndrome[1]

Extract

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The responsibility for the contents of the report lies solely with IQWiG.

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Key statement

Research question

The aim of the present investigation is

- to assess the benefit of hyperbaric oxygen therapy (HBOT) compared with any other treatment option

in each case in patients with diabetic foot syndrome (DFS) with regard to patient relevant-outcomes.

Conclusion

For the outcome of **wound closure**, the present benefit assessment provides a hint of a benefit of adjunctive HBOT compared with standard wound care alone in patients with DFS**.**

For other patient-relevant outcomes (**mortality, minor and major amputations, adverse effects of treatment, health-related quality of life**, and **length of hospital stay**), the data provide no hint of a benefit or harm of adjunctive HBOT compared with other treatment options in patients with DFS.

For the outcomes of **pain, cardiovascular morbidity**, and **dependency on outside help or need for long-term care**, no conclusion can be inferred on the benefit or harm of adjunctive HBOT compared with other treatment options in patients with DFS, as no data were available in this regard.

Due to a lack of adequate data, no separate conclusions on benefit according to subgroup or therapeutic indications are possible.

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ATA	atmospheres absolute
CI	confidence interval
DFS	diabetic foot syndrome
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HBOT	hyperbaric oxygen therapy
HrQoL	health-related quality of life
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
OR	odds ratio
PAOD	peripheral arterial occlusive disease
RCT	randomized controlled trial
SF-36	Short Form 36
$TcPO_2$	transcutaneous oxygen partial pressure

1 Background

On 20 February 2015 the Federal Joint Committee (G-BA) wrote to the Institute for Quality and Efficiency in Health Care (IQWiG) to commission the assessment of hyperbaric oxygen therapy (HBOT) for diabetic foot syndrome (DFS).

DFS is a secondary disease in patients with diabetic neuropathy and/or angiopathy and is characterized by one or more wounds of the foot at the level of or below the ankle [1,2]. DFS can occur in patients with type 1 or type 2 diabetes. The wounds can be accompanied by necrosis or infections [2,3]. DFS greatly restricts affected patients (e.g. in their mobility) and considerably decreases quality of life [2,4,5]. The most serious consequences of DFS include amputations, for instance in the forefoot area (minor amputation) or at the level of the lower limb (major amputation) [6].

In Germany, the prevalence of DFS in diabetes patients is about 3% [7,8]. About 6.5% of men and 7.4% of women develop DFS during the course of their diabetes illness [9]. A Germany study found that about 70% of amputations of the lower limbs are related to diabetes [10].

The most important risk factor contributing to the development of DFS is regarded to be peripheral diabetic neuropathy [11,12], where the patient's perception of pain is affected by the damaged nerves. Minor trauma, such as pressure spots caused by unsuitable shoes, abnormal biomechanical stress or open wounds, are often not noticed at all [11]. This makes early treatment difficult and promotes the development of a foot ulcer. In addition, peripheral arterial occlusive disease (PAOD) and the accompanying ischaemia, or a mixed form of PAOD and neuropathy can promote the development of DFS [11,12]. Depending on the extent of neuropathic damage, pain symptoms can vary or even be completely lacking [11,13,14]. The Wagner-Armstrong classification is mainly used to grade the severity of DFS. On the one hand, this covers the depth and extent of wounds and on the other, the existence of infections and/or ischaemia [15,16].

If a wound is present, healing is already impaired in diabetes patients [17]. If in addition a patient is suffering from a further concomitant disease, this may cause an additional delay in the wound healing process [2]. After diagnostic clarification, standard treatment is undertaken, depending on the location, size and depth of the wound. This comprises drug therapy, wound debridement, bandaging, off-loading, and surgical procedures [2,18]. In the event of vessel stenosis or occlusion, a revascularization procedure in often performed before wound debridement. HBOT is recommended as an adjunctive treatment option if all revascularizing measures have been exhausted and amputation is imminent [19,20]. HBOT is regarded to be beneficial primarily in patients with a low oxygen concentration in the tissue [21,22].

HBOT comprises inhalation of pure oxygen (or an air mixture with an oxygen proportion of more than 21%, but normally 100%) with a pressure higher than normal atmospheric pressure. In practical application, an absolute pressure of 2 to 3 bar (2 to 3 atmospheres

absolute [ATA]) is usually used. During HBOT the patient is in a pressure chamber. A treatment session usually lasts 45 to 120 minutes and takes place daily over a period of several weeks [22]. Local administration of oxygen, where only the affected leg is placed in a pressure chamber, is distinguished from HBOT, where oxygen is primarily absorbed by the lungs [23].

Inhaling the oxygen mixture in increased ambient pressure is supposed to counteract the reduced oxygen supply in the tissue (hypoxia) [20]. A large amount of oxygen in the blood is bound to haemoglobin; under normal pressure conditions, saturation in the arterial blood is 97%. A small proportion of the oxygen is dissolved in the blood plasma; this proportion can be augmented by the increase in the ambient pressure (as in HBOT) and the associated increase in the oxygen partial pressure. In this way, tissue structures that would not be reached under normal or restricted oxygen tension can also be supplied with sufficient oxygen. By increasing the oxygen partial pressure in the body tissues, the oxygen supply is supposed to be maximized, thus improving tissue functionality in order to promote wound healing [24,25].

