The clinical use of hyperbaric oxygen in the treatment of Danish patients with diabetic foot ulcers

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ABSTRACT

INTRODUCTION: Patients with diabetic foot ulcers (DFU) suffer from diabetes-related complications and comorbidities. Hyperbaric oxygen therapy (HBOT) is a treatment modality with limited capacity used in the treatment of DFUs. It is important to ensure that HBOT is offered to patients who are suitable for this treatment regarding effect, compliance and life expectancy. The objective of the present study was to describe the population of patients with DFU who were referred to HBOT in Denmark in the 1999-2016 period.

METHODS: All patients with DFU who were treated at the HBOT chamber in Copenhagen during the study period were considered. Patients with an invalid social security number or an incorrect diagnosis were excluded. Data on comorbidities, amputation and death were extracted from the Danish National patient Registry and the Danish Civil Registration System. Continuous data were described as median values and binary data were described as proportions. The probability estimate for survival and amputation was investigated by constructing Kaplan-Meier curves.

RESULTS: The cohort included 148 patients. Patients were mainly referred from the Capital Region (92%) and multidisciplinary wound care centres were the primary referring departments (67%). Comorbidity rates were high with an initial median Charlson Comorbidity Index score of five. The five-year amputation and mortality estimates after referral were 73.5% and 51.8%, respectively.

CONCLUSIONS: The study showed that Danish DFU patients who are offered HBOT are in advanced stages of their disease, and the referral hinges on local factors such as geography and the referring source rather than on standardised procedures.

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An estimated 22,000 Danes live with diabetic foot ulcers (DFU), and the annual incidence is around 3,000 [1]. The condition is associated with shorter survival and an increased risk of amputation of the affected limb [2, 3]. Currently, 4,000 people in Denmark are living with amputation due to non-healing DFUs [1]. Mortality is increased three-fold in persons with DFUs compared with diabetics who have no DFUs [3]. A recent Danish study showed a mean survival of 2.5 years after the first amputation, with a five-year mortality rate of 43% and 52%, among patients with Type 1 and Type 2 diabetes, respectively [4]. In fact, DFU was recently shown to be independently associated with an increased risk of death, both with and without other comorbidity risk factors [3, 5-8].

DFUs and lower-extremity amputations are major medical and financial challenges for the affected individual and for society [9]. The pathogenesis of DFU is a triopathy related to neuropathy, microangiopathy and an altered response to infection. The result is functional ischaemia due to inability of the vascular bed to increase the blood flow in response to stress [10]. In recent years, randomised, placebo-controlled studies (RCT) have found that hyperbaric oxygen therapy (HBOT) accelerates wound healing in persons with DFUs. International guidelines, based on a small number of RCTs and observational studies, recommend HBOT as an adjuvant therapy for DFUs [11-14]. HBOT is currently a treatment modality with limited capacity. It is of high priority to ensure that HBOT is offered to a patient population suitable for intervention regarding effect, compliance and life expectancy.

This study aimed to describe the population of DFU patients who were treated with HBOT in Denmark during the 1999-2015 period. This includes referral pattern, comorbidity, adherence to the standard HBOT regimen, and prognosis described as survival and time to first amputation after HBOT.

METHODS

Data source and linkage

The patient cohort was identified using the HBOT database, which is an electronic registry of all patients treated at the HBO chamber at Rigshospitalet, Copenhagen, from January 1996 through 2016. Registered data include Civil Registration Number (CRN), referral diagnosis, referral source and technical treatment details.

Electronic patient records were available for patients referred after 2005.

ORIGINAL ARTICLE

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TABLE 1

Demographics and risk factors variables at the time of referral: demographics, Charlson Comorbidity Index and the number of patients who were diagnosed with specific diagnosis coupled to diabetes and other comorbidities according to The Danish National Patient Registry.
N = 148; median age = 66 (range: 34-94) years.

	n (%)
General characteristics	
Male	120 (82)
Female	28 (19)
Diabetes and diabetes specific complications	
Diabetes, Type 1	99[a] (67)
Diabetes, Type 2	127[a] (86)
Unspecified diabetes	107[a] (72)
Retinopathy	56 (38)
Peripheral neuropathy	9 (6)
Nephropathy	11 (7.4)
Comorbidity	
Hypertension	84 (57)
Dyslipidaemia	49 (33)
Dementia	1 (0.7)
Myocardial infarction	28 (19)
Congestive heart failure	37 (25)
Cerebrovascular disease	41 (28)
Peripheral vascular disease	126 (85)
Diabetes with end-organ-damage	125 (85)
Chronic pulmonary disease	22 (15)
Severe liver disease	1 (0.7)
Kidney disease: moderate-severe	33 (22)
Malignancy	19 (13)
Peptic ulcer disease	12 (8)
Connective tissue disease	10 (7)
AIDS	1 (0.7)
Foot-specified comorbidity	
≥ 1 lower extremity amputation	71 (48)
Charcot foot	10 (7)

a) Patients receiving the diagnosis as extracted from the Danish National Patient Registry, illustrating imprecisely registered diabetes subtypes in the Danish National Patient Registry.

