

## Article: Complications

# Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer

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### Abstract

**Aims** Adjunctive treatment with hyperbaric oxygen therapy has recently been shown to improve ulcer healing in patients with chronic diabetic foot ulcer. The aim of the present study is to evaluate whether hyperbaric oxygen therapy improves the health related quality of life in these patients.

**Methods** Prospective randomized placebo-controlled double-blinded study setting using SF-36.

**Results** A total of 75 patients were included in the study; 38 were randomized to hyperbaric oxygen therapy and 37 to placebo (hyperbaric air). The overall mean physical and mental summary scores for the entire study population at baseline were  $29.6 \pm 8.8$  and  $47.5 \pm 12.4$ , respectively. There was a significant difference between baseline and 1 year follow-up responses to the mental summary score and two of the eight (SF-36) (?) domains in the -hyperbaric oxygen group, whereas no significant improvement of health related quality of life was seen in the placebo group. Comparing quality of life in patients who healed their ulcer (healers) with those who did not (non-healers), post-treatment levels of the mental health summary score, social functioning and role limitations due to physical and emotional health were significantly improved in healers. No differences were seen in any SF-36 (?) domain in non-healers.

**Conclusions** Hyperbaric oxygen therapy improves long-term health related quality of life in patients with chronic diabetic foot ulcers, possibly attributable to better ulcer healing.

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**Keywords** diabetic foot ulcer, health-related quality of life, hyperbaric oxygen therapy

### Introduction

Foot ulcers are common, serious and costly complications of diabetes associated with reduced mobility and deficits related to daily living activities, which have a harmful influence on individuals' health-related quality of life (HRQL) [1–3]. Quantitative as well as qualitative studies confirm that diabetic foot ulcers have a negative impact on physical functioning, psychological status and social situation [1,4,5].

Hyperbaric oxygen therapy has been proposed as a treatment modality for diabetic foot ulcers [6,7]. We recently showed that adjunctive treatment with hyperbaric oxygen improves ulcer healing in patients with chronic diabetic foot ulcers [8]. The

aim of the present study is to evaluate whether hyperbaric oxygen therapy improves health related quality of life in these patients.

### Patients and methods

The Hyperbaric Oxygen in Diabetic patients with chronic Foot Ulcer (HODFU) study is a single-centre prospective randomized double-blinded placebo-controlled study, evaluating the effect of hyperbaric oxygen therapy compared with treatment with hyperbaric air (placebo) in patients with diabetes and chronic foot ulcers. The primary outcome of the study was to evaluate the effect of hyperbaric oxygen therapy compared with placebo on healing of the index foot ulcer. The study was performed in an ambulatory setting. Treatment sessions were given in a multiplace hyperbaric chamber, ideally 5 days a week for 8 weeks (40 treatment sessions). The treatment period could be

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extended to 10 weeks, but the number of treatments was not allowed to exceed forty. A hyperbaric oxygen treatment session included a period of compression in air for 5 min, followed by a treatment period at 2.5 absolute atmospheres for 85 min and then a decompression period of 5 min. Patients from both groups could be treated in the same session, as study gases were administered by masks, and air or 100% oxygen entered the chamber through separate 'double-blinded' pipes [9]. Study treatment was given as an adjunct to regular treatment at the multidisciplinary diabetes foot clinic.

Patients were recruited for study participation at the Diabetic Foot Clinic. Inclusion criteria for study participation were as follows: age over 18 years, known diagnosis of diabetes at time of inclusion, diabetic foot ulcer with a duration of at least 3 months, treatment at a diabetic foot clinic for at least 2 months, need for or possibility of vascular surgery ruled out by a vascular surgeon, and written informed consent. Exclusion criteria were as follows: contraindications for hyperbaric oxygen therapy (severe obstructive pulmonary disease, untreated thyrotoxicosis, untreated pneumothorax, woman of fertile age without contraceptive methods and ongoing treatment with cisplatin, doxorubicin or disulfiram), vascular surgical intervention in the lower limbs within the last 2 months, C-reactive protein >30 mg/L, known malignancy, myocardial infarction or stroke within last 30 days, misuse of alcohol or other drugs, investigator's opinion or participation in another clinical trial. Patients were stratified based upon arterial toe blood pressure ( $\leq 35$  vs.  $> 35$  mmHg) before being randomly assigned to either of the two treatment arms. Randomization was done in blocks of 10, using sealed envelopes. Ulcers were primarily classified according to the Wagner grading system, and ulcer areas were measured using the portable wound measurement system, Visitrak Digital system (Smith & Nephew, Hull, UK) [10]. The index ulcer was defined as the ulcer with the largest area and duration of at least 3 months at time of inclusion.