Adverse effects of HBOT include, for example, barotrauma and ear drum ruptures, airway irritations, and temporary vision disorders [26]. However, overall the rate of adverse effects is nowadays under 2% and thus HBOT is regarded to be safe [27].

2 Research question

The aim of the present investigation is

- to assess the benefit of HBOT compared with any other treatment option

in each case in patients with DFS with regard to patient relevant-outcomes.

3 Methods

The target population of the benefit assessment consisted of patients with diagnosed DFS. HBOT was the test intervention. No restriction applied to the control intervention.

The following patient-relevant outcomes were analysed for the investigation:

- Mortality
- Morbidity, in particular
  - wound closure
  - amputation (minor and major amputation),
  - pain
  - cardiovascular morbidity (coronary, cerebrovascular, peripheral arterial)
- Adverse effects of treatment
- Health-related quality of life (HrQoL), including activities of daily living
- Dependency on outside help or need for long-term care
- Length of hospital stay

Subjective outcomes (e.g. HrQoL) were considered only if they were recorded with validated measurement tools (e.g. validated scales).

Only randomized controlled trials (RCTs) were included in the benefit assessment. No restrictions applied to study duration.

A systematic literature search for primary literature was conducted in the following databases: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. In addition, a search for relevant systematic reviews was conducted in MEDLINE and Embase parallel to the search for relevant primary studies. Searches were also conducted in the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database. The last search was conducted on 18 December 2015.

Systematic reviews and publicly available trial registries were also searched. Furthermore, publicly accessible documents from regulatory authorities, documents sent by the G-BA, and publications that had been provided in the hearing procedure for the preliminary report were also screened. In addition, the authors of relevant study publications were contacted to clarify important questions.

The selection of relevant studies from the result of the searches in bibliographic databases, publicly accessible trial registries, documents sent by the G-BA, and potentially relevant

study publications from systematic reviews was performed by 2 reviewers independently of each other.

Data were extracted into standardized tables. To evaluate the qualitative certainty of results, the risk of bias at the study and outcome level was assessed and rated as low or high, respectively. The results of the individual studies were organized by outcomes and described.

If the studies were comparable regarding the research question and relevant characteristics and no relevant heterogeneity was observed, the individual results were pooled quantitatively by means of meta-analyses.

In order to be able to assess the benefit of adjunctive HBOT in respect of wound closure with complete re-epithelialization and without the potential influence of concomitant therapy, effects caused by plastic-surgical wound closure (e.g. after a wound suture, skin transplantation, or flap surgery) were not considered.

If in addition several time points of analysis were reported in a study, the results after 3 to 9 months were primarily considered in the respective meta-analysis and conclusion. This was to ensure that the analysis across studies covered those periods in which it is expected that treatment-related differences will show, insofar as present.

4 Results

4.1 Results of information retrieval

The systematic literature search in the bibliographic databases was conducted on 18 December 2015 and resulted in a total number of 320 hits for screening after exclusion of duplicates. In the title and abstract screening, 251 hits were excluded as not relevant. Hence, 69 potentially relevant hits remained from the bibliographic search, which were screened in full text: 47 of these hits were excluded due to a lack of relevance; 11 hits were relevant systematic reviews, which were screened for relevant studies. According to the consistent opinion of both reviewers, a total of 11 publications on 9 studies thus fulfilled the criteria for study inclusion defined for the present report.

In January 2016 the search in further information sources identified a full-text publication (Fedorko 2016 [28]) on a known relevant study, for which only the publication on study design [29], as well as a trial registry entry [30] were available, without published results so far. Information from queries to authors was considered in the assessment. The search in trial registries identified 1 completed and 1 discontinued study (both without published results so far) as well as 2 ongoing studies whose relevance could not be conclusively clarified.

4.2 Characteristics of the studies included in the assessment

A total of 9 RCTs from 12 publications and 2 registry entries were identified as being relevant for the research question of the present benefit assessment (Abidia 2003 [31], Doctor 1992 [32], Duzgun 2008 [33], Faglia 1996 [34], Fedorko 2016 [28-30], Kessler 2003 [35], Khandelwal 2013 [36], Löndahl 2010 [37-40], and Ma 2013 [41]). In all studies HBOT was provided in the intervention group as an additional measure to standard wound care; in all studies the control group received the respective standard wound care. In the following text, the study characteristics are described separately for each study.

In the **Abidia 2003** study, 18 diabetic patients with an ischaemic foot ulcer (Wagner grade I-II) that had been present for a median of 6 (intervention group) and 9 (control group) months, as well as with neuropathy, were randomized. The study was conducted on an outpatient basis in England between April 1999 and April 2001. Patients had a mean age of 72 (intervention group) and 70 (control group) years and the mean depth of the ulcers was 2.3 mm (intervention group) and 1.6 mm (control group). The intervention group participated in a total of 30 HBOT sessions over 6 weeks (90-minute sessions with 2.4 ATA). The control group also received additional hyperbaric therapy, but with normal ambient air (sham treatment). Two patients who discontinued the study were not included in the final analysis, so that the analysis after 6 weeks, as well as after 6 and 12 months, was only available for 16 patients.