The Danish National Patient Registry (DNPR) contains information on persons who have been admitted to somatic hospital departments since 1977. As of 1995, ambulatory and emergency department patients are also included in the register. Each hospital discharge or outpatient visit is recorded with one primary diagnosis and up to twenty secondary diagnoses, classified according to the International Classification of Diseases, tenth edition (ICD-10) since the end of 1993, and according to the ICD-8 before then. The DNPR also contains codes for surgery and procedures according to the Surgery and Treatment Classification from 1977 until 1999, and according to the ICD-10 thereafter.

The Danish Civil Registration System (CRS) was established in 1968, and all persons who are alive and living in Denmark since 1968 are registered with their CRN. Among many other variables, the CRS includes continuously updated information on vital status. Data were linked at individual level through the CRN.

Study population

All patients treated for DFUs in the HBO chamber at Rigshospitalet, Copenhagen, from January 1999 through December 2015, were identified via the HBOT database. Patients referred before 2005 were excluded if they had no diabetes diagnosis registered in the DNPR. Patients referred after 2005 were excluded if a DFU was not described in their electronic patient record up to the time of referral.

Variables and definitions

Data on referring source, hospital and region as well as number of referrals and completed HBOT sessions were obtained from the HBOT database. Using the DNPR, we extracted diagnoses coupled to comorbidities and lower-extremity amputations up to the time of the first HBOT session. Data on survival were obtained through the CRS. Minor amputations were defined as below and through the ankle, and major amputations were above the ankle. The Charlson Comorbidity Index (CCI) was calculated based on discharge diagnostic codes found in the DNPR from 1977 until the time of referral [15]. The standard HBOT was defined as a minimum of 30 sessions of 90 minutes of continuous oxygen breathing to a pressure of 2.4-2.5 atm abs.

Data analysis

Continuous variables were described as median values with range and inter-quartile range, and binary variables were described as proportions. Percentages are calculated from a total where unknown has been excluded. We measured the time from first HBOT to death and to first amputation, both for patients who had previous amputations and patients who had not undergone any amputations prior to their referral to HBOT, and constructed Kaplan-Meier survival curves. Statistical analyses were performed with STATA, version 13.1.

Approval

The study was approved by the Danish Health and Medicines Authority and the Danish Data Protection Agency. The study was exempted from approval from the Regional Ethics Committee as no intervention was involved [16].

Trial registration: not relevant.

RESULTS

A total of 213 patients with DFU were extracted from the HBOT database. Sixty-five patients were excluded, five of whom were foreign citizens with a temporary CRN, three had invalid CRNs and one patient was registered twice in the database. Of the remaining 204 patients, 150 patients had electronic patient records.

Of those, 44 patients were excluded because their DFU diagnosis could not be confirmed in their records. Finally, we excluded 12 of the 54 patients with a paper record only who had never been diagnosed with diabetes according to the DNPR. The final cohort included n = 148 patients with DFU who had been treated in the HBO chamber during the 1999-2015 period.

Characteristics of referred patients

Demographics and risk variables at the time of referral are presented in **Table 1**. The median patient age was 66 years (range: 34-94 years) with 82% men, and the majority had diabetes end-organ damage (85%). The most common comorbid conditions were cerebrovascular disease (28%), congestive heart failure (25%), chronic kidney disease (22%) and myocardial infarction (19%). **Figure 1** shows the distribution of CCI scores for the entire cohort with a mean of 5.2 (standard deviation (SD): ± 2.2). A large proportion (79%) of patients had CCI scores > 3, and 44% of referred patients had a CCI score ≥ 6. In the investigated cohort, 71 (47%) patients had undergone amputations at the time of referral; and among them, a total of 277 amputating procedures were made; 130 minor and 147 major. Ten patients were diagnosed with the limb-threatening inflammatory diabetic complication of Charcot foot.