All patients in the HODFU study completing the predefined level of receiving at least 36 out of 40 scheduled treatment sessions were included in the present study. This study was approved by the Ethics Committee at Lund University, Sweden. All participants provided written informed consent.

All patients completed a self-reported (Please define SF 36 in full here – use abbreviation subsequently) health measurement questionnaire to evaluate their physical and mental function and their HRQL both before hyperbaric oxygen therapy and at the 12 month follow-up visit [11,12]. The SF-36 questionnaire measures eight domains, including physical functioning, bodily pain, general health perception, vitality, social functioning and role limitations due to physical, emotional and mental health. The SF-36 has also been developed into a two-factorial model with a physical (PCS) and a mental component summary scale (MCS) [13,14]. Evaluation of reliability and predictive validity of SF-36 indicate that SF-36 includes frequently represented health concepts [15,16].

## Statistics

Mean and standard deviation were used for baseline variables that were normally distributed; otherwise, median, quartiles and non-outlier range were used. The SF-36 domain data are given as means and standard errors of the mean.

Comparisons were tested with Wilcoxon's matched pair test or Mann-Whitney *U*-test when appropriate. Differences in frequencies were analysed with contingency tables, chi-square or (if less than 5 observations in a cell) Fischer's exact test.

The relation between ulcer healing and SF-36 outcome was tested using multiple regression analysis with each SF-36 domain as a dependent variable and age, sex, diabetes duration, ulcer duration, presence of renal failure requiring dialysis, previous major amputation, baseline ulcer area and Wagner grade, baseline levels of the other SF-36 domains, study treatment group (hyperbaric oxygen or placebo) and ulcer healing at 12 month follow-up visit as independent variables.

A two-sided *P*-value below 0.05 was considered statistically significant. Correction for multiple testing was performed using partial Bonferroni correction. Statistical analysis was performed with the use of Statistica software, version 9.0 (Statsoft Inc., Tulsa, OK, USA).

## Results

A total of 75 patients were included in the study; 38 were randomized to the hyperbaric oxygen and 37 to the placebo group (hyperbaric air). Two patients in the placebo group died during the first year of follow-up. In the hyperbaric oxygen group, two patients did not fill out the SF-36 at 12 month follow-up due to their deteriorated medical condition. These four patients are not included in the comparative evaluation.

As given in Table 1, patients' baseline characteristics did not significantly differ between hyperbaric oxygen and placebo groups. Median ulcer duration at inclusion was 11.8 and 10.3 months (hyperbaric oxygen vs. placebo, NS.). Ulcer healing rates at the 12 month follow-up were 61% in the hyperbaric oxygen and 27% in the placebo group ( $P = 0.009$ ). Outcome did not differ between patients with Type 1 and Type 2 diabetes.

The overall mean physical and mental summary scores for the entire study population at baseline were  $29.6 \pm 8.8$  and  $47.5 \pm 12.4$ , respectively. There was a significant difference between pre- and post-treatment responses to mental summary score and two of the eight SF-36 domains in the hyperbaric oxygen group, whereas no significant improvement of Health Related Quality of Life was seen in the placebo group (Figs 1 and 2). Ulcer healing was related to improved SF-36 score in the domains role physical, vitality and social functioning.