The **Doctor 1992** study was conducted in India over a period of 2 years and was the first published RCT on HBOT in DFS. A total of 30 diabetic inpatients with a chronic foot ulcer were included. The mean age was 56 (intervention group) and 60 (control group) years. The

patients were followed up until the end of their hospital stay. No information on the precise time point of analysis was available. About 20% of study participants suffered from neuropathy or a non-palpable distal pulse. The patients participated in 4 sessions over a period of 2 weeks (45-minute sessions with 3 ATA), which was a considerably shorter treatment period than in the other studies. However, due to missing information it is unclear which ulcer grades were included, how many patients were included in the respective treatment groups, and after which follow-up period the final wound status was recorded for the analysis.

In **Duzgun 2008** all 100 diabetic study participants recruited between January 2002 and the end of 2003 in Turkey had an infected diabetic foot ulcer (Wagner grade II-IV), which had not healed despite adequate wound treatment for at least 4 weeks. The proportion of patients with neuropathy and/or angiopathy was not reported. The patients admitted to hospital had a mean age of 58 (intervention group) and 63 (control group) years and were assigned in equal parts to the HBOT group (30 to 45 sessions over 20 to 30 days; 90-minute sessions with 2 to 3 ATA) and to the control group without additional hyperbaric therapy. The mean follow-up period for both groups was 92 weeks and thus considerably longer than in the other studies. In addition to the ulcers healing independently, Duzgun 2008 also reported the number of plastic-surgical wound closures. However, these were not considered for the present benefit assessment.

In a study conducted in Italy with an inclusion period between August 1993 and August 1995, **Faglia 1996** randomized 70 inpatients with a mean age of 62 (intervention group) and 66 (control group) years with diabetic ulcer (Wagner grade II-IV); 68 of them were considered in the analysis. Nearly all study participants suffered from neuropathy and the mean ankle-arm index was about 0.65, indicating moderately severe PAOD. The control group received standard would care; the intervention group additionally participated in 38 HBOT sessions (90-minute sessions with 2.2 to 2.5 ATA). In addition, according to the protocol, concomitant to the study treatment 13 patients in each group received peripheral vascular therapy (percutaneous transluminal angioplasty or bypass surgery). The unclear follow-up period and the unclearly defined time points of analysis made the interpretation of results difficult.

A total of 107 diabetic patients with chronic foot ulcer (Wagner grade II-IV) were randomized for **Fedorko 2016**, which was conducted in Canada between September 2009 and May 2012. Of these 107 patients, 2 patients per treatment group were not considered in the final analysis after 12 weeks. Patients in whom revascularization was indicated or had been performed within the previous 3 months were excluded from the study. The proportion of patients with neuropathy and/or angiopathy was not reported. Both treatment groups received standard wound care. The mean age of patients was 61 (HBOT group) and 62 (sham group) years. Patients in the HBOT group received 30 additional outpatient hyperbaric treatments with 100% oxygen over a period of 6 weeks (90-minute sessions with approx. 2.49 ATA); in contrast, for patients in the control group the hyperbaric pressure of the breathing air (with an oxygen proportion of 27%) was only 1.27 ATA, with an identical treatment frequency and duration.

The French study **Kessler 2003,** conducted throughout the whole of 1999, investigated only diabetic patients with non-ischaemic ulcers (Wagner grade I-III) and without local infection. The ulcers had to have been present for at least 3 months and have a wound depth of less than 2 mm. The 28 randomized study participants were a mean 60 (intervention group) and 68 (control group) years old and all had sensomotoric neuropathy. One patient in the intervention group discontinued the study with otitis after barotrauma before completion of the 20 inpatient HBOT sessions conducted over a period of 2 weeks (90-minute sessions with 2.5 ATA); this patient was not considered in the analysis after 30 days.

The 3-arm study **Khandelwal 2013** was conducted in India between December 2007 and March 2009. A total of 60 diabetic patients were included with a mean age of only about 43 to 45 years and with absence of vascular insufficiency of arteries proximal to the ulcer. No information was provided in the publication on the existence or severity of neuropathy. The study participants had been suffering from a diabetic ulcer (Wagner grade III-IV) for at least 8 weeks. They were treated either with up to 30 HBOT sessions (60-minute sessions with 2.5 ATA) and wound care without antiseptics or solely with antiseptic foot baths with Edinburgh University Solution of Lime (EUSOL) as well as with hydrogen peroxide and povidone iodine. The third treatment arm with platelet-derived growth factor applied as a wound gel was not considered in the present report, as this form of treatment is not regarded to be the medical standard in Germany. The study was conducted either on an inpatient or outpatient basis and the analysis was conducted following completion of treatment after 10 weeks or in the event of early wound closure.

The **Löndahl 2010** study randomized 94 diabetic patients with a median age of 69 (intervention group) and 68 (control group) years and with a foot ulcer (Wagner grade I-V) present for a median of 9 and 10 months, respectively. At study inclusion it was evaluated whether adequate distal perfusion was ensured or existing peripheral vascular disease was nonreconstructable. The median toe blood pressure was 50 (intervention group) and 55 (control group) mmHg. No information on existing neuropathy was reported. This outpatient study was conducted between June 2002 and June 2009 in Sweden. Over a period of 8 to a maximum of 10 weeks both groups received (up to) 40 sessions of hyperbaric therapy (85-minute sessions with 2.5 ATA) – the intervention group with pure oxygen, the control group with normal ambient air instead (sham treatment). Four patients who died during the study were excluded from the analysis, so that the analysis on wound closure and amputation after 12 months was available only for 90 patients. HrQoL at the end of the study was only recorded for 71 patients who had participated in at least 35 HBOT sessions during the study. An analysis after 24 months planned in the study protocol has not yet been reported.