Referral pattern

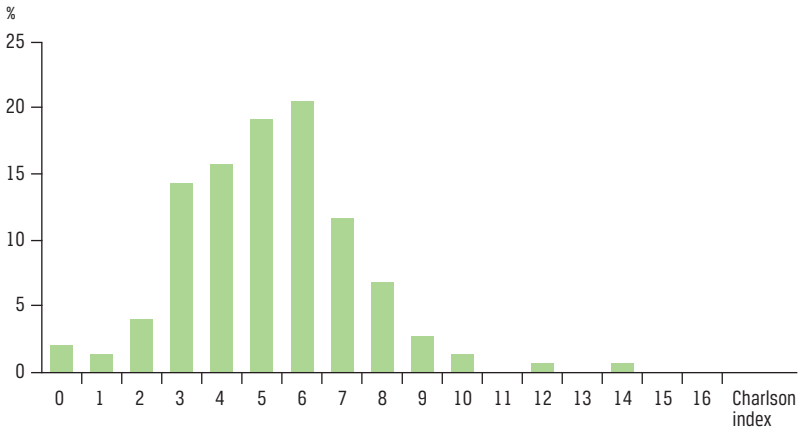
The number of patients referred for HBOT of a DFU increased abruptly in 2010 with a mean of 5.4 per year patients during the period of 1999-2009 and 15.5 patients per year between 2010 and 2015. The majority (92%) of patients were referred from the Capital Region, seven patients (5.2%) were referred from the neighbouring Zealand Region, one patient from the Region of Southern Denmark and three patients were referred directly from their general practitioner. Information regarding originating region was inaccessible in 15 cases. Patients were primarily referred from out-patient clinics (74%), and the remaining patients were referred during a hospital admission. The referring sources included a wide range of specialties, but patients were most often referred from a multidisciplinary wound care centre (67%) (**Table 2**).

Treatment duration

Half of the patients (53%) completed the prescribed 30 sessions of HBOT. Of those, 19 (24%) patients were referred more than once for treatment of a DFU, meaning that the sessions were temporally separated by two or more HBOT courses. The actual number of patients who complied with the therapeutic treatment protocol was 59 patients (40%).

FIGURE 1

The distribution of Charlson Comorbidity Index with proportions of patients[a].



a) Mean = 5.2 (standard deviation: ± 2.2), median = 5 (interquartile range: 4-6).

Survival and amputation estimate

Overall, the median survival after first HBOT was 4.6 years with a one- and five-year cumulated mortality of 14.2% (95% confidence interval (CI): 9.5-21.0%) and 51.8% (95% CI: 43.2-61.0%), respectively. The overall

TABLE 2

Referral by region and specialty: the number of patients referred from each referring source and of patients referred from each region.

	Patients, n
Referring specialty	
MWCC[a]	84
Orthopaedic	19
Vascular surgery	7
Nephrology	5
Plastic surgery	6
Urology	1
Endocrinology	1
General practitioner	3
Unknown	22
Total	148
Region and hospital	
Capital Region:	
Rigshospitalet	20
Bispebjerg Hospital	75
Steno Diabetes Centre	9
Hospital of Northern Zealand	10
Others	8
Region Zealand	7
Region of Southern Denmark	1
General practitioner	3
Unknown	15
Total	148

MWCC = multidisciplinary wound care centre.
a) Provides orthopaedic and endocrinological expertise.

median time to first amputation (all levels) after referral to HBOT was 0.9 years with a five-year cumulative risk of amputation of 73.3% (95% CI: 64.4-71.7%) (**Figure 2**A and B).

A sub-group analysis showed a median survival time after referral to HBOT of 5.6 years for patients who had not undergone amputating procedures at the first HBOT, and 4.2 years for patients who were referred with amputations. The one-year cumulated mortalities were the same, whereas the five-year cumulated mortality was 43.1% (95% CI: 32.2-55.9%) for patients who were not amputated at the first HBOT and 61.0% (95% CI: 48.5-73.8%) for previously amputated patients (Figure 2C).