Comparing health Related Quality of Life in patients who healed their ulcer (healers) with those who did not (non-healers), post-treatment levels of social functioning and role limitations due to physical and emotional health were significantly higher in

**Table 1** Patient baseline characteristics

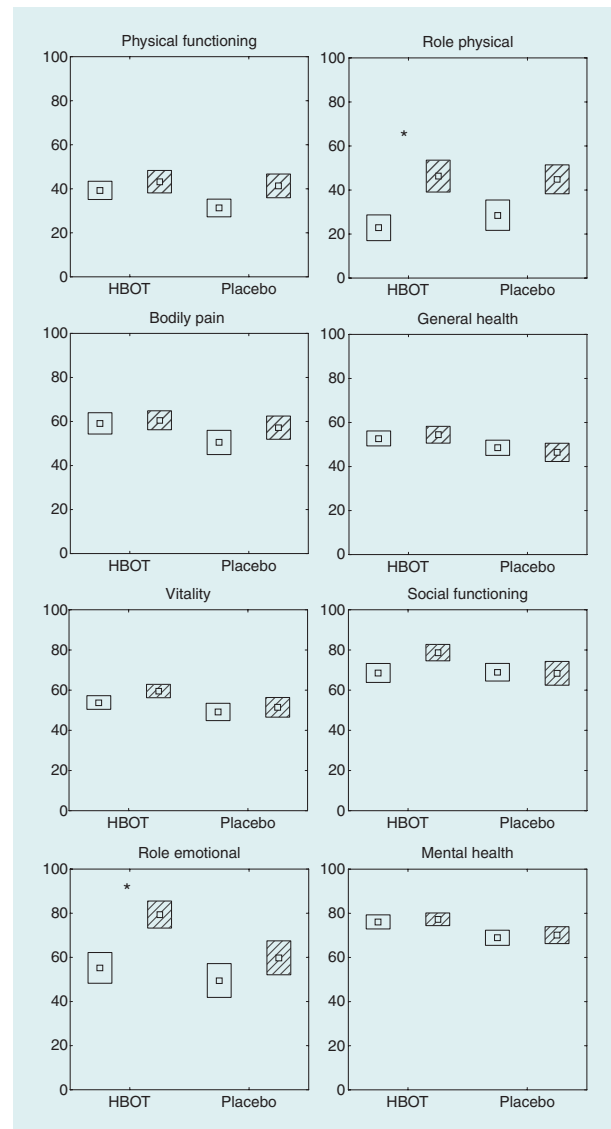
	HBOT	Placebo	P-value
Number of patients	38	37	—
Age (years)	67 (56–75)	71 (66–77)	n.s.
Sex, male/female (%)	76/24	86/14	n.s.
Diabetes Type 1/2 (%)	26/74	32/68	n.s.
Diabetes duration (years)	22 (10–32)	21 (16–51)	n.s.
Hypertension (%)	76	76	n.s.
Dyslipidaemia (%)	87	89	n.s.
Coronary heart disease (%)	44	46	n.s.
CABG (%)	18	27	n.s.
PCI (%)	16	16	n.s.
Heart failure (%)	32	30	n.s.
Atrial fibrillation (%)	21	32	n.s.
Cerebral vascular disease (%)	16	16	n.s.
Nephropathy (%)	89	84	n.s.
Dialysis (%)	5	3	n.s.
Renal transplantation (%)	5	3	n.s.
Ulcer duration (months)	11.9 (5.7–22.2)	10.3 (7.4–16.7)	n.s.
Ulcer size (cm <sup>2</sup> )	3.5 (1.3–6.4)	2.8 (1.2–5.6)	n.s.
Wagner grade 2 (%)	26	22	n.s.
Wagner grade 3 (%)	58	65	n.s.
Wagner grade 4 (%)	16	14	n.s.
Ulcer localization			
Toe (%)	34	49	n.s.
Forefoot (%)	27	22	n.s.
Midfoot (%)	13	16	n.s.
Hindfoot (%)	21	5	n.s.
Malleoli (%)	3	8	n.s.
Previous major amputation (%)	18	8	n.s.
Previous minor amputation (%)	32	51	n.s.
Previously vascular intervention (%)	66	54	n.s.
Toe blood pressure (mmHg)	50 (30–85)	52 (30–74)	n.s.
Ankle blood pressure (mmHg)	101 (80–155)	102 (90–125)	n.s.
TcPO <sub>2</sub> basal (mmHg)	45 (32–55)	54 (43–69)	n.s.