The Chinese study **Ma 2013** investigated a total of 36 diabetic patients between January 2010 and January 2012. The patients were about 60 years of age and suffered from non-ischaemic foot ulcer (Wagner grade I-III) present for a mean of about 11 months in the intervention group and about 14 months in the control group. The results for all patients included were analysed after 2 weeks, directly after completion of 20 inpatient HBOT sessions (90-minute

sessions with 2.5 ATA) by the intervention group. During these 2 weeks the control group merely received standard wound care. The respective proportion of patients with neuropathy and/or angiopathy was not reported.

4.3 Overview of extraction of data relevant for the report

For the present report, data on the following outcomes could be extracted from a total of 9 studies included: mortality, morbidity, adverse effects of treatment, HrQoL, and length of hospital stay. The events identified for wound closure, as well as for minor and major amputations, are presented in the present report under the outcome of morbidity.

No data were identified on the patient-relevant outcomes of pain, cardiovascular morbidity, and dependency on outside help or need for long-term care (see Table 1).

Table 1: Overview of extraction of patient-relevant outcomes; data availability

Outcomes / Study	Mortality	Morbidity: Wound closure	Morbidity: Amputation (minor and major amputation)	Morbidity: Pain	Morbidity: Cardiovascular morbidity	Adverse effects of treatment	Health-related quality of life	Dependency on outside help or need for long-term care	Length of hospital stay
Abidia 2003	–	●	●	–	–	●[a]	○[c]	–	–
Doctor 1992	–	–	●	–	–	○	–	–	●
Duzgun 2008	–	●	●	–	–	–	–	–	–
Faglia 1996	–	–	●	–	–	●[a]	–	–	●
Fedorko 2016	–	●	●	–	–	●[a, b]	–	–	–
Kessler 2003	–	●	–	–	–	●[a]	–	–	–[d]
Khandelwal 2013	–	●[e]	–[f]	–	–	–	–	–	–
Löndahl 2010	○	●	●	–	–	●[a, b]	○[c]	–	–
Ma 2013	○[g]	●	●[g]	–	–	●[a]	–	–	–[d]

–: No data available or evaluable; ○: Data available and evaluable; ●: Data considered in meta-analysis

a: The meta-analysis was performed for barotrauma of the ears as an adverse effect.

b: Further meta-analyses were performed for the occurrence of hypoglycaemic events and a lack of pressure compensation in the ears as an adverse effect.

c: Due to the lack of numerical data the results were not pooled in meta-analyses.

d: After completion of the 2-week HBOT period the patients were discharged from hospital independently of the respective wound and health status. Thus this information cannot be used for the outcome “length of hospital stay”.

e: Besides wound closure, this study also investigated time to wound closure; these data solely referred to patients who had achieved successful wound closure and thus could not be considered in the analysis, as more than 30% of the data on this outcome were missing.

f: This outcome was mentioned only in the title and background section of the publication, but not in the methods or results section (no results data available).

g: The outcomes “mortality” and “amputation” were reported only as an adverse event.

4.4 Assessment of risk of bias at the study and outcome level

At the study level only Fedorko 2016 and Löndahl 2010 were assessed as having a low risk of bias. These were also the only 2 studies for which a registry entry and a published study protocol were available. All other 7 studies were assessed as having a high risk of bias. In these studies it mostly remained unclear whether concealed allocation to the treatment groups had been ensured ("allocation concealment") and whether patients and treating medical staff had been blinded. This increases the risk of selective allocation to groups and potential inequality in treatment, particularly in the standard wound care of both study arms. In addition, due to the missing study protocols and/or trial registry entries, it was unclear whether these studies had been reported completely and in a non-selective manner.

Only 2 of the 9 studies (Fedorko 2016 and Löndahl 2010) described the generation of the randomization sequence in detail, while the other studies mostly referred only to a randomization table. It was not described which group of persons had access to this table and to what extent this made allocation of the recruited patients to the groups predictable; this could only be clarified for Faglia 1996 by means of an enquiry to the authors. Concealed allocation to the treatment groups by means of sealed envelopes was only reported in the studies by Abidia 2003, Fedorko 2016, and Löndahl 2010. Despite enquires to authors, for 2 of these studies (Abidia 2003 and Löndahl 2010) it remained unclear whether these envelopes were numbered consecutively and were opaque. In addition, only these 3 studies included sham treatment with hyperbaric ambient air as supplementation to standard wound care in order to blind the participating patients and the treating medical staff with regard to group allocation.

The risk bias of the results on mortality, wound closure, amputation (minor and major amputation) and on adverse effects of treatment was also only assessed as low for Fedorko 2016 (only wound closure and amputation) and Löndahl 2010. Besides the high risk of bias at the study level, for the other 7 studies the largely lacking blinding of outcome assessors and the accompanying risk of detection bias, as well as the unclear number of analysed patients and/or missing data on the length of follow-up and on the time points of analysis of the treatment groups, led to a high risk of bias.