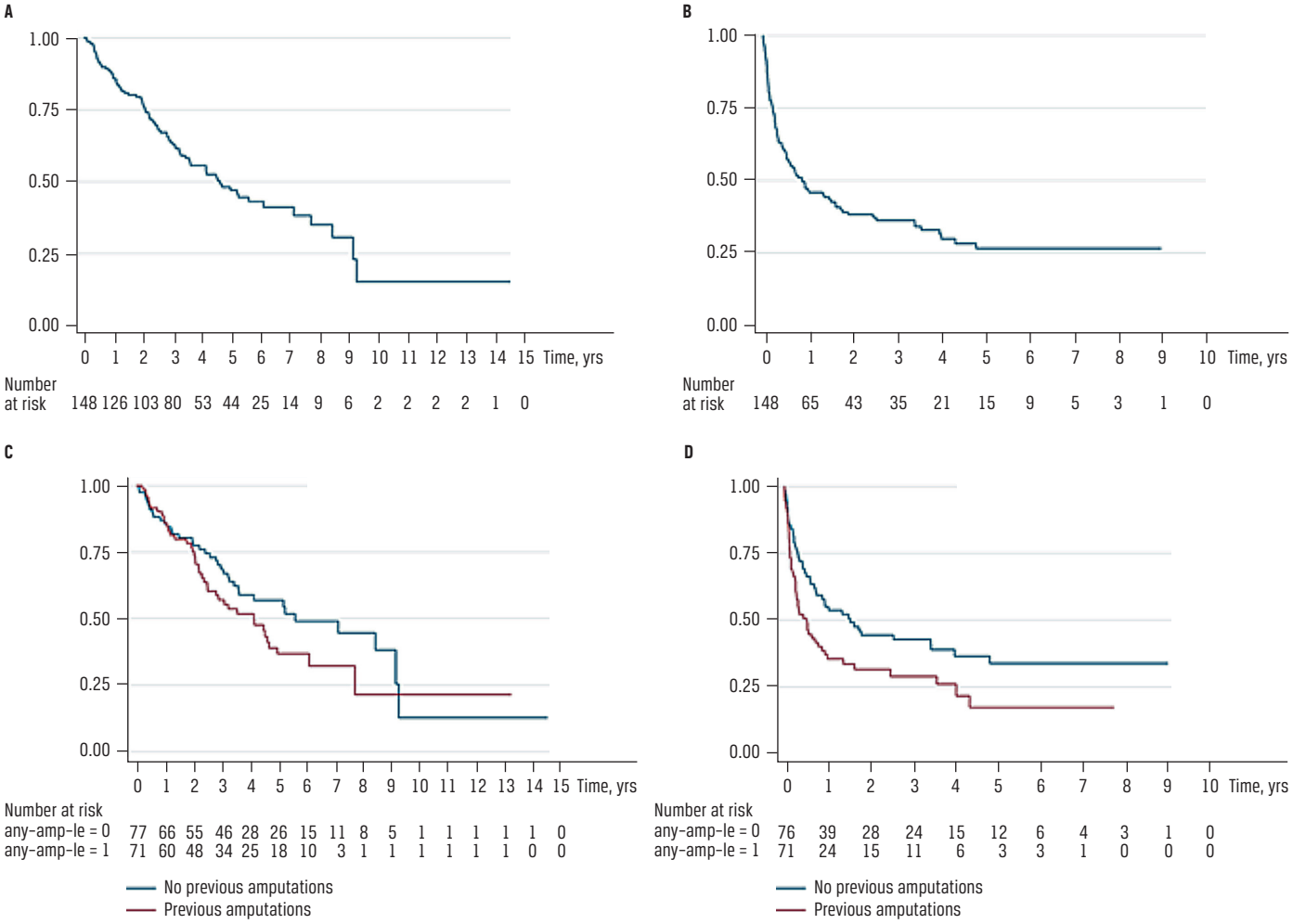
The median time to first amputation (minor or major) after referral to HBOT was 0.5 years for previously amputated patients and 1.5 years for previously non-amputated patients. The one- and five-year cumulated risk of amputation was 44.3% (95% CI: 33.9-56.4%) and 66.6% (95% CI: 54.7-78.3%) for patients who had not been amputated at the time of referral, and 61.5% (95% CI: 50.2-72.9%) and 81.9% (95% CI: 67.5-92.6%), respectively, for patients who had been amputated prior to their referral (Figure 2D).

DISCUSSION

The principal findings of this study were that the population of patients who are treated with HBOT for DFU has a high prevalence of comorbidity with an initial median CCI score of five, as well as a poor prognosis with

FIGURE 2

Kaplan-Meier survival and amputation estimate in the population of diabetic foot-ulcer patients referred to hyperbaric oxygen therapy (HBOT) in years of observation. A. Kaplan-Meier estimate of overall survival: time to death after HBOT start. B. Kaplan-Meier estimate of overall amputation after referral to hyperbaric oxygen therapy: time to first amputation after HBOT start. C. Kaplan-Meier survival estimate after referral to hyperbaric oxygen therapy of previously amputated and non-amputated patients: time to death after HBOT start. D. Kaplan-Meier amputation estimate after referral to HBOT for previously amputated and non-amputated patients: time to first amputation after HBOT start.



five-year amputation and mortality estimates of 73.5% and 51.8% after referral to HBOT, respectively.