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; TCPO<sub>2</sub>, transcutaneous oxygen pressure.

healers (Table 2). No differences were seen in any SF-36 domain in non-healers (data not shown).

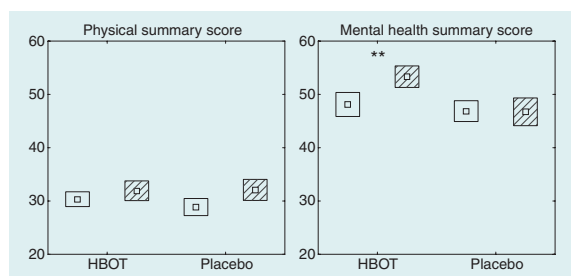
## Discussion

Previous studies evaluating the effect of diabetic foot ulceration on patients' physical and psychosocial functioning have shown that foot ulcers are a source of severe disability [1,4,5,17,18].



**FIGURE 1** Health-related quality of life scores for each of the eight SF-36 domains in hyperbaric oxygen therapy (HBOT) and placebo groups at baseline (open squares) and 12 month follow-up visits (filled squares). A higher score indicates better Health Related Quality of Life. Data are given as means and SEM (box). \* $P < 0.05$ , \*\* $P < 0.01$ .

Accordingly, our study demonstrated low baseline summary scores for both physical (PCS 30) and mental health (MCS 48) compared with norms for an age-matched Swedish population (PCS 44 and MCS 52) [19]. This finding is compatible with those seen in patients with non-healing diabetic foot ulcers shown in several studies, including that by Nabuurs-Franssen *et al.* (PCS 33 and MCS 49) [18]. These Health Related Quality of Life scores are comparable to those stated for patients treated for breast cancer (PCS 46 and MCS 50) and for patients who had recently had myocardial infarction (PCS 41 and MCS 46) [20,21]. Thus, the reduction in physical and mental functioning in our patients with diabetic foot ulcers is similar to findings reported in patients with other serious medical conditions.



**FIGURE 2** Physical and mental summary scores for SF-36 in hyperbaric oxygen (HBOT) and placebo groups at baseline (open squares) and 12 month follow-up visits (filled squares). A higher score indicates better Health Related Quality of Life. Data are given as means and SEM (box). \* $P < 0.05$ , \*\* $P < 0.01$ .

Healing of diabetic foot ulcers leads to improved quality of life [4,22]. Thus, Armstrong *et al.* prospectively showed that healing of neuropathic foot ulcers by off-loading was associated with improvement of all SF-scales except bodily pain [4]. Also, Abidia *et al.* evaluated 18 patients with diabetes with Wagner grade 2 foot ulcers in a randomized placebo-controlled hyperbaric oxygen treatment study, showing significantly improved SF-36 domains in terms of general health and vitality, but no change in physical or mental health summary scores in the hyperbaric oxygen group. At 1 year follow-up in that study, five of eight ulcers had healed following hyperbaric oxygen, compared with none following placebo treatment [23]. In another small study by Lin *et al.* in 15 patients with foot ulcers (11 patients with diabetes), overall health related quality of life improved after hyperbaric oxygen therapy. This improvement was linked to self-perceived wound severity [24].

In the hyperbaric oxygen group of our study, Health Related Quality of Life at the 12 month follow-up visit was significantly higher than before treatment in terms of the SF-36 domains role limitations due to physical and emotional health and mental health summary score. These findings remain when comparing

baseline and 12 month follow-up in healers of the hyperbaric oxygen group as well as for all included healers, but not for non-healing patients. Our findings are thereby consistent with those of previously reported studies demonstrating marked improvement of Health Related Quality of Life linked to ulcer healing.