In the assessment of the results on HrQoL, both studies reporting this outcome (Abidia 2003 and Löndahl 2010) were rated as having a high risk of bias. Abidia 2003 reported only the results in the running text, without providing numerical scale values. In addition, the time points of analysis and results for the 2 patients who discontinued the study were missing. Moreover, the risk of bias had already been assessed as high at the study level. In contrast, for HrQoL, Löndahl 2010 analysed only 71 patients with at least 36 HBOT sessions and thus only about 76% of the total population. Furthermore, reporting of HrQoL in this study was restricted to a graphic presentation of results without presenting effects, which required separate calculations by IQWiG and thus made the assessment of potential differences between treatment groups difficult.

As with the assessment at the study level, both studies providing information on the length of hospital stay (Doctor 1992 and Faglia 1996) also showed a high risk of bias at the outcome level due to a lack of information on the blinding of outcome assessors and the unclear number of patients analysed (Doctor 1992). Moreover, in both studies no information was available on the extent to which medical staff deciding on hospital discharge were blinded regarding the allocation of patients to treatment groups and on whether objective parameters existed for the decision to discharge.

4.5 Results on patient-relevant outcomes

The time points of analysis of reported results varied between 2 (Ma 2013) and a mean of 92 (Duzgun 2008) weeks after the start of the studies. For 2 of the 9 studies (Doctor 1992 and Faglia 1996), the length of follow-up and thus the respective time points of analysis remained unclear. For Fedorko 2016 and Löndahl 2010, no data are so far available for the analyses after 12 (Fedorko 2016) and 24 (Löndahl 2010) months, which were planned before the start of the studies.

The results for patient-relevant outcomes (see Table 2) were mostly reported without differentiation according to ulcer grade, age or sex of the patients. Only 2 studies reported the results on the rates for wound closure (Duzgun 2008) and amputations (Duzgun 2008; Faglia 1996, only for major amputations) classified according to the Wagner grade.

In Fedorko 2016 the indication for a minor or major amputation (as primary outcome) was made on the basis of several criteria. As not all of these criteria are to be rated as patient relevant and the results were not reported separately according to the respective criteria, as with the other studies included, only the amputations actually performed during the course of the study are considered in the present report.

Table 2: Overview of results for all patient-relevant outcomes

Patient-relevant outcome	Results
Mortality	A common estimate was not calculated as only 1 of the 2 studies reported results, which showed no statistically significant difference between treatment groups.
Morbidity	
Wound closure	OR 1.95; 95% CI [1.09; 3.49]; p = 0.025[a]
Amputation	Major amputation: heterogeneous data, no calculation of a common estimate
	Minor amputation: heterogeneous data, no calculation of a common estimate
Pain	No data reported
Cardiovascular morbidity	No data reported
Adverse effects of treatment[b]	▪ Barotrauma of ears: OR 1.84; 95% CI [0.54; 6.28]; p = 0.332 ▪ Hypoglycaemia: heterogeneous data, no calculation of a common estimate ▪ lack of pressure compensation in the ears: heterogeneous data, no calculation of a common estimate
Health-related quality of life	No calculation of a common estimate, as only one study reported numerical results, which only showed a statistically significant difference between treatment groups in favour of HBOT for the dimension "emotional role function".
Dependency on outside help or need for long-term care	No data reported
Length of hospital stay	Hedges' g = −0.35 (95% CI [−0.75; 0.05]); p = 0.084[c]

a: The effect estimate was determined by means of a sensitivity analysis without the extreme values of Duzgun 2008.
b: Barotrauma of the ears, hypoglycaemia and the lack of pressure compensation in the ears were reported as the only adverse effects in more than one study.
c: Replacement methods were applied to replace the missing data on variance in Doctor 1992. In this analysis a standard deviation of 10 days was assumed.

CI: confidence interval; HBOT: hyperbaric oxygen therapy; OR: odds ratio

4.5.1 Results on mortality

Only 2 of the 9 studies reported results on mortality (Löndahl 2010 and Ma 2013). In Löndahl 2010, 1 patient in the HBOT group and 3 in the control group died before the analysis after 12 months, while no deaths occurred in the 2-week study period in Ma 2013. No meta-analysis was therefore performed for this outcome. As the proportion of events occurred was not statistically significant between the treatment groups of Löndahl 2010 (p = 0.298), the data provide no hint of a benefit or harm of adjunctive HBOT compared with other treatment options.

4.5.2 Results on morbidity

4.5.2.1 Results on wound closure

Wound closure was reported in 7 studies (Abidia 2003, Duzgun 2008, Fedorko 2016, Kessler 2003, Khandelwal 2013, Löndahl 2010, Ma 2013). In contrast to the other studies, no events occurred in Ma 2013 and thus no difference between treatment groups was shown. However, due to the low patient numbers, this has no relevance for the assessment overall. Both studies with a high qualitative certainty of results (Fedorko 2016 and Löndahl 2010) showed discrepant effects. Substantial heterogeneity (I^2 = 70.4 %; p = 0.005) was shown in the meta-analytical pooling of all 7 studies with a total of 412 patients, so that no overall effect was estimated. In this meta-analysis the statistically significant effect estimate of Duzgun 2008 stood out with an extreme value compared with the other 6 studies. In addition, the 95% prediction interval covered the zero effect. Potential causes for the extreme deviation of the effect estimate of Duzgun 2008 from the other studies could not be identified. An initial sensitivity analysis excluded Duzgun 2008. The effect estimates of the other studies were now largely homogeneous (I^2 = 7.6%; p = 0.363). The overall estimate for the 6 studies with a total of 312 patients was statistically significant and with regard to wound closure, the odds ratio (OR) of 1.95 (95% CI [1.09; 3.49]) showed a statistically significant advantage of HBOT compared with the control group. For the outcome of wound closure this initially led to an indication of a benefit of adjunctive HBOT compared with standard wound care.