Strength and limitations

The strengths of this study were the relatively large number of study subjects as well as its nationwide design, because HBOT of DFUs primarily takes place at a single location in Denmark. Furthermore, the quality and completeness of the national Danish registries provided data on the exact date and level of amputation [17], complete mortality follow-up and an even collection of comorbidity data.

The limitations of the study include

- Imprecise registration of diabetes subtype: 78 patients were registered with both diabetes Type 1 and Type 2, which indicates that the DNPR cannot be used reliably to diagnose the subtype of diabetes in DFU patients.
- Information bias regarding comorbidity and diabetes complications. Study results are limited to CCI scores at the time of referral and Kaplan Meier estimates of survival and amputation. Comorbid conditions might be missing.
- Selection bias; three patients were described as having diabetes in the electronic patient record without being registered with this diagnosis in the DNPR. However, the confirmation of the diabetes diagnosis in electronic patient records and the DNPR ensured a high probability of a correct diagnosis in all included patients.
- The study design did not allow for evaluation of the relationship between grade of ulceration, peripheral vascular disease, response to treatment and mortality.

Previous literature in the field

Our cohort had a high level of comorbidity (Figure 1). A non-HBOT study from the United Kingdom of new-onset DFU patients with an equivalent age found a mean CCI of 1.2 (SD: ± 1.6) at the first DFU hospital visit and a one-year mortality rate of 8.1% and a five-year mortality rate of 42.2% [3]. The survival rates in that study were comparable to ours, despite a remarkably higher median CCI score in our cohort (mean = 5.2 (SD: ± 2.2)). HBOT is a systemic treatment that improves microcapillary tissue perfusion, and which may have a cardio-protective effect in diabetic patients with foot ulcers [18]. We speculate whether the equivalent mortality rate of previously amputated and non-amputated patients in the two first years after HBOT is indicative of such an effect (see Figure 2C). The significant burden of disease was also evident from the high number of amputations in our study. Half of the referred patients (47%) had already received an amputation before they were referred to HBOT. To our knowledge, no previous studies have compared survival and amputation rates for patients referred to HBOT with and without previous amputations. Our data show that the prognosis is noticeably poorer if patients have been amputated before their referral to HBOT. The high burden of comorbidity entailed a low rate of treatment completion in the investigated cohort. A Swedish HBOT study including patients with DFU with less severe foot ulcers reported an adherence of 80%, whereas only 40% of our patients completed the prescribed 30 sessions of HBOT [11].

Possible mechanisms and implications

According to international guidelines, HBOT is recommended as adjuvant therapy in patients with full-skin foot ulcers that have shown no significant improvement after 30 days of standard wound care [14]. An expected high number of Danish DFU patients meet these criteria for adjuvant HBOT. However, currently there is no standard practice for referral of patients with DFUs to HBOT in Denmark. The Danish Health Authority's latest clinical guideline on DFU treatment [1] states that HBOT should; 1) not be routine, and 2) be reserved for patients in whom all other treatments have been attempted, and 3) should only be used in established scientific investigations.

The significant burden of comorbidity in our study population is indicative of a practice of late referral to HBOT. In the absence of a Danish national clinical guideline for referral of DFUs to HBOT, a pattern has developed where only the fraction of the population with the most complicated DFUs and the highest burden of disease is referred to this potentially advantageous treatment. However, the administration of HBOT for such advanced disease stages is untimely if the debilitating consequences of DFUs should be prevented. In our cohort, 47% had already been amputated at the time of their referral with an average of four amputations per patient. Previous reports have revealed that HBOT reduces the risk of major amputation in patients with DFU if HBOT is initiated timely [19].

The HBO chamber located at Rigshospitalet has a regional service covering both the Capital Region and the Zealand Region for all elective HBOT procedures. In the present study, we found that persons with DFUs attending wound care treatment at two specific hospitals in Copenhagen (71%) were far more likely to be offered HBOT than people with DFUs who lived in the Zealand Region, even though the prevalence of DFU is evenly distributed across the country [20]. This illustrate that in the absence of a national clinical guideline, the referral of DFU patients to adjunctive HBOT in Denmark is influenced by geography, attending physician or local procedures, causing unequal access to treatment of this debilitating disorder.

CONCLUSIONS

In the present study, the referral of patients with DFU to adjuvant HBOT in Denmark hinged on local factors rather than standardised procedures, and the patients were in advanced stages of their disease at the time of referral. The study results endorse the need for a large-scale randomised controlled trial that can define a HBOT-sensitive target group of patients with DFU in order to instigate evidence-based use of HBOT and reduce the risk of HBOT overuse.

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