In contrast to our findings, none of the previous studies has shown improvement in mental health summary scale after diabetic foot ulcer healing. This might be explained by several factors. To our knowledge, this is only the second prospective study, with more than 20 patients, having evaluated Health Related Quality of Life in patients with diabetic foot ulcers over a period of 12 months, i.e. the present study has a longer follow-up time. Furthermore, our findings might partly be related to an enhanced social interaction during the treatment period, and in a previously published paper, using focus interview methodology, participants in the HODFY study reported enhanced social relations [25]. Finally, in the present study mean ulcer duration was 5 months longer and the ulcers in our study population seem to be more severe in terms of ulcer depth according to the Wagner grading scale, ulcer size, ulcer location and usage of antibiotics, compared with the long-term follow-up study by Ribu *et al.* [26]. In the study by Armstrong *et al.* the ulcers were smaller, more superficial and had shorter duration [4]. Likewise, healers in our study were older, and had deeper ulcers with longer duration compared with the healers in the study by Nabuurs-Franssen *et al.* [18].

The present study is among the first to evaluate the impact of an adjunctive treatment modality on long-term Health Related Quality of Life in patients with chronic diabetic foot ulcers. According to a focus-group interview study of 19 HODFU study participants after 6 weeks of treatment, one main experienced advantage of hyperbaric oxygen therapy was development of positive contacts and social relations with other patients during the treatment sessions [25]. This social interaction, during a 8-week-long treatment period, might thus, in combination with enhanced ulcer healing, improve long-term wellbeing by

**Table 2** SF-36 domain scores in patients with healed foot ulcer at the 12 months follow-up visit

SF-36 domain	Overall study population ( $n = 33$ )			Hyperbaric oxygen group ( $n = 23$ )			Placebo group ( $n = 10$ )		
	Baseline	12 month follow-up	$P$ -value	Baseline	12-month follow-up	$P$ -value	Baseline	12-month follow-up	$P$ -value
Physical functioning	37 ± 4	44 ± 5	n.s.	40 ± 5	41 ± 6	n.s.	32 ± 9	50 ± 9	n.s.
Role limitation due to physical health	31 ± 7	64 ± 7	$P < 0.01$	30 ± 8	61 ± 8	$P < 0.05$	32 ± 14	70 ± 12	n.s.
Bodily pain	58 ± 5	66 ± 5	n.s.	62 ± 6	66 ± 5	n.s.	48 ± 10	67 ± 10	n.s.
General health	50 ± 3	51 ± 4	n.s.	55 ± 4	54 ± 4	n.s.	43 ± 6	46 ± 11	n.s.
Vitality	54 ± 4	60 ± 4	n.s.	55 ± 4	61 ± 4	n.s.	52 ± 8	58 ± 10	n.s.
Social function	71 ± 4	83 ± 4	$P < 0.05$	72 ± 5	84 ± 4	n.s.	66 ± 6	81 ± 10	n.s.
Role limitation due to emotional health	62 ± 7	81 ± 6	$P < 0.05$	65 ± 8	87 ± 6	$P < 0.05$	53 ± 16	67 ± 14	n.s.
Role limitation due to mental health	74 ± 3	77 ± 3	n.s.	78 ± 4	80 ± 3	n.s.	66 ± 6	71 ± 9	n.s.
Physical health summary score	31 ± 2	34 ± 2	n.s.	31 ± 2	33 ± 2	n.s.	30 ± 4	38 ± 4	n.s.
Mental health summary score	49 ± 2	53 ± 2	n.s.	50 ± 3	55 ± 2	n.s.	47 ± 3	48 ± 5	n.s.

Data are given as means ± SEM for the overall study population, the hyperbaric oxygen and the placebo group, respectively. A higher score indicates better HRQL.

increased social interaction, improved self-confidence and reduced depression, and thereby at least partly explain the divergence in improvement of mental health summary scale between our study and other studies.

In conclusion, hyperbaric oxygen therapy improves long-term health-related quality of life in patients with chronic diabetic foot ulcers, possibly attributable to better ulcer healing.

## Competing interests

Nothing to declare.

## Acknowledgements

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