As the relevance of the antiseptic control arm of Khandelwal 2013 remained unclear for the analysis of wound closure, a further sensitivity analysis was performed in which Khandelwal 2013 (in addition to Duzgun 2008) was completely excluded. This analysis did not show a statistically significant overall estimate and thus no hint of a benefit of adjunctive HBOT compared with standard wound care. Likewise, no hint of a benefit can be inferred after inclusion of the results of Duzgun 2008 in the sensitivity analysis.

Under consideration of the uncertainty mentioned, the evidence for the outcome of wound closure is downgraded overall and on the whole this leads to merely a hint of a benefit of adjunctive HBOT compared with standard wound care.

4.5.2.2 Results on amputation (minor and major)

4.5.2.2.1 Results on major amputation

Seven studies reported the results on amputation rates (Abidia 2003, Doctor 1992, Duzgun 2008, Faglia 1996, Fedorko 2016, Löndahl 2010, Ma 2013). Across ulcer grades, a statistically significant difference between treatment groups in favour of HBOT was shown for major amputation rates in 3 of 7 studies (Doctor 1992, Duzgun 2008 and Faglia 1996). In an analysis by Duzgun 2008 differentiated according to ulcer grades, all observed major amputations occurred in the control group and exclusively in patients suffering from Wagner grade IV ulcers. No reason for this extreme difference between treatment groups could be identified. Likewise, in Faglia 1996 a statistically significant difference between groups was

shown in favour of HBOT only in patients with Wagner grade IV ulcers, the highest ulcer grade included. If one looks at the 2 studies with a high qualitative certainty of results (Fedorko 2016 and Löndahl 2010), in Fedorko 2016 no major amputation was performed in either treatment group and in Löndahl 2010 no statistically significant difference was shown between treatment groups (p = 0.531). The meta-analytic pooling of the results of all 7 studies with 445 patients showed moderate heterogeneity (I^2 = 54.7 %; p = 0.065), so that no overall effect was estimated. As the 95% prediction interval of the OR includes "1", no statistically significant treatment effect can be inferred.

Overall, for the outcome of major amputation a non-directed effect was shown; hence the data provide no hint of a benefit or harm from adjunctive HBOT compared with other treatment options.

4.5.2.2.2 Results on minor amputation

In 6 of the 7 studies (Abidia 2003, Doctor 1992, Duzgun 2008, Faglia 1996, Fedorko 2016, Löndahl 2010, Ma 2013) reporting the outcome of minor amputation, no statistically significant difference between treatment groups was shown. Only Duzgun 2008 showed a statistically significant lower minor amputation rate in the HBOT group than in the control group for all ulcer grades investigated. No reason for this extreme difference between treatment groups could be identified here either.

The 2 studies with a high qualitative certainty of results (Fedorko 2016 and Löndahl 2010) showed no statistically significant difference between treatment groups for the outcome of minor amputation. No common estimate was calculated in the meta-analytical pooling of the results of all 7 studies with 445 patients due to considerable heterogeneity (I^2 = 76.4 %; p < 0.001). As the 95% prediction interval of the OR includes "1" no statistically significant treatment effect can be inferred.

Overall, for the outcome of minor amputation a non-directed effect was shown; hence the data provide no hint of a benefit or harm from adjunctive HBPT compared with other treatment options.

4.5.3 Results on adverse effects of treatment

Seven of the 9 studies included (Abidia 2003, Doctor 1992, Faglia 1996, Fedorko 2016, Kessler 2003, Löndahl 2010, Ma 2013) reported adverse effects of treatment. Five of these studies explicitly mentioned barotrauma of the ears as an investigated outcome, whereby only 4 studies (Faglia 1996, Fedorko 2016, Kessler 2003, Löndahl 2010) reported that this adverse effect had actually occurred. Even though barotrauma exclusively occurred in patients receiving HBOT or in those receiving sham treatment, and the effects showed the same direction in all 3 studies, neither the results of individual studies nor the overall estimate of the meta-analysis (OR 1.84; 95% CI [0.54; 6.28]) for the outcome of barotrauma of the ears showed a statistically significant effect between the treatment groups.

Moreover, hypoglycaemia and the occurrence of a lack of pressure compensation in the ears were reported as an adverse effect that had occurred in 2 studies (Fedorko 2016 and Löndahl 2010); the corresponding results were pooled in a meta-analysis. Both meta-analyses showed heterogeneous effects in different directions; hence no difference between treatment groups is proven.

Likewise, no statistically significant difference between treatment groups was shown for any of the other adverse effects reported. Hence, for none of the adverse effects do the data provide a hint of a benefit or harm from adjunctive HBOT compared with other treatment options.

4.5.4 Results on health-related quality of life

The outcome of HrQoL was reported only in 2 studies (Abidia 2003 and Löndahl 2010). In this regard Abidia 2003 provided only qualitative statements in the running text; numerical results on the Hospital Anxiety and Depression Scale (HADS) and the Short Form-36 (SF-36) questionnaire were not reported in this context. The authors did not see a difference between treatment groups during the course of the study and at the end of study. In contrast, Löndahl 2010 analysed only about 76% of the total study population using the SF-36 questionnaire, namely those patients who had received at least 36 hyperbaric treatment sessions. Out of the 8 dimensions and 2 sum scales, a statistically significant difference in favour of HBOT was reported only for the dimension of emotional role function. On the basis of the corresponding graphic presentation of results, no clear, but only an approximate reading of HrQoL data and thus only an approximate calculation of effects was possible.

For these reasons, no meta-analytical pooling of results was performed for this outcome and the data provide no hint of a benefit or harm from adjunctive HBOT compared with other treatment options.

4.5.5 Results on length of hospital stay

Only 2 studies (Doctor 1992 and Faglia 1996) reported the length of hospital stay actually required. Both studies showed a reduction in stay of about 7 days (mean) in favour of HBOT versus the control group; this difference was not statistically significant.

As the analysis in Doctor 1992 did not include data on variance, replacement methods with different assumptions were applied for the meta-analytical pooling of results. Neither of the 2 assumptions for Doctor 1992 showed a statistically significant difference between treatment groups (Hedges' g von −0.35 (95% confidence interval [CI] [−0.75; 0.05]) and −0.23 (95% CI [−0.62; 0.17])). Hence, for this outcome the data provide no hint of a benefit or harm from adjunctive HBOT compared with other treatment options.

4.5.6 Subgroup characteristics and other effect modifiers

Subgroup analyses according to age, sex and severity of DFS were not possible due to a lack of adequate data. In addition, a subgroup analysis according to intensity of HBOT was dispensed with, as no meaningful classification of studies was possible due to the widely differing treatment schemes.

4.6 Studies of unclear relevance

The search in publicly accessible trial registries identified 2 unpublished studies (one had been completed in 2013 and the other discontinued in 2015), as well as 2 ongoing studies of unclear relevance.

According to the entry in the trial registry, data collection for Chen [42] had already been completed in June 2013. However, no publication of the results of the 38 patients could be identified and an enquiry to authors in this regard was not answered. According to the response to an enquiry to authors (see Table 7 of the full report), the study by the David Grant U.S. Air Force Medical Center (named in the preliminary report after the corresponding authors, Slade / Sevilla [43]) was interrupted after inclusion of only one patient and, according to the updated registry entry, was aborted in August 2015 after inclusion of only 2 patients. No results were reported here either.

According to the information on the study website [44], the ongoing DAMOCLES study [45], for which a study protocol [46] was identified in the literature search, has in the meantime finished patient recruitment and will only be completed at the end of 2016, so that the results could not be considered for the present final report.

According to the registry entry, the study by Smolle-Juettner [47] has not yet started recruiting patients and the study is planned to end in October 2017.

In 2 (David Grant U.S. Air Force Medical Center and Smolle-Juettner) of these 4 studies of unclear relevance, the control group is blinded by sham treatment in addition to standard wound care.

Whether the results of these 4 studies, with a total of over 200 planned patients, can make a suitable contribution to answering the research question of the present report can only be conclusively answered when the data become available. Whether and precisely when this will be the case is currently unclear.

4.7 Evidence map

Table 3 below presents the evidence map for patient-relevant outcomes.

Table 3: Evidence map for patient-relevant outcomes

Mortality	Morbidity					Adverse effects of treatment	Health-related quality of life	Dependency on outside help or need for long-term care	Length of hospital stay
	Wound closure	Amputation		Pain	Cardiovascular Morbidity				
		Minor amputation	Major amputation						
⇔	⇗	⇑⇓	⇑⇓	–	–	⇑⇓[a]	⇔	–	⇔

⇗: Hint of a benefit of adjunctive HBOT compared with standard wound care.

⇔: No hint, indication, or proof of a benefit or harm from adjunctive HBOT compared with other treatment options; homogeneous result.

⇑⇓: No hint, indication, or proof of benefit or harm from adjunctive HBOT compared with other treatment options, heterogeneous result.

–: No data reported.

a: The meta-analytical pooling of data showed a homogeneous result only for barotrauma of the ears, without a hint of a benefit or harm of adjunctive HBOT compared with other treatment options.

HBOT: hyperbaric oxygen therapy

5 Classification of the assessment result

The present benefit assessment shows that adjunctive HBOT for DFS can promote complete wound closure and thus wound healing compared with standard wound care alone. In contrast, no hint of benefit or harm could be inferred for any of the other patient-relevant outcomes for which data were available. On the one hand, statistically significant results were often not available, while on the other, most studies had considerable methodological weaknesses and marked clinical differences were found. Besides the variation in inclusion criteria, the widely differing time points of analysis impede the comparability of study results. In addition, the risk of bias is increased by the unclear concealed allocation to treatment groups and the accompanying risk of selection bias and a systematic shift in treatment effects. The frequent lack of blinding could result in treatment inequalities between the groups compared and thus in considerable bias.

In contrast to the other studies included, the 2 earliest studies (Doctor 1992 and Faglia 1996) did not report wound closure as a pivotal patient-relevant treatment goal. The focus of Faglia 1996 was however on the avoidance of major amputations in patients with largely higher ulcer grades; Doctor 1992 primarily investigated the surrogate outcome of bacterial colonization of the ulcer, as well as the reduction in amputation rates by adjunctive HBOT. As both study authors additionally reported other outcomes with statistically non-significant results, one can assume that there was no selective reporting or publication bias for the outcome of wound closure.

Even though the outcome of wound closure was recorded in 7 of the 9 studies and the data provide a hint that adjunctive HBOT statistically significantly increases the rate of complete wound closures in patients with DFS, only 3 studies defined this outcome. Abidia 2003 and Löndahl 2010 regarded the goal of wound closure as achieved as soon as complete epithelization of the ulcer was evident. In contrast, Duzgun 2008 merely distinguished between wound closure with and without additional plastic-surgical treatment. On the basis of the available results, no statement can be made regarding the persistence of the wound closures that occurred. None of the studies investigated the resilience of the newly formed skin or the recurrence rate of ulcers. Only Löndahl 2010 required maintenance of the closed wound until the next visit after 1 to 3 months, so that the healed ulcer could be counted as complete wound closure.

With a high qualitative certainty of results, besides a statistically significantly higher wound closure rate, Löndahl 2010 also showed a higher rate of major amputations for HBOT patients versus the control group; this difference was not statistically significant. On the basis of the available data it cannot be clarified to what extent the ulcer grades and the presence of neuro- and/or angiopathy can be regarded as potential effect modifiers. A subgroup analysis of this study [48] was not included in the present benefit assessment (see A6.3 of the full report for further details). For the per-protocol population after 9 months, this subgroup analysis showed a correlation between the transcutaneous oxygen partial pressure ($TcPO_2$) measured on the

back of the foot at the start of the study and the wound closure rate observed. Both in the HBOT and in the control group, the median $TcPO_2$ values at the start of the study were statistically significantly higher in patients with later wound closure than in those without wound closure. In addition, the wound closure rate in HBOT patients with an initial $TcPO_2$ of more than 50 mmHg after 9 months lay between 73 and 100%, whereas no wound closure was observed in patients with an initial $TcPO_2$ of less than 25 mmHg. Even though this difference is not statistically significant and the pathophysiological connection between the absence of critical ischaemia in the extremities and the effect of HBOT on wound healing seems plausible, no specific indication for HBOT (e.g. for patients without POAD or with pure neuropathy) or a valid $TcPO_2$ threshold value can be inferred from this. On the one hand, the subgroup data were exclusively based on the per-protocol population; on the other, the results were reported without numerical presentation of frequencies and only for the HBOT group, so that no comparison with the control group is possible.

The heterogeneity shown in the meta-analyses of minor and major amputations could be explained by the fact that the range of patients clearly differed between studies. For instance, the proportion of patients with gangrene or necrosis (Wagner grade IV) in the studies by Duzgun 2008 and Faglia 1996 was 45% and 62%, whereas Abidia 2003 and Ma 2013 did not include such patients. As expected in the latter 2 studies, only few amputations were required. In contrast, the overall amputation rates (major or minor amputations across groups) in Duzgun 2008 and Faglia 1996 were 45% and 69%. Nevertheless, some of the results of these 2 studies display inconsistencies concerning the direction and strength of their effects. No connection between the Wagner grade and the effect of HBOT on the amputation rate can be determined from these results. On the basis of the available data it cannot be judged to what extent adjunctive HBOT leads to a potential shift from major to minor amputations and thus to less impairment of patients.

In the 7 studies included that draw a conclusion on the adverse effects of HBOT, the incidence rate of barotrauma was about 2 to 3% per patient. Under consideration of the multiple pressure chamber sessions conducted in the studies, this incidence rate largely corresponds to those reported in the literature. Even if no hint of harm from adjunctive HBOT could be inferred from the study data, it should generally be borne in mind that the risk of barotrauma of the ears is much higher with hyperbaric therapy than with pure standard wound care without adjunctive hyperbaric therapy.

A main reason for the difference in the length of hospital stays (about 7 days less) between the HBOT and the control group in the Doctor 1992 and Faglia 1996 studies is presumably the statistically significantly higher major amputation rate in both control groups. In addition, Faglia 1996 reported that the major amputations were performed after about 58 days following hospital admission in the HBOT group but only after about 73 days in the control group. Overall, in both studies it however remained unclear who was responsible for hospital discharge, what the corresponding decision-making parameters were, and whether the allocation to the respective treatment group was known in this context.

6 Conclusion

For the outcome of **wound closure**, the present benefit assessment provides a hint of a benefit of adjunctive HBOT compared with standard wound care alone in patients with DFS**.**

For other patient-relevant outcomes (**mortality, minor and major amputations, adverse effects of treatment, HrQoL**, and **length of hospital stay**), the data provide no hint of a benefit or harm of adjunctive HBOT compared with other treatment options in patients with DFS.

For the outcomes of **pain, cardiovascular morbidity**, and **dependency on outside help or need for long-term care**, no conclusion can be inferred on the benefit or harm of adjunctive HBOT compared with other treatment options in patients with DFS, as no data were available in this regard.

Due to a lack of adequate data, no separate conclusions on benefit according to subgroup or therapeutic indications are possible.

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Please see full report for full reference list.

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